

Chapter 1

THE DISEASE OF CANCER

President Richard Nixon famously declared ‘war on cancer’ by signing into law the National Cancer Act in December 1971. Since then, no area of medical research has had more investment worldwide in terms of money, manpower and effort than cancer. Across the world, universities, medical schools, hospitals, publicly-funded research institutions, private research institutions, large pharmaceutical companies and small biotech companies have formed a collective effort that over the almost four decades since 1971 has worked towards the dream of reducing cancer from a death sentence to a curable disease at best, or to a disease that could be lived with at worst.

What is the report card for all of that intense effort?

- ✚ We have made some ground in understanding the risk factors associated with the development of many cancers. For example, we know that sunlight predisposes to melanoma; that smoking predisposes to a certain type of lung cancer, and along with alcohol predisposes to cancer of the mouth and the oesophagus; that eating vegetables pickled in a certain way is linked to cancer of the stomach; that exposure to asbestos is linked to mesothelioma; that infection with hepatitis C virus is linked to cancer of the liver (hepatoma); that infection with genital papillomaviruses (wart virus) is linked with cervical cancer; that carrying certain genes increases the risk of a certain type of breast cancer.
- ✚ Good progress also has been made in the field of early diagnosis of certain cancers. Such as mammography for breast cancer, the PSA blood marker for prostate cancer, the CA125 blood marker for ovarian cancer, and PAP smears for cervical cancer. The availability of these early diagnostic procedures has meant that these cancers no longer need to be fatal.
- ✚ Radiology has made considerable strides with the development of procedures such as CT, MRI and PET scans, providing more accurate evaluation of the size and spread of tumors.
- ✚ Radiotherapy has become more sophisticated, providing safer and more targeted radiation of tumors.
- ✚ The range of chemotherapies has increased considerably, providing doctors with a considerably more extensive range of treatment choices.

Despite this progress, 1 in 2 people still will develop a life-threatening cancer in their lifetime, and 1 in 4 will die from that cancer. In the Western world, cancer is the second-most common cause of death, exceeded only by heart disease. The following statistics from the

American Cancer Society for the USA are fairly representative of the extent of the disease of cancer in Western, first-world countries.

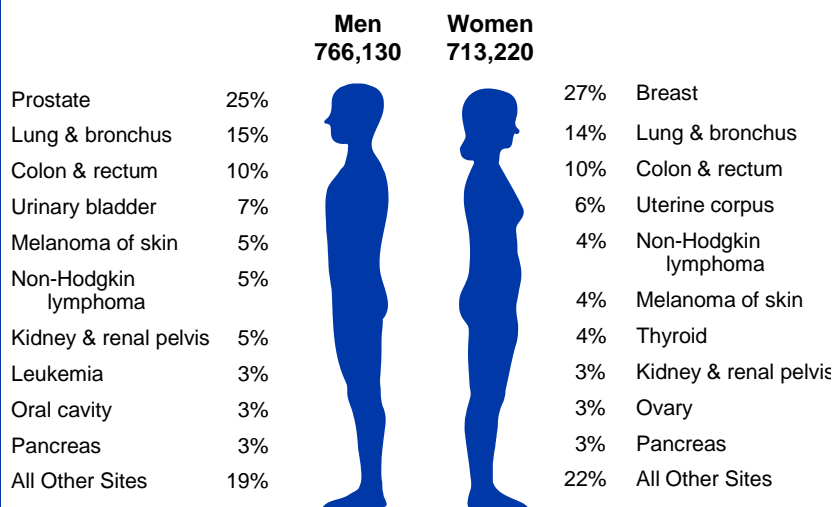
US Mortality, 2006

Rank	Cause of Death	% of all deaths
1.	Heart Diseases	26.0
2.	Cancer	23.1
3.	Cerebrovascular diseases	5.7
4.	Chronic lower respiratory diseases	
5.	Accidents (unintentional injuries)	5.0
6.	Diabetes mellitus	3.0
7.	Alzheimer disease	3.0
8.	Influenza & pneumonia	2.3
9.	Nephritis*	1.9
10.	Septicemia	1.4

*Includes nephrotic syndrome and nephrosis.
 Source: US Mortality Data 2006, National Center for Health Statistics, Centers for Disease Control and Prevention, 2009.

In 2009, it is estimated that approximately 1.5 million new cases of cancer will be diagnosed in the US, in the following proportions. Cancer of the prostate and breast will be the most commonly diagnosed cancers, followed by lung and colon-rectal cancers. Collectively, these four cancers will account for about 50% of all new cancer diagnoses in men and women.

2009 Estimated US Cancer Cases*



*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
 Source: American Cancer Society, 2009.

For men, their lifetime probability of developing a particular form of cancer is shown below.

Lifetime Probability of Developing Cancer, Men, 2003-2005*

Site	Risk
All sites†	1 in 2
Prostate	1 in 6
Lung and bronchus	1 in 13
Colon and rectum	1 in 18
Urinary bladder‡	1 in 27
Melanoma§	1 in 39
Non-Hodgkin lymphoma	1 in 45
Kidney	1 in 57
Leukemia	1 in 67
Oral Cavity	1 in 72
Stomach	1 in 90

* For those free of cancer at beginning of age interval.

† All Sites exclude basal and squamous cell skin cancers and in situ cancers except urinary bladder.

‡ Includes invasive and in situ cancer cases

§ Statistic for white men.

Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.3.0 Statistical Research and Applications Branch, NCI, 2008. <http://srab.cancer.gov/devcan>

The probability for women is shown below.

Lifetime Probability of Developing Cancer, Women, US, 2003-2005*

Site	Risk
All sites†	1 in 3
Breast	1 in 8
Lung & bronchus	1 in 16
Colon & rectum	1 in 20
Uterine corpus	1 in 40
Non-Hodgkin lymphoma	1 in 53
Urinary bladder‡	1 in 84
Melanoma§	1 in 58
Ovary	1 in 72
Pancreas	1 in 75
Uterine cervix	1 in 145

* For those free of cancer at beginning of age interval.

† All Sites exclude basal and squamous cell skin cancers and in situ cancers except urinary bladder.

‡ Includes invasive and in situ cancer cases

§ Statistic for white women.

Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.3.0 Statistical Research and Applications Branch, NCI, 2008. <http://srab.cancer.gov/devcan>

What these statistics show is that despite the enormous effort that has gone into understanding the causes of cancer and its management, it remains the modern scourge. But it is not all doom and gloom. For some cancers, once-fatal diseases have become curable or largely curable thanks to better surgical techniques and more powerful and better targeted chemotherapies. The death rate from testicular cancer has been reduced over the last 50 years

from about 100% to virtually 0%. In the case of childhood leukaemias, the overall survival rate over that time has been increased from about 5% to about 70% today. Then there is the recent, exciting development with cervical cancer where the availability of a papillomavirus vaccine should see the risk of cervical cancer being reduced to virtually zero in vaccinated women.

But unfortunately this high level of success has been the exception rather than the rule. At the other end of the spectrum lie those diseases where little progress has been made in early diagnostic procedures or surgical techniques or chemotherapies and where overall survival rates remain poor and essentially unchanged from 50 years ago. This includes cancers involving nerve cells such as glioma (primary brain cancer) and neuroblastoma (cancer of developing nerves in children) and cancers of the liver, pancreas and gall-bladder.

In the middle of this spectrum lie the greater bulk of cancers, including the more common forms that we develop such as cancer of the breast, ovary, prostate or bowel, where success has been mixed. Picked up early enough, most of these cancers have significantly better survival outcomes than 50 years ago. But where the cancer has established a reasonable foothold, survival rates remain poor.

Prostate cancer is a good example of this vast middle ground of the cancer spectrum. In its early stages when still confined to the prostate gland, improved surgical technique means that surgical removal of the gland (prostatectomy) usually is curative. The availability of the PSA blood test and modern biopsy procedures has made this early detection possible. Fifty years ago, most cases of aggressive prostate cancer were not detected until the cancer had spread outside of the prostate gland, at which stage the cancer is regarded as being inoperable. Even here, advances in radiotherapy have meant that, providing the cancer has not spread too far, then the modern patient has some chance of beating the disease. But once the disease has spread well beyond the prostate gland and has spread to tissues such as bone, modern medicine offers little more than an extension of 3-6 months of life compared to 50 years ago.

Lung cancer, breast cancer, ovarian cancer, bowel cancer and melanoma all largely follow this same pattern – we are much better at picking up the cancer at an early stage than 50 years ago, and the earlier the diagnosis is made the more likely the patient is to be cured. Mammography for breast cancer, colonoscopy for bowel cancer, and routine dermatological screening for melanoma, plus strong community education campaigns that have brought self-examination to the forefront, have all contributed to improved rates of early diagnosis. However, once these cancers are established, modern therapies invariably are little more than palliative (meaning that they extend life by some months) with the same poor survival rates as 50 years ago.

Why this undramatic and very patchy success in the cancer field? The answer quite simply is that despite the massive amount of research that has gone on in the field, we have made remarkably little progress in understanding the underlying nature of cancer. With considerably less investment, we have gained tremendous insights into the nature of other degenerative diseases such as heart disease, diabetes and arthritis, leading to significant advances in the management of those diseases. In the case of heart disease, we have a pretty good understanding of the different disease events taking place in the artery wall, the risk factors predisposing us to those changes, and even how to prevent or reverse many of those disease changes. Understanding how certain blood proteins and cholesterol interact to initiate the disease process, how lifestyle factors such as obesity, lack of exercise and smoking

exacerbate the disease process, and the nature of and contribution of hardening of the artery wall (hypertension), have been pivotal in bringing about an enormous lowering of the risk of developing and dying from heart disease.

