

# 1 Historical background

Although cancer is described in ancient manuscripts, it is only in the last 150 years that there has been clear recognition of the nature of the disease. At the end of the eighteenth century, cancer was widely believed to be contagious; not until the early twentieth century did clear evidence begin to emerge that cancer, while not itself infectious, may be caused by infectious organisms. As we enter the twenty-first century, there is sufficient understanding of infection-associated cancer to allow ambitious prophylaxis schemes to be undertaken.

## Antiquity of cancer

It is probable that cancer has existed for hundreds of millions of years, since the emergence of the first complex multicellular organisms. In a multicelled organism it is vital for cell growth and division to be tightly regulated; indeed cancer can be defined as a breakdown of the regulation of cell growth, division and death. There are reliable descriptions of malignant tumours in modern invertebrates, implying that cancer antedated the emergence of vertebrates.

In fossilized bones, in contrast, it is often possible to delineate very fine details of internal structure and, in some cases, evidence of erosion caused by soft tissue swellings; some bones show changes consistent with specific cancers, or bone metastases<sup>1</sup>. There is a general consensus that there is physical evidence of malignant disease in dinosaurs. Fossilized remains of a caterpillar from over 20 million years ago have been found to contain tumours which may have been caused by viral infection<sup>2</sup>.

Plant tumours such as crown galls have been compared with animal cancers<sup>3,4</sup>; it has been known for a century that one of the commonest causes of such growths is a bacterial infection – *Agrobacterium tumefaciens*<sup>5</sup>.

## The Kanam mandible

The Kanam mandible is a jawbone fragment from an early hominid, who is estimated to have lived between 500 000 and 1 million years ago; it was discovered by Louis Leakey in Kenya in the 1930s<sup>6</sup>. The inner surface of the jawbone bears a tumour mass often cited as the oldest example of a human cancer. Some have suggested it to be an osteogenic sarcoma, others consider it to be a Burkitt lymphoma (BL)<sup>7</sup> (a tumour associated in sub-Saharan Africa with Epstein–Barr virus infection). Unfortunately however a recent re-examination using sophisticated technology concluded that ‘...both macro and microanatomy are consistent with bone pathology secondary to fracture’<sup>8</sup>. It would seem that the unfortunate owner of the Kanam mandible suffered not cancer but a broken jaw. There is no obvious candidate to replace the Kanam mandible as the oldest known hominid cancer. Many prehistoric bony remains bear probable tumours but none has an unequivocal hallmark of cancer. Stathopoulos, in a book chapter on ‘Bone tumours in antiquity’<sup>9</sup> lists many of these. Newby and Howard state ‘The oldest specimen of a human cancer was found in a female skull dating from the Bronze Age (1900–1600 BCE)’<sup>10</sup>; unfortunately they give no source to support this assertion.

## The cancer papyruses

The oldest written descriptions of cancer are found in Egyptian papyruses which date to around 1500 BCE and are based on tracts from around 2500 BCE. Many elements of the papyri are difficult to interpret, due to changed terminology and disease concepts. The Edwin Smith papyrus describes surgical cases; at least one case seems to be a cancer (of the breast)<sup>11</sup>. The papyruses are purely case histories with no speculation as to causes of cancer. It is probable that, like other natural phenomena in the prescience era, they attributed development of cancer to supernatural causes.

## Graeco-Roman literature

Hippocrates (460–375 BCE) is credited with the first use of the term cancer (Gk crab)<sup>12</sup>; possibly because the growths reminded him of a moving crab. He used the terms ‘*carcinus* (a tumor), *carcinoma* (a malignant tumor) and *cancer* (a non-healing malignant ulcer)’<sup>13</sup>. Hippocrates believed that severe, incurable and ulcerated cancers arose from an excess of black bile, while thin bile was responsible for non-ulcerated, curable cancers.

