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A HISTORY OF CANCER AND ITS TREATMENTS

Many people know me as a Clinical Oncologist, whereas I see myself as a cyclist on a 35-year detour into Oncology. The picture¹ shows me in Roncevalles, on the border between France and Spain and the signpost shows my destination, Santiago de Compostela, 800 kilometres away. When I joined Oncology, I felt like I was setting off on a similar lengthy pilgrimage to change the world. Identifying the first recorded case of cancer is a challenge, as the diagnosis was vexing in ancient times. Atossa, around 520 BC, was a Persian queen who developed a “tumour” in her breast. It discharged and expanded within the breast. Democedes was a captive Greek slave in her royal household, and a renowned healer. He offered her a cure for her problem if she would grant him whatever he requested. She agreed, and he got to work with poultices and balms. The “cancer” resolved. As agreed, he made his request, that she ask her husband, king Darius, to invade Greece. Darius agreed, and Democedes volunteered for the advance scouting party. On reaching the Greek border, Democedes skipped across and was home and free. All were happy, but I have doubts. The discharging and enlarging lesion could have been a bacterial or tuberculous abscess, and not a cancer. This lack of histological proof bedevils the early accounts.

The evidence from mummies in Ancient Egypt, spanning the three millennia BCE, is more definitive. Mummies were desiccated and their visceral organs removed and replaced by linen, so metastatic lesions in bone are diagnosed based on lytic and sclerotic bone lesions on imaging, with missing soft tissue primary tumours. Many mummies have had CT scans, with a small number of bone lesions found. This is not surprising, given that their age at death was around forty years. In a reconstructed lumbar spine CT scan, there were distinctive sclerotic bony lesions and my colleagues specialising in prostate cancer would readily call this as metastatic prostate cancer. The

Daily Mail newspaper in 2011 labelled this as the “earliest case of prostate cancer in the world”.

The aetiology of cancer has been a topic for philosophical and scientific debate. In early times the causes were conjectural. Hippocrates, a Greek physician around 400 BCE, described the body as containing four fluids (humours) which were blood, phlegm, yellow bile and black bile. He associated an excess of black bile (so-called melancholy) with cancer. He was very influential, and his theory predominated until about the 11th century. Virchow was an astute pathologist and in the 1840’s he made fundamental observations on cancer cells. These were new insights. He described them as autonomous cells derived from previous cells. He suggested that cancer cells resembled cells in the tissue from which they arose; for example, breast cancer cells resembled a normal breast cell. This became widely accepted by the start of the 20th century.

The next insight was the discovery of DNA by Watson and Crick. I was a medical student in 1975, only 20 years after DNA was discovered, and DNA division and base pairs were “cutting-edge” new science. The modern understanding that cancer is a disease of DNA, and that DNA mutations lead to loss of control of cell proliferation, was in its infancy.

Why has cancer become so common? Firstly, in the 20th century, fatal infections began to wane, due to public health measures. Typhoid disappeared and tuberculosis declined. In the 1940’s antibiotics arrived, treating many previously fatal infections. However, as well as fewer deaths from infection, there were many more cases of cancer. The UK data presented by Cancer Research UK have shown that cancer incidence of cancer rises dramatically with increasing age, being at least 5 times more likely for people in their eighties compared to those in their forties, as illustrated in the figure.¹ Data on life expectancy over the centuries are interesting. Before 1850, life expectancy was stubbornly around 35 years, but in the last century it has increased dramatically, now reaching into the 80’s. Before the mid-19th century, there were virtually no middle-aged or elderly people around to get cancer, and therefore cancer was quite rare. As the elderly population increases, cancer is more common, and this upward trend will continue.

What is the role of environmental factors? I suggest that this follows a pattern. A factor is identi-

¹ Not included

fied, its impact is mitigated, and after a lag period, related cancer cases decline. For example, Sir Percival Pott identified the first occupational cancer. He associated scrotal cancers with young boys working as chimney sweeps. Soot was a chronic irritant and its presence in the scrotal skin caused these rare, but often fatal, cancers. The public outcry over this led to massive improvement in working conditions for the boys, although many more actually died when smothered in soot falls in the chimneys. Public opinion responds to drama more than simple numbers!

Doll & Bradford Hill reported in 1964 that doctors who smoked were more likely to get lung cancers. Despite this revelation, smoking remained very prevalent, due in part to the suppression of evidence by tobacco companies. Eventually the message has emerged, leading to fewer smokers who each smoke less. Lung cancer incidence is now declining, after the expected time lag.

A key environmental factor in Belfast was asbestos, widely used in ship building and engineering. Asbestos is a light irritant fibre which enters the airways and lodges deep in the alveoli. It causes asbestosis, pleural plaques, lung cancer and mesothelioma with a latency of up to 40 years. The fascinating aspect here is the timeline. The first compensation case was settled in the 1920's. Industry research quantified the issues in the 1930's, medical research came in the 1960's and then big settlements in the 1970's. Only then was asbestos banned, but cases are still arising. Of note, the most common cancer due to asbestos is lung cancer, not mesothelioma, because combined exposure leads to a dramatic increase in lung cancer risk.