Cancer stands in stark contrast. With cancer, we still haven't even got to first base in understanding why the cancer cell behaves the way it does and what makes it different to other healthy cells in the body.

One of the few things that we do know about a cancer cell is that it is a rogue cell, disobeying all attempts by the body to control it. It is like having an alien cell in the body – it is part of the body, but it is running its own agenda. All the complex checks and balances and controls that the body exerts over the trillion of cells in its care are completely ignored by the cancer cell.

Another thing that we are fairly certain about is that this roguish behaviour is brought about by permanent damage to the genetic apparatus of the cell. Each cell in the body contains a full complement of our individual genetic code – this is our DNA, making up the thousands of genes that define us as humans and as individual humans. At a macro level, genes determine such things as what colour eyes we have, how tall we are, how good we are at ball games, and so on. Permanent damage to any one of these genes in a single cell somewhere in the body is hardly likely to result in the formation of a rogue cell. The genes that are at risk in terms of cancer are those operating at the micro level. These are the genes that have the task of controlling how an individual cell behaves in the body – how it interacts with its neighbouring cells, how long the cell will survive, and what specialised functions it needs to develop (that is, is it going to become a bone cell responsible for laying down bone or a kidney cell that will make urine). The way a cell communicates with its neighbouring cells and responds to messages coming from elsewhere in the body goes to the most fundamental aspects of cell behaviour. This is the blueprint present in every cell in our body that ensures an integrated and smoothly functioning body. It is easy to see then that any damage to this blueprint could well set a cell on the path to becoming a rogue cell, totally out of step with its neighbouring cells.

What is the nature of this DNA damage? DNA is living material, and like any living material it is subject to damage. Just exposing your skin to sunlight for a few seconds causes an enormous amount of DNA damage in the cells in all layers of your skin. The DNA packed tightly in each cell is like a ball of twine. Sunlight passing down through the outer layers of your skin is like a hot needle being passed through that ball of twine, burning each bit of string that it touches. The ball of DNA is packed so tightly that a single ray of sunlight probably 'burns' at thousands of points in a single cell. Like the burns to string caused by a hot needle, so the burns of the DNA cause breaks, breaks which if not repaired quickly could lead to irreversible damage.

The smooth operation of our genes, particularly those genes controlling the most basic functions of the cell, is so critical to life that our cells need to be constantly checking on the integrity of our DNA in the face of this background level of damage. Each cell has a set of enzymes that are constantly on patrol, checking on the physical appearance of our genes. When they detect an abnormality, they immediately set about excising the damaged gene and replacing it with a new one. As a final security measure, if the damage is so severe that it can't be repaired, then that same repair apparatus then will activate a self-destruct process known as *apoptosis* in which the cell essentially dissolves from the inside. The dead cell then

is replaced by a new healthy cell. This cycle of damage + repair, or damage + attempted repair + apoptosis + cell replacement, is something that is going on in every tissue of our body every minute of our life from the time of birth.

As critical as this quality control mechanism is in our body, it is not fool-proof. Occasionally it will go wrong, and it is in this potential error that cancer has its roots.

The odds of it going wrong might be miniscule, maybe of the order of 1 in every ten million repairs, but with DNA damage occurring on an almost constant basis, eventually an error will occur. That error could be at any point – it could be in the repair process itself, meaning that the damage is going to be resistant to repair; or it could be in the ability of the cell to recognise that it has a fatal flaw in its DNA; or it could be in the ability of the cell to activate its self-destruct mechanism. Whatever the reason, the cell now has a permanently damaged gene, and if that gene happens to be critical to the fundamental behaviour of the cell, then it has the potential to turn into a rogue cell that will live forever and ignore all bodily commands.

Where does this DNA damage come from? It essentially comes from just living. We used the example above of sunlight, but our bodies are exposed to cancer-causing agents (so-called *carcinogenic agents*) every day of our lives. You would need to lock yourself in a cave with filtered air from the moment of birth not to encounter such agents. Carcinogenic chemicals are present in the air that we breathe and in the food that we eat; we are constantly being exposed to background radiation from sunlight and naturally-occurring radioactive materials in our environment; viruses with cancer-causing potential also are lurking out there. We elevate the level of exposure to these cancer-causing factors through risky behaviour such as cigarette smoking (lung cancer), chewing tobacco (cancer of the lip and tongue), over-indulging in both smoking and alcohol (throat and oesophageal cancer), eating highly pickled foods (gastric cancer), inhaling asbestos fibres (mesothelioma), suffering sunburn (melanoma), being exposed to excessive radiation (leukaemias), and having long-term exposure to certain types of papillomaviruses (cervical cancer). Whereas in the case of radiation, the damage is in the form of a cut to the DNA, in the case of carcinogenic chemicals and viruses, they cause damage by attaching themselves to the DNA, changing its shape, and thereby changing its function.

Whereas risky behaviours elevate the likelihood of permanent DNA damage to almost guaranteed proportions, the reality is that all of us are exposed to a low-level background risk by simply living. The reason why most of us don't succumb to cancer from an early age in the face of this potentially destructive onslaught is due simply to the remarkable capacity of our cells to detect and limit the damage.

Up to this point, there is no guarantee that the damaged cell will become cancerous, and the chances are that it won't. It simply means that it has the potential to become cancerous. Cells at this stage are known as *pre-cancerous* cells, and we make them by the millions every day of our lives. The reason that most of us manage to get through to at least middle-age without developing cancer is that something else needs to happen to pre-cancerous cells to tip them over into becoming a fully-blown cancer cell. What that 'something else' is remains largely unknown. It could be a series of small events or it could be one single catastrophic event – we simply do not know. The good news is that it is very rare for that to happen. It is thought that the vast majority of pre-cancerous cells never progress any further. They simply sit in our tissues, minding their own business, and not causing any problems.

As we noted, what causes that pre-cancerous cell to make the final leap into a cancer cell remains pure conjecture. It almost certainly differs from one type of cancer to another. Not everyone who smokes gets lung cancer and not every woman who carries the familial gene for breast cancer gets breast cancer. Something else determines that risk of conversion – it could just be our genes that determine that risk, or it could be a secondary virus or chemical in our environment. With the exception of those cancers found in early childhood (eg. leukaemia and neuroblastoma), and the high rate of breast cancer in woman before estrogen levels fall with the onset of menopause, the risk of developing most of our cancers increases with increasing age, suggesting at least for most cancers that the cause is a steady accumulation of carcinogenic damage the longer we live.

Irrespective of what causes the leap from a pre-cancerous to cancerous state, the outcome is the same - the cancer cell attains a life of its own, completely outside of the body's control. We control the cells in our body in two main ways. The first way is a highly intricate communication system based on chemicals such as hormones and cytokines – some of these come from within the cell itself, others from neighbouring cells, and others from distant organs and tissues. These signals are there to ensure that each cell conforms and follows an integrated plan for the body. Those signals tell the cell what function it should be performing, where it should be in the body, when it needs to move or to stay still, when it needs to divide, and when it needs to die. Cancer cells are able to operate completely outside of this command system. Freed from any commands, cancer cells are able to grow in total disregard of the rest of the body.

The second way that we control our cells is through the immune system. Our immune cells are meant to detect anything foreign in the body or any tissue that is damaged and remove it. Cancer is foreign tissue in the sense that it is behaving as not being part of the body, and it certainly is damaged. But by a process that we have yet to understand, cancer cells are able to resist all attempts by the body's immune cells to attack them and destroy them. It is not as though the cancer cell has an invisible shield around it.....the immune cells show absolutely no interest in the cancer cells.

Another area of cancer that is poorly understood is the highly variable behaviour of cancer. The disease processes in heart disease, arthritis and diabetes are reasonably predictable and generally stay with certain basic rules of behaviour. Cancers, on the other hand, vary enormously in how quickly they grow and how aggressively they spread from their point of origin. At one end of this spectrum, the least aggressive cancers are referred to as being *benign*. A benign cancer typically grows very slowly and remains localised at its point of origin. An example of a benign cancer is basal cell carcinoma (BCC), the most common cancer of the skin. At the other end of the spectrum is another form of skin cancer, melanoma. Melanoma grows very rapidly and is inclined to spread away from its point of origin at a very early stage, settling out in almost any other part of the body. Fast-growing cancers are referred to as being *malignant*, and *metastatic* when they spread to distant parts of the body. It would be incredibly rare for a BCC to be anything but a benign, localised, non-life-threatening cancer. Equally, it would be highly unusual for an advanced melanoma to be anything but life-threatening. Aside from these two reasonable certainties, all other cancers fall somewhere between these two extremes, with each cancer being as individual as the patient, and each cancer having a high degree of unpredictability about its behaviour. For example, we do not know why some cases of prostate cancer are very slow-growing while others are highly aggressive. In men with the slow-growing form, aggressive treatment is uncommon. The prognosis typically is very good and these men are more than likely to live

well into old age without any serious consequences from their cancer. The aggressive form of prostate cancer, on the other hand, can be almost as aggressive as a melanoma, with rapid doubling times and a strong propensity to metastasise. This form of prostate cancer generally carries a poor prognosis.

Once cancers reach a certain size, the body essentially becomes nothing more than a source of nourishment for the cancer to the extent that it will deprive the rest of the body of vital nourishment. Death from cancer usually is a result of combination of malnourishment and disruption by the cancer of the normal functioning of major organs through pressure or invasion.