The first specific text on tumours was Galen’s ‘De Tumoribus Praeter Naturam’ (Tumours contrary to nature)<sup>14</sup> written almost 2000 years ago. To Galen, tumours meant all swellings, including conditions such as dropsy and even obesity. He embraced the Hippocratic ‘humoral’ theory of the nature of disease, including cancer – unfortunately for the next 1500 years no one successfully challenged

anything written by Galen. In 1543, Vesalius, Professor of Anatomy at Padua, was the first to seriously challenge Galen's errors on anatomy<sup>15</sup> ushering in a new understanding of anatomy; unfortunately Galen's humoral theory of disease continued to hold sway. Vesalius also '*wrestled with the knotty problem of clinical differentiation of tumours*'<sup>16</sup>. Physicians in the late sixteenth century did not differentiate clearly between neoplastic growths and other forms of swelling, thus Benoît (translated by Hunton) wrote, '*Every Cancer almost is incurable, or hardly cured, sith it is indeede a particular and worst kind of Leprosie*'<sup>17</sup>.

## Humours, tumours and cell theories

In 1700, Deshaies Gendron published a closely reasoned argument that cancers were not '*inflammatory masses composed of fluted humours*' but rather solid structures composed of body tissues and capable of destructive growth<sup>18</sup>. In clear contradiction of Galen's teachings, he based this on '*clinical studies and observations of cancerous materials*'<sup>19</sup>. Sadly, the dead hand of Galen lay heavy and Gendron's work was rejected and lay forgotten for many years. It was to be more than a century before medicine emphatically discarded the humoral theory.

At the end of the eighteenth century, cancer was widely thought to be an infectious disease; because of which the first cancer hospital in France (opened in 1779) was forced to move from the city. This was largely influenced by two seventeenth-century clinicians, who argued from analogy to other 'tumours' such as leprosy and elephantiasis – both of which are transmissible<sup>16</sup>. Beckett, writing in 1712, explicitly rejected the analogy between cancer and elephantiasis, declaring that '*tho' a Cancer has some similitude to an Elephantiasis, they are different Diseases*'<sup>20</sup>.

Cancer patients continued to be refused admission to many hospitals as late as the mid-nineteenth century. Records of the Women's Hospital in New York show that the Board of Lady Supervisors refused admission of cancer patients to the hospital 'pavilions' – clearly due to a belief that all growths, including cancer, were contagious. The surgeon Marion Sims challenged the Board head-on and continued to admit, and operate upon, patients with early stage cancer. Unfortunately, the result was Sims's dismissal; he went on to become President of the American Medical Association<sup>21</sup>, so this contretemps clearly did not permanently blight his career.

Reports of 'cancer houses' persisted into the twentieth century and there are still many people who fear that cancer itself is infectious. Alternative explanations exist for multiple cases at a given address; familial cancers may have affected several related occupants of the same dwelling, there may have been shared exposures to environmental carcinogens or there may have been transmission within families of organisms like *Helicobacter pylori* which are known to increase cancer risk.

At the commencement of the nineteenth century with the flourishing of scientific medicine there was a great deal of interest in the nature, causes and treatment of cancer. In 1800/1801, French anatomist Marie François Xavier Bichat '*laid down the principles that all tissue was similar in structure, that each type of tissue was a unit of*

life capable of reproducing itself, and that tumours, cicatrices (scars) and cysts were not inflammations but an overgrowth of cellular tissue<sup>19</sup>; like Gendron, Bichat appears to have been far ahead of his time; it was to be more than 50 years before Virchow published his famous axiom '*omnis cellula e cellula*' – all cells arise from existing cells<sup>22</sup>.

In 1802, in London, a group of prominent physicians and lay people formed the "Institution for Investigating the Nature and Cure of Cancer"<sup>23</sup>. They formulated a list of 13 key questions, most of which are as relevant today as when they were formulated two centuries ago:

- (1) What are the diagnostic signs of cancer?
- (2) Does any alteration take place in the structure of a part, preceding that more obvious change which is called cancer? If there does, what is the nature of that alteration?
- (3) Is cancer always an original and primary disease, or may other diseases degenerate into cancer?
- (4) Are there any proofs of cancer being a hereditary disease?
- (5) Are there any proofs of cancer being a contagious disease?
- (6) Is there any well-marked relation between cancer and other diseases? If there be, what are those diseases to which it bears the nearest resemblance, in its origin, progress and termination?
- (7) May cancer be regarded at any period, or under any circumstances, merely as a local disease? Or, does the existence of cancer in one part, afford a presumption, that there is a tendency to a similar morbid alteration in other parts of the animal system?
- (8) Has climate, or local situation, any influence in rendering the human constitution more or less liable to cancer, under any form, or in any part?
- (9) Is there a particular temperament of body more liable to be affected with cancer than others? And if there be, what is that temperament?
- (10) Are brute creatures subject to any disease, resembling cancer in the human subject?
- (11) Is there any period of life absolutely exempt from the attack of this disease?
- (12) Are the lymphatic glands ever affected primarily in cancer?
- (13) Is cancer under any circumstances susceptible of a natural cure?

