CHAPTER ONE

Flesh of our Own Flesh

In which we learn that cancer is more than 200 different diseases, but they all share some common characteristics – the most important being that, if p53 is functioning properly, a cell cannot turn malignant.

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Tumours destroy man in a unique and appalling way, as flesh of his own flesh which has somehow been rendered proliferative, rampant, predatory and ungovernable.

Peyton Rous

'The question that's obsessed me for the whole of my career is: why is cancer so rare?' Gerard Evan, a professor of molecular biology at the University of California, San Francisco, and Cambridge, England, pauses to let his comment sink in. He knows it will startle me, for the statistics most commonly quoted in the media paint a bleak picture: that one in three of us will be diagnosed with cancer at some point in our lives and one in four of us will die of the disease. But Evan, talking to me in his office in the Sanger Building in a leafy corner of Cambridge about his years of research at the most fundamental level of the genes, is looking at cancer from the viewpoint of the cells, not of the whole human being. It takes just one rogue cell which has lost its normal regulatory machinery and run haywire to trigger cancer, yet billions upon billions of cells in our bodies that are growing and replicating themselves all the time do so typically for 50, 60 years or more without producing a tumour. And in two in three of us they never do. 'I mean, if you were doing the lottery you'd never gamble on this!' continues Evan. 'Cancers do arise, but clearly we've evolved amazingly elaborate and

effective mechanisms to restrict the spontaneous evolution of autonomous cells within our bodies. And even though we bomb ourselves with mutagens and carcinogens and do all sorts of things we shouldn't do, still most people die of heart disease; they don't die of cancer.'

A measure of just how resistant our cells are to corruption is the fact that a goodly chunk of our DNA – nature's instruction manual for building our bodies – can be traced back to the original single-celled organism known as the 'last universal common ancestor' of all life on earth (often referred to by the acronym LUCA), whose existence was first proposed by Charles Darwin in his book *On the Origin of Species,* published in 1859. In other words, some of our genes are more than 3.5 billion years old and have been passed down faithfully from one generation to the next over unimaginable eons of time.

The term 'cancer' represents not one but a collection of around 200 different diseases which share this common characteristic: they all originate from a single cell that has become corrupted. The great majority of cancers – well over 80 per cent – are carcinomas, which means they are in the epithelial cells that form the outer membranes of all the organs, tubes and cavities in our bodies, and include our skin. The connective tissue, which provides the structural framework for our bodies, and support and packaging for the other tissues and organs – it includes, for example, bone, cartilage, fibrous tissue such as tendons and ligaments, collagen and fatty tissue – appears extremely resistant to turning malignant. Sarcomas, which are cancers of the connective tissue, account for only about one in a hundred cases.

No one yet knows the reason for this bias, though speculation is intense. Could it be that epithelial cells tend to divide more often than connective tissue cells and the opportunity for mutation is much greater? Our skin, for instance, has an intense programme of self-renewal with

cells at the base layer dividing and undergoing processes of differentiation and maturation as they push up towards the surface, where they are eventually sloughed off (that's what causes the tidemark around the bathtub). The lining of the gut, too, is constantly renewing itself, and the sloughed cells are excreted. However, an argument against high rates of proliferation being the main reason why epithelial cells are at greatest risk of malignancy is the fact that some of the most cancer-prone epithelial cells are not ones that divide most frequently. Some suggest that it is because epithelial cells are a first line of defence against the outside world and are more likely to come into contact with cancer-causing agents. But this argument too has weaknesses, since epithelial and connective tissue cells are equally exposed to carcinogens in some organs, notably the prostate, yet the epithelial cells are the more vulnerable.

Looking for answers to this conundrum, one lab took samples of healthy breast tissue, teased apart connective tissue cells from epithelial cells and watched what happened when they attacked them with chemical carcinogens in their Petri dishes. To their surprise, they saw that the two cell types reacted completely differently, though they still don't know exactly how or why. That's the Holy Grail, as it might point to chinks in cancer's armour as targets for new drugs.

Tumours typically arise from the pool of stem cells in a tissue that are responsible for the repair and replacement of cells as part of the routine maintenance of our bodies. It can take years, even decades, for a rogue cell to grow into a tumour that is detectable. This is because it depends on progressive breakdown of the cellular machinery through the mutation and/or loss of crucial genes that regulate growth, replication, repair and timely death of cells – mutations that occur independently and, crucially, don't result in the cell being eliminated, which is the normal fate of damaged cells. The growing tumour is parasitic: it competes with the normal cells around it for nutrients and oxygen,

and it can't grow much beyond 1–2mm (1/25th–1/12th of an inch) in diameter unless it develops its own blood supply.