Surgery remains the most effective and certain way to treat cancer, but that does require certainty that the cancer is completely contained to the tissue removed by surgery. For many aggressive or advanced cancers, however, this certainty does not exist, and in these cases surgery often is used for 'debulking' purposes, which means reducing the cancer load in the body so that other forms of therapy might be used.

For inoperable cancers, radiotherapy and drug therapy (chemotherapy) are the treatments of choice. Radiotherapy can have very good results with some cancers, while in other cases its best outcome is a means of reducing the bulk of the cancer through its ability to destroy large numbers of cancer cells. The main restriction with radiotherapy is that there usually is a limit to the number of times that it can be used because of its destructive properties against surrounding healthy tissue. For example, in the case of brain cancer (glioma), radiotherapy typically is limited to one application.

That brings us to chemotherapy, which for the bulk of cancers remains the ultimate hope once the cancer has moved beyond the operable stage and when radiotherapy is no longer appropriate. Treating cancer with drugs presents a number of significant challenges. One of those challenges is that tumours can, and usually do, become resistant to anticancer drugs. A good initial response to therapy with apparent disappearance of tumour all too often is followed months or years later by the return of the cancer, often growing more rapidly than before. One of the reasons for this is that individual cancers are not necessarily homogenous. The earlier, simplistic belief was that a cancer arose from a single abnormal cell that went on to provide a single line of identical cancer cells. We now know that to be incorrect. Cancers generally are heterogeneous, meaning that they contain a number of different strains of cancer cells, all related and all of the same type, but with slightly different characteristics. One of the main practical implications of this is that the different strains of the cancer within an individual cancer patient can have very different sensitivities to a particular anticancer drug. Killing off the drug-sensitive strains might provide an immediate and dramatic response to chemotherapy, but the removal of these competing strains simply provides an opportunity for the less drug-sensitive strains to grow despite ongoing chemotherapy. Hence the rapid regrowth of a cancer following an earlier, dramatic response to chemotherapy.

Another challenge is the difficulty in knowing how extensive the cancer has grown. In almost every other disease, the extent of the disease is known and the response to treatment is readily tracked. This is not so with most forms of cancer. For aggressive cancers such as breast and ovarian cancer, it is not possible to know how extensive this disease is at the time that treatment starts resulting in some patients being under-treated and others being over-treated.

Another challenge is getting a drug through the bloodstream into a solid mass of cancer cells at levels that can be effective. Most cancers form solid masses (known as *tumours*) that have an entirely different architecture to the surrounding normal tissue. Tumours generally have an abnormal blood supply compared to healthy tissue to the extent that tumours often outstrip the capacity of the blood supply to meet the tumour's demand for nutrients. This usually leads to death of the centre of the tumour mass as it continues to grow outwards. Getting the drug to go uniformly at sufficiently high levels throughout the tumour mass in the face of this abnormal blood supply is a challenge. Once a cancer becomes established and has formed multiple tumours, chemotherapy becomes increasingly less effective in large part because of its inability to penetrate the increasingly expanding tumour masses.

There are about 20 anticancer drugs in regular use today to manage cancer. There are many more drugs used in cancer therapy to manage pain and other symptoms of cancer, but what we are focusing on in this story is those drugs that are used in an attempt to slow down, or to stop, or even to eliminate the cancer. Some of these drugs have been around for 40 years, while others are only a year or two old. The choice of which drug or cocktail of drugs that you receive depends on a number of factors - the type of cancer (each type of cancer tends to be sensitive to particular drugs), the stage of the cancer (early or advanced) and how far it has spread – these are all factors that the oncologist will weigh up in deciding on the best therapy.

To summarise, the report card on the effort to date would hardly be complimentary, probably saying something like 'some progress made, but considerably more application and effort required'. For some cancers, the outlook has improved significantly over the past 40 years. For those cancers, the disease will have little or no impact on the person's life. Unfortunately these cancers are all too few. The reality for most cancer sufferers is that the prospect of surviving the cancer has improved very little over the past 40 years. Certainly that is the case with the most common cancers of the breast, prostate and large bowel. We have some idea of some of the risk factors for each of these cancers, although we still have virtually no idea what causes them. In each case we have made good progress in detecting the early stages of the cancer, but once it gains a foothold, modern chemotherapy and radiotherapy offer little more than a delaying tactic, providing just a few more months of life. For these, and other relatively common cancers, the original dream of turning cancer into a disease that we live with continues to be just that – a dream.

Learning how to deal with cancer through prevention and treatment remains the largest, single challenge facing medicine. Cancer is to the 21st century what infectious diseases were to the 20th century. The story told in this book hopefully offers a glimmer of hope in that quest.

A HISTORY OF CHEMOTHERAPY

Up until just after the Second World War, there was no concept that drugs could be used to stop cancers growing. Surgery was essentially the only option, and then only reserved for the most easily removed tumours. Having an established, aggressive cancer at that time was in effect a death sentence.

The first attempt at chemotherapy for cancer using scientific rationale was in 1946, and in one of the great ironies of medicine, owes its origins to war and to the notion of inflicting harm and misery on people. In the six decades since, the science of cancer chemotherapy has lurched ahead in fits and starts, with occasional periods of excitement and great promise breaking decade-long periods of little or no progress.

The history of chemotherapy is marked by a number of key developments.

1. First patient, first anticancer drug

Remarkably, the beginnings of chemotherapy are to be found in chemical warfare and a tragic, but ultimately fortuitous, war-time bungle. The story starts in the First World War with the development by Germany of nitrogen mustard gas that was used to such deadly effect in the trenches of Belgium and France. The gas was highly toxic, burning the skin, eyes and lungs of soldiers who inhaled it. Chemical warfare subsequently was banned by international treaty, so ensuring that the Second World War was essentially free of the use of toxic gases in the field. However, despite the treaty, both sides in the war were carrying out research into chemical warfare on a clandestine basis, with the US stockpiling nitrogen mustard gas in case Germany decided to use it as it had some 25 years earlier in France.

In 1943, after the Allies had landed in Italy and were pushing up towards Germany, the US sent a supply of nitrogen mustard gas by ship to the Italian front, storing it in the Italian port of Bari. On the night of December 2, German bombers attacked the port, inflicting considerable damage including the warehouses holding the nitrogen mustard gas, releasing the gas across the city and exposing military personnel and civilians alike to the gas. Compounding the tragedy, neither military nor civilian physicians were informed about the presence of mustard gas in the city, leading to failure to properly treat hundreds of people affected by the gas. The extent of the damage associated with the release of the mustard gas is shrouded in controversy to this day, in part because of confusion over the proportion of casualties attributed directly to the bombing, and in part because of the highly classified nature of the event, with Churchill ordering that all records of the event be destroyed. Whatever the truth, it is uncontested that a considerable number of military personnel and

civilians died as a result of exposure to mustard gas. The ongoing argument is over the extent of the casualties.

Aware of the implications of what had happened, the US military sent pathologists to Bari to conduct autopsies on the casualties. The extent of what they found has never been disclosed, but one thing that they did find and did disclose is an unexpected finding of profoundly low levels of white blood cells in gas-affected bodies, with shrinkage of lymph nodes being particularly noted. Curiously, this effect had never been noted in the First World War despite the casualty rate from mustard gas poisoning running into the tens of thousands.

This discovery so piqued the interest of the US Department of Defence that it recruited two pharmacologists, Drs. Goodman and Gilman, to look at the potential therapeutic applications of such an effect. Lymphoma, or cancer of lymph nodes, was an obvious target. The thinking was obvious - here is a cancer characterised by malignant swelling of lymph nodes, while on the other hand, nitrogen mustard gas was capable of shrinking lymph nodes in healthy people. The first step of the army pharmacologists was to come up with an injectable form of the gas that would allow a more defined dose to be delivered. To do this, they played around with the chemical structure of the nitrogen mustard molecule in order to convert it from a gaseous form to a liquid form. This sort of effort is the basis of organic chemistry – changing the structure of chemicals in the same way that oil molecules can be turned into molecules of petrol, or diesel, or kerosene, or plastics.

One of the new structures that they settled on for further testing was the drug **mustine**. After confirming that mustine reduced lymphomas in mice, they then collaborated in 1945 with a thoracic surgeon, Dr. Linskog, to use **mustine** in a patient with non-Hodgkin's lymphoma. The effect was dramatic, with the lymph nodes showing significant shrinkage. Unfortunately the response only lasted a few weeks, but the significance of this event was the promise of the principle that cancer could be treated by chemotherapy.

At the time, there was no real understanding of how the drug was working. Here was a drug whose heritage was a capacity to inflict severe burns on the skin, eyes and lining of the lungs, and yet there was nothing particularly obvious at the time to link a burning effect to how it might be functioning as an anticancer agent. It would be another decade before it was discovered that **mustine** was working by attaching itself to the DNA of the cancer cell in a way that prevented the DNA from functioning normally. Just as the cancer had been caused in the first place by DNA damage, **mustine** was doing the same thing, only many times greater. The initial damage that led to cancer in the first place, by definition must have been relatively mild in order for the cell to survive and to evolve into a cancer cell. The amount of damage being inflicted on the DNA by **mustine** was so great that the cell had no option but to die. When used as a chemical warfare agent, the nitrogen mustard gas was inflicting lethal damage on the DNA of the cells lining the respiratory tract. In Dr Linskog's patient, it was doing the same thing, but concentrating its action on the lymphoma tumour.

Ironically, although these early scientists were completely in the dark as to exactly how **mustine** was working, their discovery set the pattern for the way in which the vast majority of anticancer drugs would be developed over the next 60 years. The overriding principle that has guided the development of anticancer drugs has been that irreversible damage to a cancer cell's DNA will put that cell's ability to survive in jeopardy.