Theories other than contagion were put forward, perhaps the most prominent being the lymph theory and the blastema theory; the former suggested that cancers arose from local accumulations of lymph, the latter acknowledged that cancers were formed of cells but held that these arose from budding elements, blastema, found between normal cells. Rudolph Virchow argued correctly that all cells (including those in tumours) arise from existing tissues – '*omnis cellula e cellula*' and also identified chronic inflammation as a mechanism of carcinogenesis; – one pathway by which infection can lead to malignant transformation. Virchow mistakenly believed that cancers '*spread like a liquid*'. Thomas Hodgkin, after whom

Hodgkin lymphoma is named, recognized that metastasis occurred by spread of elements of the original cancer; *'At the same time, I would by no means deny the possibility, or even probability, that some of the nucleated cells may find their way into the blood, and be arrested at particular parts, giving rise to productions similar to the original tumour, more especially when the latter has advanced to the softening stage, and the lymphatic glands have become affected'*<sup>24</sup>.

From the late 1800s into the early twentieth century, both scientists and lay people believed that cancer could be initiated by a single local trauma (as opposed to chronic irritation). Despite the failure to induce tumours in animals by deliberate injury this belief was maintained and is still a popular folk explanation for the aetiology of cancer. It is probable that this was based, at least in part, on incidents when a tumour was first noticed following an injury close to its location.

The interval between the first recognition of the virus as a distinct biological entity and the first proposal that they might play a significant part in cancer causation was remarkably short<sup>25</sup>. In 1892, the first virus (tobacco mosaic) was identified by Ivanovsky, in 1898 foot-and-mouth disease became the first animal virus to be identified, by Loeffler and Frosch, while in 1901, yellow fever was the first human virus identified, by Reed; as early as 1903 Amédée Borrel proposed that viruses might be common causes of cancer<sup>26</sup>. In a little over a century not only was it established how important and widespread viruses are as human carcinogens, it was also research on cancer and viruses which led to *'the concept of the oncogene, the identification of the p53 tumor suppressor, and the function of the retinoblastoma tumor suppressor'*<sup>25</sup>.

### **'False dawns' and delayed recognition**

In 1910 Peyton Rous, working at the Rockefeller Institute in New York, reported *'the first avian tumor that has proved transplantable to other individuals'*<sup>27</sup>. Just one year later, Rous published the first experimental proof of transmission by a cell-free preparation of a malignant tumour<sup>28</sup>. In 1908, Ellerman and Bang had described similar experiments with transfer of avian leukaemia<sup>29</sup>, indeed Rous made reference to their work in his 1910 paper – *'Ellerman and Bang have shown chicken leukaemia to be transmissible, and in some of their animals aleukemic lymphomata resulted from inoculation. But they have also shown, as have Hirschfeld and Jaeoby, that the disease is dependent on a filterable virus.'* Prior to the 1930s, few researchers or clinicians regarded leukaemia as a malignant disease, so these seminal reports were not seen as relevant to cancer aetiology.

Many used a strangely circular logic to dispute the malignant nature of the tumours reported by Rous; they argued that as the tumours had been induced by an infectious agent and it was well known that infectious agents do not cause cancer the growths could not be malignant. Rous clearly anticipated this challenge as he states in his paper *'It is evident from the foregoing description that our tumor of the fowl possesses to a marked degree those characters of morphology and behavior which distinguish the true malignant neoplasms, especially the sarcomata'*<sup>28</sup>. An alternative, equally

facile argument, was that filtration had been inadequate to remove all cell-fragments and that cells from an existing tumour had been transplanted<sup>30, 31</sup>. Many of those who did accept Rous's achievement still insisted that it had no relevance for humans, or indeed any mammals; they considered transmissibility to be a peculiar feature of avian tumours<sup>32</sup>, without offering any rationale why this might be the case. Rous *et al.* went on to confirm their findings and to demonstrate that other avian tumours were transmissible in a similar fashion<sup>33</sup>.