What distinguishes a malignant tumour from a benign one is the former's ability to spread – to send out microscopic shoots that penetrate the walls and invade neighbouring tissue, and to seed itself in distant sites from breakaway cells carried in the bloodstream or lymph system. Blood-borne dissemination is particularly efficient at spreading cancer, with the blood depositing its cargo of delinquent cells along natural drainage sites, most commonly the liver and lungs.

Our understanding of the mechanics of cancer has advanced at revolutionary speed in the last 40 years, as one technological breakthrough after another in molecular biology has enhanced scientists' ability to explore the workings of the cells – the building blocks of all life on earth. But the sheer volume of data churned out has threatened at times to overwhelm the cancer research community. Robert (Bob) Weinberg has been involved since the early 1960s and has played a big part in the revolution. 'The plethora of information is just overwhelming,' he told an audience of mostly fellow scientists who had gathered in a lecture theatre at Massachusetts Institute of Technology, MIT, to hear him speak of his life in science and of the personal experiences that had formed him.

'When I was a graduate student there were two journals one paid any attention to: the *Journal of Molecular Biology* and *PNAS* (*Proceedings of the National Academy of Sciences*). That was it. Today?' Weinberg shrugged mightily and spread his hands. 'More than the stars in the sky. I think PubMed* now has 12 or 15 million papers in it, and the only way I can deal with this is to continually ask people who have distilled information in their own minds how this or that problem is evolving.' Laboratory scientists today can generate important data up to 10,000 times faster than he could when he started out in cancer research, Weinberg told his audience.

* A free database of references to papers on life sciences and biomedical topics set up in 1996]

In his own lab at MIT, where he has spent most of his working life, Weinberg puts pressure on people to draw lessons and develop ideas from what they observe, not simply accumulate data. It's little surprise, then, that he should have become preoccupied with bringing some order to the explosion of information about cancer that in many ways mirrors the disease's own chaotic growth. Attending a conference in Hawaii in 1998, Weinberg took a walk down to the mouth of a volcano with fellow scientist Doug Hanahan, who had also caught the molecular-biology bug at MIT as an undergraduate. Mulling over their common frustration as they walked, the two conceived the idea of writing a review that would seek to clarify what Weinberg calls the 'take-home lessons' of research.

'Cancer research as a field was a very broad and disparate collection of findings, and we thought there might be some underlying principles through which we could organise all these disparate ideas,' he said. 'We came up with the notion that there were six properties of cancer cells that were shared in common with virtually all cancer cells and that defined the state of cancerous growth.' 'The Hallmarks of Cancer' was published in 2000 and far from disappearing 'like a stone thrown into a quiet pond', as Hanahan and Weinberg had predicted, knowing how quickly most journal articles are read and forgotten, their paper has become the descriptive cornerstone of cancer biology and a clear framework into which new pieces of the jigsaw can be slotted. The six characteristics they identified as being common to virtually every cancerous cell are that, in lay terms:

- the forces pushing them to grow and divide come from within the corrupted cell itself, rather than being signals from outside;
- cancer cells are insensitive to forces that normally stop cell division at appropriate times;
- they are resistant to being killed by the mechanisms that normally remove corrupted cells;

- they are immortal, meaning they can divide indefinitely, whereas normal cells have a finite number of divisions controlled by an internal 'clock' before they stop dividing, become senescent and eventually die off;
- they develop and maintain their own blood supply;
- they can spread to other organs and tissues and set up satellite colonies, or metastases.

In 2011 the two scientists updated and refined their 'Hallmarks' paper, adding further general principles, including the fact that the metabolism in cancer cells – particularly the way they use glucose to provide energy – tends to be abnormal; and that they are able to evade detection and destruction by the body's immune system.

Crucially for the story I'm telling here, p53 plays a role in all these traits. 'As I read the paper by Hanahan and Weinberg, I said, "This is conceptually brilliant!"' comments Pierre Hainaut, who spent many years investigating cancer genetics at the World Health Organization's International Agency for Research on Cancer, IARC, in Lyon, France. 'But then I thought: where is the unity? Clearly it must be a more coherent programme than just a succession of boxes. What is holding it together? And then I realised: my goodness, it's p53!

'There are many genes that have a mechanistic role in one hallmark trait or another, and this will spill over to two or three hallmarks. But p53 is the one that links all the hallmarks together. This means that from a molecular viewpoint there is one basic condition to get a cancer: p53 must be switched off. If p53 is on, and hence functioning properly, cancer will not develop.'