Some drugs inflict so much damage on the DNA that the cancer cell simply cannot survive. These are known as *cytotoxic* drugs. These drugs usually result in almost immediate shrinkage or even complete disappearance of the cancer. Other drugs are less damaging, to the point where the cell is too damaged to divide but not so damaged that it will die. These drugs are known as *cytostatic* chemotherapies. The effect of these drugs is to stop the growth and spread of the cancer, without necessarily shrinking the cancer.

The principal downside of this approach is that such drugs are by their very nature non-selective. A drug that disrupts DNA function doesn't distinguish between the DNA of a cancer cell and that of a normal, healthy cell. An anticancer drug once inside the body is perfectly able to penetrate any tissue in that body and to attach itself to any and all DNA, irrespective of whether it is healthy or cancerous DNA. The saving grace, the reason why most cytotoxic anticancer drugs can shrink cancers without shrinking our liver or heart to the same extent, is that the effect of the drug is dependant on the extent of DNA activity in the tissue. It is only when a cell is actively dividing that its DNA is at risk of damage from the drug. Cells that are sitting quietly, functioning normally but not dividing, are not at any particular risk of damage from the cytotoxic drug. That is the case for most of the major organs in our body. The rate of cell turnover in most parts of the body (such as the liver or heart) is so relatively low, that they are spared the worst effects of cytotoxic drugs.

The danger in this strategy lies with those parts of the body that have a high rate of cell turnover. Notably, the lining of the gut which is replaced every few days; red and white blood cells have a limited lifespan and need to be regenerated within the bone marrow of the long bones on a regular basis; and hair is being constantly produced within the hair follicles of the skin. This means that tissues such as these are going to be highly susceptible to the effects of DNA. The side-effects of gastro-intestinal toxicity are severe nausea, vomiting and diarrhoea. The side-effects of bone marrow toxicity are low levels of red blood cells, resulting in anaemia, and low levels of white blood cells, predisposing the patient to serious infections. The side-effect of hair follicle toxicity is baldness. These unwanted consequences on healthy tissue have exactly the same underlying mechanism of action as the burning symptoms seen in the eyes and lungs of World War 1 soldiers, and those seen in the citizenry of Bari.

The use of cytotoxic anticancer drugs is based on the simple principle that the most rapidly dividing cells in a cancer patient's body are the cancer cells, making them proportionally more likely to take up the drug than any other tissue. But tissues such as bone marrow and the gut inevitably will be hit by some collateral damage, making chemotherapy a delicate balance between poisoning as many cancer cells as possible while sparing as many healthy cells as possible - a delicate clinical dance between curing and harming. The side-effects of such chemotherapy also mean that there is a limitation to the number of times that the therapy can be given or the length of time that it can be given. It is highly likely that chemotherapy with such anticancer drugs could effectively destroy most cancer cells in the body if they could be given in sufficiently high doses for enough time, but that would come at the cost of almost total destruction of the body.

This delicate see-sawing between killing cancer cells and killing healthy cells also means that this approach is less likely to work with those cancers that are relatively slow-growing. Prostate cancer is an example of a slow-growing cancer. Chemotherapy with the kind of anticancer drugs that we are considering here is uncommonly used in early stage prostate cancer because the length of time that the treatment would need to be given as a function of

the slow rate of turnover of the cancer would result in unacceptably high levels of side-effects.

Anyway, back to our history. The mechanism by which **mustine** damages DNA is referred to as *alkylation*, a chemical term referring to the way in which the drug attached itself to the DNA, changing the DNA's structure to the point where it could no longer function normally. In the 1950s, this discovery went on to spawn a family of anticancer drugs known as *nitrogen mustard alkylating agents*. Of these, the drugs **chlorambucil** (1957), **melfhalan** (1957), **cyclophosphamide**, (1959) and **streptozotocin** (1982) are probably the best-known members of this family, and remain in wide use today for the treatment of cancers such as breast cancer, ovarian cancer, bladder cancer and chronic lymphocytic leukaemia. And despite its 60-year old age, **mustine** continues to be used occasionally today, mainly in a combined form with estrogen called **estramustine**, to treat prostate cancer.

2. Second anticancer drug

Mustine represented a promising start. Its effect on lymphoma was less than striking, but it did serve to prove that a cancer could respond to a toxic drug without jeopardising the life of the patient. What was required now was the development of drugs with more powerful actions. That step came just a few years later as a result of work coincidentally underway in Boston at Harvard Medical School. This work concerned the role of folic acid in cancer. As with **mustine**, the Boston work was not based on any particular understanding of cancer or the fact that damaging a cancer's cell DNA was a good strategy to pursue for drug development. Instead, the work was based on an astute sense of logic along with a single-minded determination by a paediatric pathologist, Dr. Sidney Farber (1903-1973).

The background to this work was a discovery a few years earlier in 1937 that a form of anaemia known as 'tropical anaemia' in children in Bombay (Mumbai), India, was correctable by supplementation with brewer's yeast. The unknown factor in the yeast initially was called Wills factor, after Lucy Wills its discoverer, but subsequently identified as folic acid (or vitamin B9). These days we recognise that folic acid is an important nutrient because it is an essential building block of DNA and therefore is in high demand for rapidly growing cells, which is why nutritionists recommend folic acid supplementation for pregnant women and infants. But back in the 1940s, the connection between folic acid and DNA and cell growth had yet to be made. The extent of understanding about the role of folic acid in the body was based on the Wills work showing that folic acid corrected anaemia in children by stimulating the growth of bone marrow, the source of both red and white blood cells.

Sydney Farber was attracted to this story because of his interest in the treatment of leukaemia. Farber worked at the Children's Hospital in Boston which handled many cases of childhood leukaemia. At that time, this was a largely untreatable, painful disease that often led to death within weeks of diagnosis. Farber's logic was simple – if folic acid stimulated healthy bone marrow to make red and white blood cells, then perhaps it also played a critical role in the excessive activity of bone marrow in producing white blood cells in leukaemia patients. He reasoned that by blocking the uptake of the cancer cells in bone marrow of folic acid, the production of leukaemic cancer cells might be slowed.

Chemists at Lederle (now part of Wyeth) had successfully synthesized folic acid in 1945. In collaboration with Lederle, Farber had drugs designed that looked like folic acid, but which

could not work like folic acid. The notion was that they would look sufficiently like folic acid to fool cells into taking them up, but once inside the cell would fail to provide whatever benefit the folic acid was thought to be providing. One of these drugs, **aminopterin**, proved very effective at doing this. When **aminopterin** was injected into the body, its levels in the body vastly exceeded the level of folic acid, leading to cancer cells taking it up to a much greater extent than folic acid. The rapidly dividing cancer cell with its high demand for folic acid needed to service its DNA expansion, suddenly found itself with non-functioning DNA because it contained **aminopterin** and not folic acid.

In 1947, Farber treated a group of 16 children who were seriously ill with acute lymphoblastic leukemia with **aminopterin** and achieved remission in 10 patients, meaning that the clinical symptoms of the leukaemia disappeared. As with **mustine** in lymphoma patients, the remissions with **aminopterin** proved to be fairly short-lived, but again this was a key step in reinforcing the principle that aggressively-growing cancer cells could be successfully challenged by drugs.

Farber published his findings in 1948 to curiously mixed reactions. The cancer research community, including his Harvard University colleagues, was largely dismissive. Part of this reaction appeared to be professional jealousy and had to do with a discovery of such magnitude being made by an unknown scientist working in a forgotten basement laboratory with little in the way of research funding. But there also was the accusation that leukemia was incurable and that affected children should be allowed to die in peace and dignity without needlessly suffering side-effects of chemotherapy. In the context of the day, where the idea that childhood leukaemias were curable by chemotherapy was unthinkable, such a view is perhaps understandable. And it has to be said that this is a debate that is as pertinent today as it was then, particularly in relation to the use of chemotherapy to extend life marginally in terminal cancer patients at the expense of quality of life. However, that point remains that Farber's work opened the door to research that ultimately shifted childhood leukaemias from a fatal disease to a largely curable disease. Interestingly, it was the non-research community, the doctors at the coal-face who were dealing with dying children, who gave Farber his greatest support and encouragement. Their eagerness to embrace anything that gave them an ability to alleviate suffering in children with leukaemia ensured that chemotherapy, at least for leukaemias, had a firm foundation.

Aminopterin was replaced 5 years later by a more powerful version known as **methotrexate** (1953), and that drug remains a standard anticancer drug in use today. In 1958, **methotrexate** was shown to be an effective cure of choriocarcinoma, a rare cancer of the placenta in pregnant women. Despite its rarity, the significance of this discovery was that it was the first report of a solid cancer being cured by chemotherapy and was a critical step in establishing the concept of using chemotherapy to treat solid cancers as well as leukaemia where the cancer cells are single and unattached and not formed into a mass structure.

3. Co-coordinating the research effort

As pivotal as the pioneering efforts of individuals such as Sidney Farber were to the establishment of the principle of chemotherapy, there is no doubt that it was the subsequent major injection of funds by governments and drug companies that ensured that chemotherapy expanded to meet its potential, and the one institution that stands out in this regard is the US

National Cancer Institute. The extent of that impact is evidenced by the fact that by the mid-1990s, the NCI had played a role in the development of two-thirds of all anticancer drugs in use at that time.