Rous carried out an unsuccessful search for mammalian tumour viruses – his failure led him to move away from work on infectious causes of cancer. Rous was eventually drawn back into researching viral oncogenesis in the early 1930s when Richard Shope published his findings on the induction of tumours in rabbits by papillomaviruses<sup>34,35</sup>. Those who were determined that infection played no part in the aetiology of human cancer deployed the same peculiar arguments used against Rous; some claimed that these could not be true cancers as they were caused by infection, while others conceded that this was proof that cancer could be transmissible in mammals but were insistent that this had no relevance for humans. Shope and Rous were to enter into a very productive collaboration – many of their discoveries are still central to understanding of viral induction of cancer. Rous's biography on the Nobel Prize website ([www.nobelprize.org](http://www.nobelprize.org)) describes him and Shope as friends as well as collaborators; despite this, they appear to have published no joint papers.

In 1926, there was a major stimulus to the notion of infection as a significant cause of cancer. A Nobel Prize was awarded to Johannes Fibiger for apparently demonstrating that a nematode worm caused stomach cancer in laboratory rats<sup>36,37</sup>. Fibiger, a Danish medical researcher, was studying tuberculosis in rats when he observed that three of his animals had developed stomach tumours. These appeared to be associated with the ingestion of nematodes present in cockroaches fed to the rats. In reality, the diet was the crucial factor; Fibiger's rats were vitamin A deficient, which has been shown to cause stomach cancer in mice<sup>38–40</sup>, the nematodes were not involved in the cancer.

Fibiger's Nobel Prize is often said to have been awarded on the basis of a (subsequently disproved) claim that he had found the first infectious cause of cancer, yet his lecture makes it clear that he considered infection as a cause of cancer to be well established by the time of his key papers and that he, *correctly*, saw his key achievement as the development of a method to systematically induce tumours in animal studies. Researchers, including Fibiger, went on to use chemical agents to induce tumours in experimental models and the value of this to cancer research cannot be overstated. In his Nobel Prize lecture, Fibiger makes it clear that he believed that his results were associated with the specific nematode he had isolated from his animals, which he named *Spiroptera neoplastica*; however, he made no claim that this was the first evidence of infectious causes. In his Nobel lecture<sup>41</sup>, Fibiger states

*'...Schizostomum hæmatobium's aetiological importance in the development of cancer of the bladder must be considered as proven. Nor can it be doubted that other Trematodes, such as Opisthorchis felineus, Schizostomum japonicum and Clonorchis sinensis can, in certain cases, bring about primary carcinoma of the liver, and that Schizostomum mansoni can be the cause*

*of polyps and carcinoma in the colon.*' and later *'In the course of the research work on Spiroptera carcinoma, it became possible for the first time to induce typical, metastasizing carcinomas systematically and at will. This provided experimental proof that the start of a cancer can, in agreement with the theory of Virchow, be brought about by external, exogenic influences, and lent support to experiments on the effects of long-term irritants of other kinds'*<sup>41</sup>.

Many agree that an unfortunate consequence of Fibiger's 'mistaken' Nobel award was the delay in official recognition of Peyton Rous's work on avian tumour viruses; Rous's belated award was the first in 40 years for cancer-related work. Peyton Rous was to eventually receive a Nobel Prize for his work, but not until 1966, just 4 years before he died<sup>42</sup>. Rous was dogmatic in rejecting the notion that genetic changes played any significant part in carcinogenesis; *'What can be the nature of the generality of neoplastic changes, the reason for their persistence, their irreversibility, and for the discontinuous, steplike alterations that they frequently undergo? A favorite explanation has been that oncogenes cause alterations in the genes of the cells of the body, somatic mutations as these are termed. But numerous facts, when taken together, decisively exclude this supposition'*<sup>43</sup>. (Oncogenes is the term Rous used for agents now know as carcinogens. It was perhaps fortunate that terminology changed since the scope for confusion with *oncogenes* is obvious.) It is, of course, now beyond dispute that cancer is essentially a genetic disorder – the lesion lies at the level of the DNA molecule and the observable tumour is a late consequence of a process that began with a single cell containing a corrupt copy of the genome<sup>44</sup>.