Hainaut – a tall, rangy Belgian with a crooked smile, boyish enthusiasm and an earnest expression behind black-rimmed specs – has been particularly intrigued by the gene's multiple roles in the activities of the cell. It's an

interest that takes him frequently out of his lab and into the wider world, to investigate the connection between mouldy peanuts and liver cancer in the Gambia, to meet families with a hereditary cancer disposition in southern Brazil, and to many other countries, from China to Iran, in pursuit of insights into the workings of p53 in our everyday lives. 'There are many, many ways to lose the function of p53,' he continues. 'Mutation is a very common one; loss of one copy of the gene is another; but there are also other ways, such as switching it off, degrading it, putting it off-site and so on. But I repeat: if the cell is retaining a perfectly intact and fully reactive p53 function, it will not give rise to cancer.'

AN ANCIENT MALADY

Cancer is a disease as old as humankind. It is mentioned in the earliest medical texts in existence, a collection of papyri from ancient Egypt dating from 3000–1500 BC. Actual specimens of human tumours have been found in the remains of a female skull from the Bronze Age, dating between 1900 and 1600 BC, and in the mummified remains of ancient Egyptians and Peruvian Incas. In 1932, the palaeoanthropologist Louis Leakey, working in the Rift Valley of East Africa, found evidence suggestive of bone tumours in the fossilised remains of one of our hominid ancestors, *Homo erectus*, who roamed the African savanna between 1.3 and 1.8 million years ago.

In fact, cancer has probably been around since LUCA first gave rise to multi-celled creatures. In 2003 a team from Northeastern Ohio Universities College of Medicine, led by radiologist Bruce Rothschild, travelled around the museums of North America scanning the bones of 700 dinosaur exhibits. They found evidence of tumours in 29 bone samples from duck-billed dinosaurs called hadrosaurs from the Cretaceous period some 70 million years ago. And evidence of tumours has been found also in the bones of

dinosaurs from the Jurassic period between 199 and 145 million years ago.

Hippocrates, living in ancient Greece around 460 BC, was the first person to recognise the difference between benign tumours that don't invade surrounding tissue or spread to other parts of the body, and malignant tumours that do. The blood vessels branching out from the fleshy growths he found in his patients so reminded him of the claws of a crab that he gave this mysterious disease the name *karkinos,* the Greek word for crab, which has translated into English as carcinoma. Hippocrates and his contemporary physicians believed cancer was a side effect of melancholia. And up to the Middle Ages and beyond, medics and patients alike reckoned the causes were supernatural and related to demons and sin and the accumulation of black bile.

This menacing theory of cancer prevailed for nearly 2,000 years before it was exploded by Andreas Versalius, a Flemish doctor and anatomist working in Padua, Italy, in the early 16th century. Versalius performed post-mortems on his patients, as well as dissecting the corpses of executed criminals supplied to him by a judge in Padua fascinated by his work: black bile, he announced, was nowhere to be found in the human body, diseased or healthy.

But it was another two centuries and more before anyone suggested that agents in our environment might be playing a part in the development of tumours. In 1761 John Hill, a London physician and botanist, produced a paper, 'Caution Against Immoderate Use of Snuff', in which he described patients with tumours of the nasal passages as a consequence of sniffing tobacco. And in 1775 an English surgeon, Percivall Pott, reported a number of cases of cancer of the scrotum in unusually young men whose only link was that they had been chimney sweeps as small boys and were likely to have gathered soot in the nooks and crannies of their bodies as they squeezed themselves up the narrow flues of homes and factories in Georgian Britain – a practice that

lasted for two centuries and frequently involved children as young as four years old. In 1779, the world's first cancer hospital was set up in Reims, France – at a fair distance from the city because people feared the disease was contagious.

The foundation of our modern understanding of cancer as a disease of the cells was laid in the mid-19th century by Rudolf Virchow, a German doctor born into a farming family, who won a scholarship to study medicine and chemistry at the Prussian Military Academy. Often referred to as the father of modern pathology, Virchow was much less interested in his suffering patients than in what they suffered from – the mechanics of disease – and preferred to spend his time in the lab poring over his microscope and doing animal experiments than visiting the sick. The idea that living cells arise from other living cells through division had been around for many decades but had been almost universally rejected, perhaps because it offended religious sensibilities about creation – in those days people really believed that maggots appeared spontaneously in rotting meat.

It was not until the strong and independent-minded Virchow, who was active in politics as well as in science and medicine, published his own observations of cell division and coined the phrase *omnis cellula e cellula* – which translates roughly as 'all cells arise from other cells' in a continuous process of generation – that the idea finally caught on. But it was the advent of molecular biology in the mid-20th century that has allowed scientists to peer ever deeper into the cell – to study the machinery of life itself in the DNA – and to begin to crack the code of cancer.