The NCI was created in 1937 by President Theodore Roosevelt as an independent research institute, and then brought under the umbrella of the National Institutes of Health based in Maryland in 1944. One of the key contributions of the NCI has been to establish methodologies for screening potential anticancer compounds at a time when drug companies were beginning to show some interest in the development of anticancer drugs, but had little or no in-house facilities to evaluate their usefulness. The NCI eventually became a one-stop shop for cancer research, where it conducted its own basic research, provided a screening resource for other researchers, provided funding for other researchers, and coordinated the clinical testing of new anticancer drugs. It is a model that other countries had emulated to a greater or lesser degree, but the amount of funding that the NCI receives has ensured that it remains the pre-eminent cancer research institute that it always has been.

4. Drugs from Nature

At the outset, scientists at the NCI and elsewhere adopted two main approaches to the discovery of anticancer drugs. The first was the approach taken by the Boston team in the development of **aminopterin**. This is known as rational drug design – meaning that you start with a known function (in this case the essential need for folic acid by the cancer cell), and you design a drug that deliberately interferes with that need. The other approach is more random.....to look for existing compounds within Nature. This approach doesn't require any understanding of how a potential drug might work, just the fact that it kills cancer cells. It is a needle-in-a-haystack approach that involves searching through the millions of species of plants, marine life, insects, coral etc for naturally-occurring chemicals with anticancer activity. Why would something like a plant or a coral or a microbe need to contain a compound capable of fighting cancer? Well, it doesn't....that is, these organisms don't succumb to any condition evenly remotely related to cancer, but most living things do need to make compounds that help them fight off predators such as a disease-causing organism, and one way to do that is to make the protective compound able to poison any threatening predator. Poisoning generally means that you disturb the invading-organisms biochemical processes to the point where it is dissuaded from attacking or perhaps is even lethal enough to kill it. And anything that is capable of causing that amount of harm to any living cell certainly has the potential to make a cancer cell sick.

This looking-for-a-needle-in-a-haystack approach is a painstakingly tedious experience that is rarely rewarding. In fact it is more like looking for a needle in 10,000 haystacks. It usually means teams of people going out and collecting samples from jungles or forests or coral reefs, and then screening chemical extracts from hundreds of thousands of samples for some evidence of an ability to stop cancer cells from growing in the laboratory. And this is exactly the effort that the NCI embarked on in the 1950s. In 1956, Dr Gordon Zubrod was appointed head of the Division of Cancer Treatment in the NCI. Dr Zubrod formerly had been in charge of development of anti-malarial agents for the US Army and had a keen interest in natural product research, holding the not unreasonable view that Nature probably holds the keys to most of our ailments, particularly the degenerative diseases such as cancer, and that it is just a matter of investing enough time and effort to find those keys.

In 1958, Dr Zubrod set about establishing an ambitious program to test over 30,000 species of North American plants for anticancer activity. The botanists charged with this collection job gathered up sack-fulls of twigs, needles, leaves and bark from thousands of different trees and bushes and sent them back to the NCI. Back in the NCI laboratories, crude extracts were made from these samples by dissolving the plant material in different solvents such as water or alcohol. These crude extracts, each containing thousands of individual chemicals, were tested for their ability to kill cancer cells growing in a test-tube. Where an extract proved to have anticancer activity, the enormous task of separating out the thousands of chemicals within each active extract then had to be undertaken in order to identify the active ingredient or ingredients. The number of man-hours involved in identifying and then purifying a single active extract runs into the hundreds of thousands.

One of the trees sampled was the Pacific yew tree, a slow-growing, old-growth forest tree on the Pacific Northwest coast of the US, with a sack of twigs and bark and leaves arriving back at the NCI in 1963. The extract from the bark (but not the twigs or needles) caused considerable excitement when it was found to have significant anticancer activity in the test-tube, triggering a lengthy 4-year process to identify the active ingredient amongst the thousands of other chemicals within the bark. That active ingredient eventually was identified as **taxol**, destined to become one of the most commonly used anticancer drugs in the modern era. The discovery and identification of **taxol** took another 8 years of painstaking research, with its chemical structure finally being published in 1971. However, that was not the end of the challenge. The chemical structure proved so difficult to synthesise that early animal studies and subsequent clinical trials of the drug had to be conducted using naturally-extracted material, a cumbersome exercise that required chemists to isolate the drug from tonnes of bark being collected from forests in the US Northwest. Given that all the bark from a fully-grown Pacific yew tree only yielded 500 mg of drug (enough for about 5 doses), few Pacific yew trees were left across North America with their bark intact. Progress was only going to be made if the drug could be synthesised, but it was to be another 10 years before that problem was cracked.

By the time the whole natural product program was abandoned by the NCI in 1981, over 114,000 plant extracts and 16,000 animal extracts had been screened for anti-cancer activity. Over that 20-year period involving tens of millions of man-hours of botanists who collected samples, chemists who conducted the extraction of samples, and biologists who tested the extracts in the laboratory, **taxol** was the only drug of any significance that they had to show for all that effort.

Taxol (1992) went on to be commercialised by the drug company, Bristol-Myers Squibb, and to become a mainstay of chemotherapy for a range of cancers including ovarian and lung cancer. Since then, chemists have found that relatively minor alterations to its structure produces new drugs with increased and different activities. As a family of compounds, taxol and its new spin-offs are known as *taxanes*. They work in a similar way to **taxol**, but do it in a better or stronger or different way. The best known of these is **docetaxol**, a drug used to treat a range of cancers including prostate, breast and lung cancer.

While **taxol** might have been the NCI's only real success in its natural products program, the institute still played a key role through its collaborative efforts in the development of a number of other important anticancer of natural origin. Drug companies and private research institutes were active in this area as well, sending their promising samples off to the NCI to take advantage of their screening resources.

Extracts from a deciduous tree (*Camptotheca acuminata*) found in Southern China were sent to the NCI and found to have promising anticancer activity in the test-tube. The active ingredient subsequently was identified in 1966 as camptothecin. In clinical studies, however, camptothecin proved to be a disappointingly weak anticancer agent, but subsequent changes to its chemical structure resulted in the development of the more powerful drugs, **topotecan** and **irinotecan**. **Topotecan** is used for small cell lung cancer and ovarian cancer, and **irinotecan** (1994) for colorectal cancer.

Another plant, the Madagascar periwinkle, similarly has provided an important family of anticancer drugs known as *vinca alkaloids*. The discovery of these drugs has its roots in herbal medicine, where extracts of the Madagascar periwinkle had been used for centuries in Madagascar for the treatment of diabetes and hypertension, and as a disinfectant. The sap of this plant was poisonous, and subsequent chemical analysis of the sap found that it contained a wide range of toxic chemicals known as alkaloids. Two of these alkaloids subsequently were identified as **vincristine** and **vinblastine**. The NCI played a key role in identifying the anticancer properties of **vincristine**, with the drug being approved in 1963 as a treatment for leukaemia. Two Canadian researchers subsequently identified the anticancer properties of **vinblastine** when it was given as a tea to animals and found to cause a profound fall in their white blood cell levels. These two drugs were used initially to treat leukaemia and lymphoma as alternatives to **mustine** and **aminopterin**, although they are used far more widely now for solid cancers such as breast and lung cancers.

The other significant anticancer agent to be discovered in this way is **doxorubicin**. This compound owes its existence to work in the 1950s by an Italian research company that had initiated a program to search for newly identified soil microbes that hopefully would have antibiotic or anticancer activity. A particular soil sample collected from the area surrounding the [Castel del Monte](#), a 13th century Italian castle, provided a new strain of bacteria that produced a bright red pigment. Coincidentally, independent French and Italian scientists subsequently discovered that this compound showed good anticancer activity against a range of mouse tumors. In recognition of this joint discovery, the two teams named the compound **daunorubicin**, after *Daunii*, a pre-Roman tribe that occupied the area of Italy where the compound was isolated, and the French word for [ruby](#), *rubis*, describing the drug's color. Clinical trials of **daunorubicin** began in the 1960s, leading to the drug being used to treat acute leukemia and lymphoma.

The Italian scientists then discovered that minor changes to the structure of **daunorubicin** increased both the strength of the anticancer activity and the range of cancers that it affected, including a range of solid cancers. They named this new compound **adriamycin** after the Adriatic sea, the name then being changed to **doxorubicin** when the drug came to market in 1974. **Doxorubicin** now is one of the most widely used drugs in the treatment of cancer.

5. Combination chemotherapy

Prior to the mid-1960s, the standard method of chemotherapy for any cancer involved the single use of available drugs. Treatment would start with one drug and then move onto a second drug when the first one either failed to work after several weeks of trying or when an

initial response was followed by a return of the cancer. The development of drug resistance remains one of medicine's great challenges whether it is in the field of infection (eg. Golden Staph), or parasites (eg. malaria) or cancer. Faced with annihilation by drugs, organisms have a remarkable capacity to fight back by developing resistance to those drugs. Cancer cells share this biological capacity along with bacteria and parasites.

Considerable experience already had been gained with this phenomenon in tuberculosis, where the general experience was that the successive use of different antibiotics usually led to the infection becoming resistant to all antibiotics. But when antibiotics with different mechanisms of action were given as a combination, the risk of resistance developing was much less likely to happen. In the mid-1960s it was decided to test this notion with cancer. One group reported on the treatment of children with acute lymphoblastic leukaemia (ALL) with a combination of four drugs – **methotrexate, vincristine, 6-mercaptopurine** and **prednisone** – with most patients showing long-term remission. Subsequent refinements of this multiple therapy approach have led to ALL becoming a largely curable disease.

A couple of years later, a second group from the NCI extended this observation to solid cancers, showing that a combination of **mustine, vincristine, procarbazine** and **prednisone** could lead to long-term remission in Hodgkin's and non-Hodgkin's lymphomas.