The 1930s also saw John Bittner's studies on murine mammary tumours. It had been shown that certain strains of mice were prone to mammary cancers and that the strain of the male was irrelevant; if the female was from a tumour-prone strain all her female offspring would share this vulnerability<sup>45</sup>. Bittner carried out what proved to be the crucial experiment; newborn mice from high-risk females were suckled by low-risk females and vice versa. The risk of mammary cancer was high only where the newborn had received milk from a high-risk female<sup>46</sup>. By 1942, it had been established that this was due to passage of a virus<sup>47</sup>; this retrovirus is called the murine mammary tumour virus (MMTV)<sup>48</sup>. (Retroviruses, such as HIV, contain no DNA in their infective particles; their genome is coded in RNA and before they can replicate they must transcribe this into DNA, using an enzyme called reverse transcriptase.) For over 30 years there has been speculation that at least a proportion of cases of breast cancer may have a viral aetiology<sup>49</sup> and suspects include MMTV or a human homologue of this virus (HHMTV), HPV and EBV<sup>50</sup>.

## **Burkitt's great tumour safari**

In 1958, Dennis Burkitt, a surgeon working for the Colonial Medical Service in Uganda, described the unusual tumour which still bears his name – Burkitt's lymphoma<sup>51</sup>. Having seen two cases in which children presented with strikingly symmetrical jaw tumours, Burkitt reviewed the records of 41 cases of children

with jaw tumours and found histology available on 29 of these; in each case there were similar undifferentiated round cells – although he made clear his uncertainty of the nature of the tumour, he initially described it as a sarcoma. By 1958 Burkitt had written these cases up ~ within 2 years Burkitt, working with histopathologist Greg O’Connor, had determined they were of lymphoid origin<sup>52,53</sup>. The 1961 papers were based on many more cases Burkitt identified by questionnaires and personal contact with physicians. Some remarkable features emerged; the tumour was very common in what Burkitt referred to as a ‘lymphoma belt’ which spanned the Equator roughly between 15° north and south with a tail extending south along the coast of east Africa<sup>54</sup>.

It occurred in children of all tribes and ethnic backgrounds living in this region but not if they lived above 5000 ft above sea level; within the belt the new tumour was far more common than any other childhood cancer. In an attempt to explain this phenomenon, Burkitt set out upon what he termed a ‘*tumour safari*’<sup>55</sup>: a 10 000 mile journey along the southern edge of the lymphoma belt; Burkitt sought to identify what changed at the boundary. The key variable was temperature – below 5000 ft and within the lymphoma belt the minimum temperature did not fall below about 60°F (15.5°C). This suggested a mosquito-borne infection as the cause, and many possible causal agents were considered, including malaria. By chance, when Burkitt lectured in London in 1961, virologist Anthony Epstein was in the audience – he was intrigued by the possibility of a viral cause and arranged for frozen tumour samples to be sent to him at the Bland Sutton Institute<sup>54</sup>.

In 1964 Epstein, with Bert Achong and Yvonne Barr, published a description of a new virus identified by electron microscopy of the samples<sup>56</sup>; which they named Epstein–Barr virus (after the cell-line from which it was isolated). Epstein describes facing a high level of scepticism<sup>57</sup>, some refused to believe that the cells were lymphoid, and others that the particles were viruses. Electron microscopy was in its infancy and many believed the observations were of artefacts of tissue fixation and processing. Within 20 years, the EBV genome had been fully sequenced<sup>58</sup> – the first human virus for which this was achieved.

There was further reluctance to concede a causal link between EBV and human cancer. At first it was called a contaminant or a passenger, of cells perhaps made susceptible by early stages of malignant transformation. This led to the definitive International Agency for Research on Cancer (IARC) 7-year study of 42 000 children in Uganda’s West Nile district<sup>59</sup>. EBV is now accepted as a key causal factor in ‘endemic’ or ‘African’ Burkitt’s<sup>60</sup>; the disease is also seen in a ‘sporadic’ form as an AIDS-defining condition<sup>61</sup> and in non-immunosuppressed patients, but it was the endemic form which yielded the first known human cancer virus. For many years it has been accepted that when children with chronic immunosuppression, due to malaria infection, acquired EBV the lack of immune surveillance allowed the virus to multiply rapidly and induce BL. It has recently been suggested that malarial infection may play a more direct role in lymphomagenesis<sup>62</sup>, and other even more complex mechanisms have been postulated, involving three different infections and a tumour promoter<sup>63</sup>.