Combination therapy comprising two or more anticancer drugs has become the standard form of chemotherapy in use today.

6. The platinum

The platinum-based drugs are worthy of highlight since, along with the **taxanes** and **doxorubicin**, they are the most widely used anticancer drugs today. Their history also underlines the extent to which a mixture of serendipity and scientific curiosity can play in the discovery of major drugs, in the same way that **penicillin** was discovered. They also play a role in the **phenoxodiol** story and are worth looking at from that point alone.

The platinum-based drugs are so-called because they are chemicals based around a central atom of platinum. They include **cisplatin** and its more recent derivatives, **carboplatin** and **oxaliplatin**.

The origins of this drug date back to 1845, when a chemist by the name of Peyrone first showed that compounds could be made based around a platinum atom. There was little interest in this family of compounds until the 1960s when a researcher at Michigan State University made a fortuitous discovery. Barnett Rosenberg was interested in the effects of electricity on the growth of bacteria when he unexpectedly found that bacteria stopped dividing when placed in an electric field. This was an exciting observation, suggesting a potentially new form of sterilization. Believing that the effect was related to the action of the electric field per se, Rosenberg spent months trying to unravel the mechanism. To his disappointment, he ultimately found that the inhibitory effect was nothing more than an artifact, with the platinum electrode being used to generate the electric field undergoing electrolysis, producing platinum-based compounds that were inhibiting the ability of the

bacteria to divide. This might have been a disappointing result for the future of sterilization, but it was a mightily important step in the future of chemotherapy.

Fortunately for chemotherapy, Rosenberg had the foresight to see the potential of this accidental discovery, deciding to work with NCI to investigate the use of platinum-based compounds as potential anticancer agents. That led them back to the original work by Peyrone over a century earlier in terms of the chemistry required to create platinum-based compounds. One of these compounds, **cisplatin** (1978), proved to be a highly effective anticancer agent, subsequently becoming one of the most widely-used chemotherapies and revolutionizing the treatment of a wide range of common cancers. In particular, it provided an effective cure for testicular cancer. It took another two decades to understand how **cisplatin** was working, which was by binding to the DNA and physically preventing the DNA from dividing.

7. Rational drug design

The era of finding new anticancer drugs by accident (such as the platinums) or by trawling through Nature (such as the taxanes) is largely over. The wheel has come full circle and we have now returned back to the roots of chemotherapy as in the case of the folic acid antagonists. This is the era of rational drug design. This is the Trojan horse approach. Step 1 being identification of a particular chemical reaction within the cell that is essential to DNA function. Step 2 being to identify a chemical that is essential to that reaction and which the cell needs to source externally. Step 3 being to design a facsimile of that chemical, that looks sufficiently similar to the original to fool the cell into taking it up, but is sufficiently different that it fails to work.

In this process, the drug starts its life on a chemist's drawing board. The odds of such a drug working are a whole lot better than the hit and miss approach of collecting samples from jungle plants, but it has one very large drawback – you need to have a target to start with. That's the main benefit of the trawling-through-Nature approach – you don't need to know how the drug works to find the drug in the first place– that can always be worked out later. But with rational drug design, knowing how the drug works and what part of the cancer cell it needs to attach to is essential pre-knowledge.

Our knowledge of the cancer process has grown sufficiently over the past two decades that, combined with the computer power and computer-assisted design, new generations of anti-cancer drugs have become possible with chemical structures not previously seen in Nature. The basic premise of rational drug design is, if you know what the target in the cancer cell looks like, then it should be possible to construct a drug that will target it and block it. This is the lock-and-key approach that is the basis of most drug discovery today. In the trawling-through-Nature approach to drug discovery, the scientist essentially is relying on the chance discovery of keys – in the same way that a beachcomber might use a metal-detector to scan an entire beach looking for a lost key. In the rational drug design approach, the scientist already has the lock, and simply has to craft a key to fit into it.

Aminopterin and its derivative, **methotrexate**, were the first examples of rational drug design. Folic acid had been identified as an essential nutrient for rapidly dividing cells, so it was just a matter of designing a drug that was close enough in appearance to folic acid to fool

the cancer cell, but was sufficiently different that it completely failed to function once it was incorporated into the cell.

The first modern example of rational drug design is the breast cancer drug, **tamoxifen**. Although, ironically, it was contraception and not cancer that was the driving force behind its discovery. The whole concept of how sex hormones worked was exciting a lot of commercial interest in the 1950s because of the world's growing interest in chemical contraception. That interest eventually led to the arrival of the oral contraceptive pill on the world scene in the early 1960s, but at the same time a number of drug companies were also looking for anti-estrogen compounds in the hope of finding a successful morning-after contraceptive. The concept was to find a compound that looked sufficiently similar to estrogen that it would fool the estrogen receptor on a cell into letting it bind to it, thereby blocking the real estrogen from getting there, but would not trigger the receptor in the way that the real estrogen would.

In 1962, a team of endocrinologists under the direction of Arthur Walpole at ICI (now Astra-Zeneca), successfully developed **tamoxifen** as an anti-estrogen. Developed as a contraceptive, the drug never was commercially successful, although ironically it did come to market in a minor way as a fertility treatment. The true application of **tamoxifen** started in the late 1960s when the link between estrogen and breast cancer started to become obvious, leading to the notion that an antiestrogen might just provide some anticancer activity. In the face of considerable reluctance by ICI, Walpole personally championed the potential therapeutic value of **tamoxifen**, with a clinical study in London in 1971, subsequently showing convincing benefit of the drug in women with advanced breast cancer. **Tamoxifen** then was approved in 1973 for such use. Remarkably, the drug failed to ignite much interest among oncologists, mainly because the survival benefit was not large. It then took some years before it was realised that this benefit was being diluted because not all cases of breast cancer express the estrogen receptor, meaning that their growth is fuelled by estrogen. Approximately 70% of cases of breast cancer are now known to be estrogen receptor-positive, and when **tamoxifen** is isolated to these cases, the clinical benefit becomes apparent. This has led to **tamoxifen** being used predominantly today in early breast cancer following a 1998 study showing that **tamoxifen** provided a clear survival benefit in women with early-stage, estrogen receptor-positive breast cancer.

The third example of rational drug design is based on antibody technology. The concept here is to develop an antibody to knock out a particular target on the cancer cell, in the same way that our immune system makes antibodies to nullify the effect of bacteria and viruses. The antibody finds its specific target, attaches to it, and completely blocks the target's ability to function. Two such antibodies are **herceptin** and **avastin** (both developed by the US company, Genentech) directed against the estrogen receptor in the case of **herceptin** (approved 1998) and a blood vessel growth factor in the case of **avastin** (approved 2004).

The difference between drugs like **tamoxifen** and **methotrexate** on the one hand, and antibodies on the other hand, is fairly minor. **Tamoxifen** and **methotrexate** look like the molecules that they are meant to replace, and they are constructed in a laboratory in a step-wise fashion by synthetic chemistry. Antibodies, on the other hand, are made by immune cells that have been vaccinated against the specific target; the resulting drug is a protein, and looks nothing like the molecule that it is intended to block. **Tamoxifen** and **methotrexate** are produced in factories using lots of strange chemicals and heat. Monoclonal antibodies like **herceptin** and **avastin** are produced from human immune cells growing in vast tanks under sterile conditions.

Tamoxifen behaves like a *pseudo*-estrogen in inserting itself into a tiny part of the estrogen receptor, and it interacts with all types of estrogen receptors. **Herceptin** in contrast targets a type of estrogen receptor known as the HER2/neu receptor and it works by physically smothering the entire receptor, thereby depriving estrogen of any chance to reach the receptor. The HER2/neu estrogen receptor is only relevant to about 20% of cases of breast cancer. This type of estrogen receptor is present in all normal breast cells and all breast cancer cells, but only at very low levels. In about 20% of cases of breast cancer, the receptor is present in sufficiently large amounts that it is significant to the cancer cells' survival, and it is here that **herceptin** provides a clinical benefit. Although considerable debate continues as to the cost-benefit nature of **herceptin**. The failure of about 70% of breast cancer cases to show any significant response, the high rate of resistance that develops to the drug, and the relatively high rate of adverse side-effects, all need to be measured against the relatively modest clinical benefit that it provides.

Avastin is an antibody directed against a protein that is responsible for promoting the growth of blood vessels. It is approved for the treatment of colorectal cancer and lung cancer. The rationale behind its development is the need of cancer tissue to have its own blood supply, capable of supplying nutrients to a rapidly growing tissue. To do this, the cancer cells produce a protein known as *vascular endothelial growth factor* whose role is to stimulate the production of blood vessels in a process known as *angiogenesis*. **Avastin** blocks this growth factor, restricting the flow of blood to the cancer tissue and slowing its growth. As with **herceptin**, the clinical benefit from **avastin** is modest, providing increased survival of several months in patients with late stage cancers.

The fourth, and final, example of rational drug design is the drug, **gleevec**, representing the epitome of this approach by bringing together all the tools of modern medicine to design a drug that is highly targeted and that finally (as with **tamoxifen**, **herceptin** and **avastin**) does not rely on the blunt instrument of damaging DNA in order to block a cancer cell. **Gleevec** represents the sort of drug that all oncologists dream about and all cancer patients wish was available for them.... a drug that will provide a rapid cure or long-term remission without any significant side-effects.

Gleevec (or **Glivec**) represents the true hope of rational drug design ... a drug that is design to hit a specific target that is unique to cancer cells and that is essential to the survival of the cancer cells, but which will spare all non-cancer cells. The cancer in question is chronic myeloid leukaemia. This cancer is characterised by having genetic material swapped between chromosomes, resulting in the formation of a new gene. This new gene produces a protein that causes the cancer cell to divide uncontrollably. Brian Druker, an oncologist at Oregon health Science University was pursuing a research program endeavouring to find a drug that would block that protein, an action that he was convinced would stop the cancer in its tracks. By chance he discovered that the large Swiss-based drug company, Novartis, had a number of test drugs that fitted this need, and one of them, **gleevec**, was selected for further studies. A Phase 1 study was started in 1998, resulting in all 31 patients in the study showing complete remissions. That outcome then was confirmed in larger trials, leading to the drug being approved in 2000 for the treatment of chronic myeloid leukaemia.

Summary

The modern oncologist has some 40 odd chemotherapies to choose from when deciding on an appropriate course of treatment for the cancer patient. That choice has meant that certain cancers, namely acute lymphoblastic leukaemia in children and testicular cancer and Hodgkin's lymphoma in adults are essentially curable. At the next level, in cases like chronic myeloid leukaemia, a high proportion of patients, if not curable, can be put into long-term remission, adding years to life. In short, if you get a cancer of the blood, or the lymph nodes, or the testes, and you start treatment early enough, then you have a high probability of leading a life as though you never had cancer.

BUT, should you get a cancer of almost anywhere else in the body and in particular the breast, prostate, large bowel, pancreas, gall-bladder, mouth, throat, oesophagus, stomach, large bowel, rectum, ovary, bladder, kidney and skin, and the cancer is aggressive and has migrated away from its point of origin, then the harsh reality is that in the majority of cases, chemotherapy will do little more than buy a few extra months, or years if you are lucky.

AND, despite all the modern advances in chemotherapy, the most effective and most commonly used drugs remain those based on the sledgehammer approach of damaging a cell's DNA, meaning that chemotherapy, even when only providing a temporary interruption to growth of the cancer, will cause inevitable and significant side-effects.

This is the environment that **phenoxodiol** has entered. It is an environment looking for another **gleevec** to effect cures or long-term remissions in the tens of millions of patients who develop cancer each year around the world and not just the 15,000 who develop a relatively rare form of leukaemia. It also is an environment wanting an effective anticancer drug that is as well tolerated as other medication such as antibiotics so that management of serious life-threatening or debilitating side-effects is not part of the treatment.

So where does **phenoxodiol** fit in the context of this history and the future of chemotherapy?

In terms of where it comes from, its heritage is a unique blend of both natural product and rational drug design.

In terms of its mechanism of action, **phenoxodiol** kills cancer cells by blocking the cell's ability to respire. More importantly, this effect is limited almost entirely to cancer cells as the target is a protein that is only found on cancer cells. This is a subtle rather than a sledgehammer effect on the cell's DNA or its ability to survive and grow, and the restriction of the target to cancer cells means that healthy tissues are completely spared.

In terms of its usefulness, the protein that **phenoxodiol** is targeting appears to be present on all forms of cancer, making the drug useful in the treatment of all cancers. The exception is leukaemia for reasons that have to do with how the body transports the drug rather than because of the action of the drug itself.

The way that **phenoxodiol** works suggests that it will find its main benefit in stopping early cancers. This perhaps could be said about most of the current anticancer drugs, although they are rarely used as in this way because of their adverse side-effects. **Tamoxifen** is the one exception where its safety profile is sufficiently good to allow it to be used in early stage breast cancer or even as a preventative in women without disease but who are at high risk of breast cancer. But even in a disease such as prostate cancer where early-stage cancer can be diagnosed, drugs such as **docetaxol** that are known to have some benefit in late-stage

prostate cancer, are rarely used much earlier on because the downside of the drug's side-effects would outweigh the clinical benefits. **Phenoxodiol** does not have that safety limitation. Its high tolerance means that it could be used much earlier on in the disease process, giving it the potential to nip the cancer in the bud.

This is the promise of **phenoxodiol**. This is the basis on which the following story is told.

HOW INEVITABLE IS CANCER?

The answer to this question is at the heart of the **phenoxodiol** story.

My background is in cancer research, and like almost everyone else concerned with cancer, I just accepted the inevitability of this disease. One in 2 of us would develop cancer at some point in our life, and 1 in 4 of us was going to die from cancer. It existed...it was just part of the human condition...so we needed to get on with finding drugs to treat it.

But the inevitability of cancer is not universal. Some cancers clearly are avoidable, being associated with known cancer-forming substances or activities (so-called *carcinogenic factors*).The following list, by no means exhaustive, details the best-known carcinogenic factors and the cancers they cause.

<u>Carcinogenic factor</u>	<u>Cancer type</u>
Chewing/smoking tobacco	Tongue, oesophagus, stomach, lung
Alcohol abuse	Oesophagus, stomach
<i>Helicobacter pylori</i> infection	Stomach
Pickled vegetables (containing nitrosamines)	Stomach
Exposure to asbestos fibres	Mesothelioma
Exposure to sunlight	Melanoma, SCC
Human papillomavirus (types 16/18) infection	Cervical cancer
Long-term exposure to soot and coal tar	Skin cancer, cancer of the scrotum
Ionizing radiation	Leukaemia

Providing that we never chew or smoke tobacco, it is highly unlikely that we will ever get cancer of the lip, mouth, throat or lungs. Providing that we never inhale asbestos fibres, it can

be guaranteed with almost 100% certainty that we will never develop mesothelioma. Providing that a woman is never exposed to human papillomavirus (types 16 and 18) infection, it is most unlikely that she will ever develop cancer of the cervix or vagina.

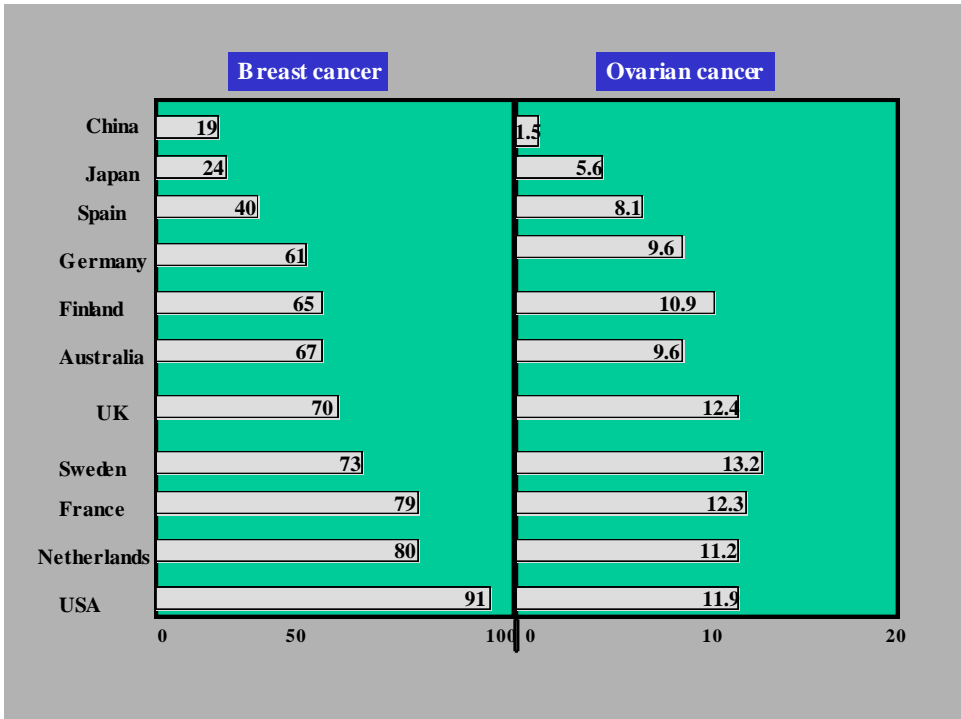
But what about the great middle-ground of cancers...the cancers that most of us will succumb to in due course? Cancers such as those of the prostate, breast, ovary, large bowel, pancreas, liver, brain and blood. Why do we accept the inevitability of these cancers? Is it because they are inevitable and simply represent a form of ageing in humans? Or is it because we haven't yet identified an associated carcinogenic factor as we have with mesothelioma? Or maybe there is a third possibility (which is the foundation of the theory that spawned **phenoxodiol**), which is that the pre-cancerous condition (the formation of pre-cancerous cells) is normal for all higher animal species, but that Nature has provided us with a means of surveillance to prevent their progression to full-blown cancerous state, and that the modern cancer epidemic simply represents a dysfunction of that surveillance mechanism.

Two observations question the inevitability of cancer. The first is that humans alone in the vast animal kingdom seem to be at risk of developing cancer at anything more than a minor incidence. There is no doubt that humans do things that animals don't do that put us at particular risk of getting cancer – like mining asbestos (mesothelioma), inhaling the smoke of burning tobacco leaves (mouth cancer, lung cancer), not having fur to protect us from sunlight (melanoma), and eating highly pickled foods (stomach cancer). However, for the other common cancers involving the breast, prostate, ovaries, blood, lymph system, pancreas and large bowel, there are no apparent causes. It can't be just that we humans live so long, because there are plenty of other species that enjoy naturally long lives. Ten percent of female apes and chimps who live 40-50 years, for example, aren't reported to develop breast cancer, or males to develop prostate cancer, or both sexes to develop colorectal cancer.

Humans are just another animal species, and it is difficult to believe that evolution endowed humans with a particular genetic fault that led us to be so prone to a degenerative disease such as cancer. The general gene pool from which our species has derived is alive and well out there in Nature without any evidence of an inherent susceptibility to degenerative diseases such as cancer.