Other forms of immunosuppression can increase the risk of BL; it is classed as an AIDS-defining malignancy. There are now recognized to be three classes of BL<sup>64</sup>:

- Endemic – African children, often with bilateral jaw lesions – almost 100% EBV+
- Sporadic – seen in adults and children in all populations – minority EBV+
- Immunodeficiency-related – mainly HIV-positive, but also transplant recipients and congenital immunodeficiency – most are EBV+

## Stomach bugs Down Under

Scarcely more than 20 years ago, two Australian medical researchers transformed our understanding of the pathophysiology of gastric ulcers. They went on to demonstrate that infection with the bacterium *H. pylori* is a key factor in some forms of stomach cancer and of certain forms of lymphoma. Initially there was scepticism about the possibility of persistent gastric infection with any organism. This has been portrayed by some as rejection by entrenched interests of new ideas, but Atwood debunks this view<sup>65</sup>.

*Helicobacter* spp. were first described as resident in the mammalian stomach in the late nineteenth century<sup>66</sup>, being described as spiral-shaped bacteria in the stomachs of dogs – ‘Even more exciting are certain spirilli I found constantly in the dog’s stomach and that, in addition to being numerous in the mucus layer that covers the mucosa, penetrate into the gland lumen of both pylorus and fundus, and sometimes reach the bottom glands’. The observation was dismissed as insignificant for many years; there was a consensus that the interior of the stomach had no resident microbial flora. This was the prevailing view when pathologist Robin Warren reported observing unidentified curved bacteria (*H. pylori*) on the gastric epithelium of patients with active chronic gastritis<sup>67</sup>. The following year, with gastroenterologist Barry Marshall, he published a paper on the association of this organism with gastritis and peptic ulceration. This paper eventually led to the award to Warren and Marshall of the Nobel Prize for Physiology or Medicine in 2006. Warren failed many times to culture the organism; standard practice was to discard cultures after 48h and success came by chance when, over Easter, a set of cultures was left in an incubator for 5 days<sup>68</sup>. Marshall famously attempted to satisfy Koch’s postulates<sup>69</sup> – one of which requires that the agent be administered to a susceptible organism and induce the disease with which it is associated – by swallowing *H. pylori*, which induced gastritis but no ulcer or cancer<sup>70,71</sup>. Fortunately, there is now an animal model<sup>72</sup>, so future researchers will be spared the gastric discomfort and extreme halitosis his experiment induced.

Previously stomach ulcers were ascribed to behavioural (and possibly genetic) factors. The archetypal ulcer victim was the highly stressed executive, with a non-stop life, too many lunchtime martinis and too much spicy food – ‘hurry, worry and curry’. Treatment was either medical, with a bland diet, modified life-style, and antacids, or surgical, involving removal of all or part of the stomach. An acid blocking drug called Zantac, rapidly became the world’s biggest selling prescription drug and ensured the fortunes of pharmaceutical company Glaxo. Use of inexpensive antibiotic regimens to eradicate *H. pylori* was found to heal the ulcers; unlike prior medical management, this was followed by very low rates of recurrence.

Marshall has claimed that after one *H. pylori* meeting in Chicago the fall in Glaxo's share price represented a reduction of about \$1 billion in the company's value<sup>65</sup>.

Within a decade of the Warren and Marshall paper, it had been established that *H. pylori* is a significant carcinogen. In 1994, following a review of the evidence, the IARC reported that *H. pylori* was classified as a carcinogen in humans<sup>73</sup>. It has been known since the time of Virchow that chronic inflammation is causally linked with cancer<sup>74</sup> and many assumed that this was the sole basis for the association between gastric ulcers and gastric cancers; more recent studies have demonstrated complex interactions at the genetic level which moderate immune responses and may directly stimulate malignant transformation<sup>75</sup>.

## Oncogenes, retroviruses and more Nobel Prizes

An understanding of malignant transformation depended on the flowering of molecular biology. Watson and Crick's description of the structure of DNA<sup>76</sup> was the first step on a road which has led to the deciphering of the human genome. A concept known as the 'central dogma'<sup>77</sup> states that DNA is transcribed to RNA which directs synthesis of proteins; RNA viruses (retroviruses) require an additional preliminary step in which they transcribe their RNA-encoded genome into DNA using the enzyme reverse transcriptase. In 1975, Baltimore, Dulbecco and Temin shared the Nobel Prize for '*their discoveries concerning the interaction between tumour viruses and the genetic material of the cell*' – essentially for the discovery of reverse transcriptase.

The avian leukaemia and sarcoma viruses discovered at the dawn of the twentieth century were retroviruses, although neither the term nor the concept existed at the time Ellerman and Bang and Rous were reporting their discoveries. In 1961, Crawford reported that Rous Sarcoma Virus contains RNA<sup>78</sup>; this led oncogenic retroviruses to be described as RNA tumour viruses.

Key concepts in the modern understanding of how a cancer develops are the oncogene and the tumour suppressor gene – these concepts are discussed in further detail in the next section. Oncogenes are significant in the history of infection-associated cancer because their existence was first recognized as elements of cancer-causing viruses.

Over 50 years after Rous described the sarcoma which bears his name, Huebner and Todaro introduced the term oncogene<sup>79</sup>. Their paper set out a theory that most or all cells of vertebrates contain integrated retroviral DNA, and that all cancers result from expression of these 'oncogenes'. The concept of integration of retroviral DNA is now well established; Weiss has suggested that as much as 8% of the human genome is accounted for by what he describes as '*fossil retroviral genomes*'<sup>80</sup>. Although the term oncogene was a new coinage, the concept of cancer-causing genes within viral genomes was not.

Initially it was thought that oncogenes were of viral origin, having evolved to allow the virus to bypass the mechanisms which normally control cell growth and division. Later it was recognized that the virus had acquired elements of the host genome thus becoming better fitted to succeed in the Darwinian arms-race<sup>81</sup> between the viral invader and the host's defence mechanisms. The discovery was

entirely unexpected; it was reported in 1976 by Bishop and Varmus<sup>82</sup>, who subsequently received the Nobel Prize for their crucial discovery. Such genes were termed cellular oncogenes or proto-oncogenes – these titles are both inappropriate as the genes are normal functional, indeed indispensable, elements of the genome. Their normal function is to promote cell growth and division in response to appropriate stimuli; malignant disease occurs when these genes are expressed aberrantly.

Viruses are predisposed to acquisition of host genes since they rely on host cell enzymes and organelles to replicate and to produce new infective viral particles. Retroviruses use reverse transcriptase to produce a DNA copy of their genome and insinuate this genome within the host genome. Transcription of the embedded viral genome will direct the production of components of the viral particle and their assembly into a complete virion. During this process, it is unsurprising that at times elements of host genome become embedded in the viral genome. This is probably a relatively common event but in many cases the acquired host genetic material will harm the virus in some way and prevent replication; when the virus remains viable even though host genes are embedded, this will usually be innocuous to the host. It has been estimated that only around 50 of the 30 000 or so genes in human cells are capable of acting as oncogenes.

Strikingly, this is not a one-way process; as cited, Weiss has estimated that as much as 8% of the human genome is litter left behind by trespassing viruses. Most of this litter is harmless, by definition, since affected hosts have continued to contribute to the gene pool. Fragments of retroviral DNA embedded in the host genome are termed ‘endogenous retroviruses’, in humans they are termed HER<sup>83</sup>. Huebner and Todaro believed that all cancers resulted from (re-) activation of such HER segments and considered the action of the viral oncogene to be a *sine qua non* of tumour development. It is now clear that there is no single pathway of oncogenesis; in some cases viral oncogenes play a vital role, whilst in others they play little or no part. For the purposes of this work, stably integrated endogenous retroviruses are not deemed to be infectious causes of cancer.

In the early 1970s, as cellular oncogenes were first being described, Harald zur Hausen was beginning the series of studies which would demonstrate that HPV is the causal agent for cervical cancer<sup>84</sup>. Zur Hausen eventually received a shared Nobel Prize for his work in this field.

Modern models of the development of malignancy in response to infection are complex, yet in many cases the mechanisms are still incompletely understood. Chapter 2 will review some basic concepts of cancer biology and microbiology and explore the current understanding of pathways by which infections may induce or drive malignant transformation.

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