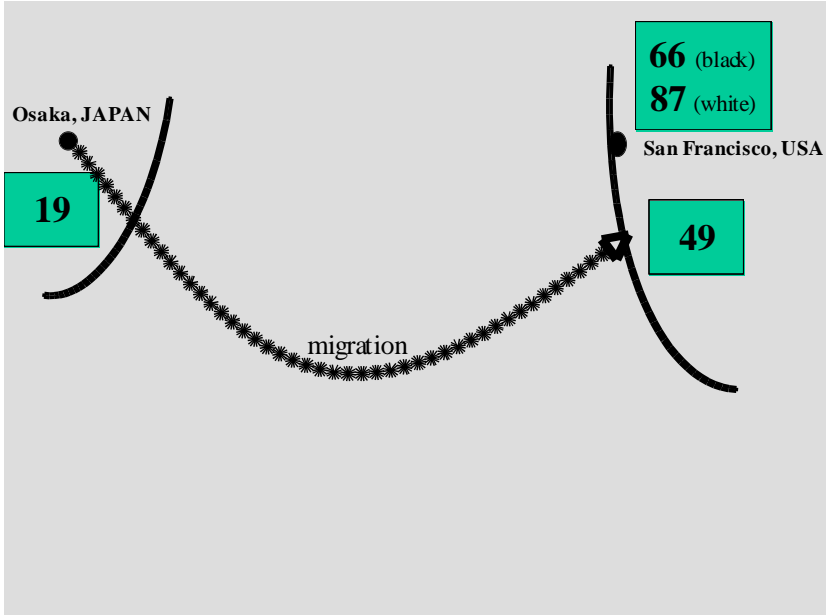
The second, and more compelling, observation is that for the most common cancers, where you are born and where you spend most of your life goes a long way to determining your risk of getting cancer.

As the figure below shows, women in Asian countries such as China and Japan are between 10-30 times less likely to develop breast or ovarian cancer than their Western counterparts. This is not due to any genetic or racial factors protecting Chinese and Japanese women, because migration studies show that they are just as susceptible as Western women to these cancers. It is just that while they live in their countries of birth, they have a much lower risk of getting these cancers. Japanese women who migrate to the USA and who maintain a traditional Japanese lifestyle and diet, retain their low reproductive cancer rates. However, if they adopt a typical US lifestyle,



Country differences in the incidences (per 100,000 women) of breast cancer and ovarian cancer.

including diet, then the incidence of reproductive cancer rises and their daughters will have almost the same rates of cancer of the breast and ovary as non-Asian women.



Change in incidence (per 100,000 women) of breast cancer between Japanese women living in Osaka, and the daughters of those women who migrated to live in San Francisco.

Endometrial (or uterine) cancer is now the 4th most common cancer in Western women, and as with breast and ovarian cancer, is far less common in Asian women in Asia. Although, again, as with breast and ovarian cancers, the incidence of endometrial cancer appears now to

be on the rise in countries such as Japan, pointing again to the fact that a high incidence of these cancers is artificial, not inherent.

With colorectal cancer, the story follows the same pattern. One of the best examples of this was documented some years ago within the Greek community in Australia. After the Second World War, there was significant migration of Greeks to Australia, and in particular from Greek islands where a traditional Mediterranean lifestyle going back centuries was enjoyed. The incidence of bowel cancer was documented in the Greeks who remained on the Greek islands and in the Greeks who migrated to Australia. The close familial relationship between the two groups meant that genetic factors were eliminated in any comparison. Where the immigrant Greeks has maintained a traditional Greek diet, their incidence of bowel cancer was comparable to that of non-immigrant Greeks, and was a very low incidence. Where the immigrant Greeks had foregone their traditional diet in favour of a typically Australian diet, the incidence of bowel cancer was approximately 4-times greater.

Again, the story is the same with prostate cancer. Men in Western countries have about a 10-times greater risk of developing cancer of the prostate than men in Asian countries, a difference that is almost completely lost within one generation when Asian men migrate to Western countries and their sons adopt a Western lifestyle. One of the more intriguing facts about the geographic influence in the development of this form of cancer came from the Korean War. Army pathologists at that time took the sad opportunity of being presented with autopsies in so many young men, to document the incidence of disease in men whose average age was 22 years. One of the fascinating things they found was the early sign of prostate cancer in a surprisingly high proportion (about one quarter) of young US soldiers. These early lesions, known as pre-malignant lesions, are found with almost all forms of cancer. Pre-malignancy represents those changes in tissues that immediately precede the emergence of an uncontrollable cancer state. Pre-malignancy of any type of tumor doesn't make it certain that you will get that cancer, but it certainly means that you have a higher risk of doing so. Cancer researchers generally consider cancer as a two-stage process at its simplest, those two stages being known as *initiation* and *promotion*. Initiation is where the conditions to form a cancer are created within a group of cells. At this stage, the cells are being to behave in a slightly abnormal way, but they still essentially are responding to the body's control mechanisms. Pre-malignant changes are very common within the body, and most of us almost certainly carry many of these in our bodies from an early age without them ever converting into a full-blown cancer. That conversion requires the intervention of some promoter such as a virus or a chemical carcinogen.

Given that so many of these US soldiers, had they lived long enough, would have gone on to develop prostate cancer, the presence of pre-malignant lesions in the soldiers' prostate glands would have been unsurprising, although to see these early signs of cancer in so many men at such a young age did come as something of a surprise. However, what came as a total surprise to the pathologists conducting the autopsies was that they found the same incidence of pre-malignant lesions in the prostate glands of young Chinese and Korean soldiers. Given that it would have been highly unusual that these soldiers, had they lived, would have gone on to develop full prostate cancer in their old age, the presence of pre-malignancy in so many of these young men was entirely unexpected. The inescapable conclusion was that young men in general are prone to the first step in the prostate cancer process (the *initiation* phase), but that the next crucial step (the *promotion* phase) did not occur in middle-aged Chinese and Korean men, while it did in US men.

What all this suggests to me is that certainly as far as cancers of the male and female reproductive tracts are concerned (prostate, breast, ovarian, uterine cancers), the development of pre-malignant lesions in reproductive tissues probably is not unusual and probably happens from an early age. It may be that it even is an entirely normal biological phenomenon common to all higher animal species. Once formed, the growth of these cancers is fuelled by sex hormones (estrogen in the case of breast, ovarian and uterine cancers; testosterone in the case of prostate cancer), so it is not difficult to believe that constant exposure of these tissues to the stimulatory effects of sex hormones could initiate early cancer changes.

But whether pre-malignancy is a normal event or not, it appears to be quite possible to live a long life without having that pre-malignancy converting into a full-blown cancer. That was what the Korean War pathology report proved in the case of prostate cancer, and what migration studies have proved in the case of breast, ovarian, uterine and colorectal cancers.

The fact that Asian women and men who live traditional lifestyles are still developing these cancers, albeit at much lower levels than in Western countries, doesn't prove that humans are inherently susceptible to these or any other forms of cancer. It simply suggests that whatever we in the West are doing wrong, they are doing less wrong, but still doing something wrong. Some of those young Korean or Chinese soldiers may have gone on to develop prostate cancer, but the statistics show that the great majority would not. That raises two possibilities – either (i) that there is something in the US lifestyle that is exposing US men to a higher level of some promoter of prostate cancer than Asian men are exposed to, or (ii) that there is something in the Asian lifestyle that is blocking the conversion of the pre-malignant state into a malignant state in the Asian men.

And what was it about the Western lifestyle that meant that a woman arriving in the West from Asia was likely to be put at increased risk of developing cancer of the breast, uterus or ovary, and that a man arriving from Asia was likely to be put at increased risk of developing prostate cancer, and that both men and women arriving from traditional cultures were likely to be at increased risk of developing bowel cancer?

Plenty of scientists before me had pondered this question, and almost everyone had reached the same conclusion that diet was almost certainly the major risk factor. The problem then became isolating one or a few risk factors from the complexity that is the human diet. Was it red meat versus white meat versus fish as the main source of protein; was it animal saturated fats versus vegetable unsaturated fats; was it fats versus simple sugars versus complex carbohydrates as a main source of energy; was it the amount of vitamins or certain minerals in the diet: was it....well, the permutations are endless. During the 1970s -1990s, the main focus was fat – how much fat in the diet, and what kind of fat. Probably no other dietary factor has been so well studied as the relationship between dietary fat and cancer. But to no avail....no relationship has ever been established, and beyond some obvious and sensible observations about the need to ensure an adequate amount of vitamins, minerals and fibre in the diet, no specific conclusions were ever reached about what the relationship between diet and the so-called 'Western' cancers.

My instinct was that the Korean War pathology report was serving as a vital lesson in this mystery, and that the answer lay hidden within that lesson. To my mind, the answer came down to those two possibilities: either Western men were doing something that actively promoted the development of prostate cancer, or Asian men were doing something that actively prevented the development of prostate cancer.

One of the things I found fascinating about the ‘Western’ cancer phenomenon was that four of the five cancers involved the reproductive tract – the prostate gland, breast, ovary and uterus. If diet in particular was playing a major role in either protecting us from or predisposing us to these cancers, then it was certainly not immediately obvious how it was doing so. And confounding this even more was the fact that the fifth cancer, bowel cancer, involved tissue that was about as far from being reproductive tissue as it was possible to be. Of course there did not have to be a common link between all five cancers, but it certainly distracted the thinking process to have such divergence.

It was at this time, a time when I was wrestling with the various possibilities but making no headway, when an unexpected incident occurred that brought all these matters into sharp focus for me.