Currently, obesity is the key reversible factor. It is a chronic pro-inflammatory condition, and cancer incidence is around 30% higher in obese people (BMI > 30 kg/m²). Its association with endometrial cancer was long known, but recent studies have shown that incidence of oesophageal or kidney is doubled, breast and colon cancer are 30% more common, and with lesser increases for other sites. As obesity is becoming more prevalent, it will cause more cancer.

Cancer treatment has evolved remarkably. The early surgeons had no anaesthesia, so surgery was barbaric, with patient tolerability the limitation of this approach. Surgery in that era caused horrific morbidity and little benefit. Therefore, in this era most treatment came from Physicians. They diagnosed, purged, bled and poisoned, to treat the mythical black bile. In summary they were no more effective, but perhaps caused less harm.

The arrival of anaesthesia in the late 19th century, followed by antiseptics, heralded more effective cancer surgery. Halstead, an American Surgeon, tackled breast cancer and, at the end of the 19th century, he developed "Halstead's radical mastectomy". This extended from full mastectomy, to include pectoralis minor, then pectoralis major, and regional lymph nodes. Despite considerable functional and cosmetic issues, it controlled disease, and was widely adopted. Less extensive surgery eventually became feasible, when accompanied by adjuvant radiation or chemotherapy. Uptake of the non-surgical approaches was slow, but by the 1990's this became accepted as best practice. Surgery cures more cases, radiation therapy comes next, and chemotherapy is catching up quickly. The role of surgery will diminish even more in future.

Cancers of breast and prostate are usually sensitive to hormone manipulation. This was achieved surgically in the past by oophorectomy and by orchidectomy. George Beatson, a Scottish surgeon, was a pioneer, reporting a clinical trial, in which three women with advanced progressive breast cancer had oophorectomy: one was cured and two got excellent remissions of limited duration. The treatment was therefore effective, even with the limited numbers. I doubt that modern therapies would get approval from this scale of trial, no matter how effective!

In his laboratory in Würzburg, Germany in 1895, Roentgen noticed an extraordinary glow around a cathode ray tube, which he named "X-rays". These "ionising" radiations caused DNA damage, impacting on cell division. Their value was recognised promptly, and, within a year, X-rays were used to treat cancer. In 1902, Marie Curie and her husband Pierre isolated radium, which was a radioactive element. By 1906 radium needles were used to treat cancer. Sadly, there was no awareness of the risks, and no radiation protection. This caused the death of many radiation pioneers from diseases relating to over-exposure. Marie Curie died of radiation-induced aplastic anaemia and there is a memorial in Hamburg to 159 radiation martyrs.

Radiotherapy developed quickly in the decades following the discovery of X-rays. The radiation energy was low (up to 300kV), with poor penetration and quality control. This meant some cures but left many patients with severe side effects. In the 1960's machines using Cobalt-60 as a radiation source became available. Beam energy was equivalent to 1.25 MV, which was 5-10 times more penetrating. When I joined Oncology, Cobalt machines were still common, but we had our first linear accelerator with beam

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energy of 6MV. Energies are now up to 15MV, with electronic refinements. Computer beam distribution planning came next, first 2D, then 3D and now even 4D, accounting for respiratory motion during the exposure. When I started at Belvoir Park Hospital, the computer could plan only a single CT slice, taking several hours. Now we plan on hundreds of slices, with multiple beams, almost instantaneously. Modern Linear Accelerators (Linacs) use highly modulated beams and giving precisely targeted volumes, with minimal dose outside the target areas. They perform CT scans during treatment, and soon they will deliver MR scanning during treatment. Images from CT, MRI and CTPET can be fused, to improve target definition. Radiotherapy is now more effective and much safer, and it is now expected to cure many cancers. Radiotherapy after surgery improves outcome most obviously in breast and rectal cancers, but also in many other cancers. It can also be combined with chemotherapy, and soon immunotherapy, to enhance cure rates. Stereotactic ablative body radiotherapy (SABR) is very precise localised radiation therapy, which can cure small early lung cancers. SABR practitioners are confident that it will displace surgery in this setting.

Systemic therapy, including chemotherapy, are treatments, usually given orally or intravenously, which circulate throughout the body and attack the tumour cells, wherever they are. The original chemotherapy agents were cellular poisons, targeting the phases of the cell cycle in the dividing cell. This targeted the most rapidly dividing cells, of which cancer had the highest proliferation rate. Bone marrow and mucosal cells were at risk, so neutropenia, infection, mucositis and diarrhoea were very common side effects. Chemotherapy was first used in acute leukaemia, with aminopterin producing dramatic responses, but relapse followed in a few months. The regimens were refined, adding other drugs. Chemotherapy started to show cures in leukaemia and lymphoma over the next few decades, but progress was poorer against solid tumours.

Chemotherapy made modest progress in the 1960's, but in 1971 President Richard Nixon, as a distraction from the Vietnam War, promoted his National Cancer Act. It funded a major research drive to "win the war on cancer". It brought a sizeable boost to cancer research and clinical trials activity. Progress was still slow and the only solid tumour showing early promise was testicular cancer in the 1970's. In other tumours many physicians viewed it as futile and toxic.

As a medical student in Trinity College, Dublin, in the late 1970's, my base hospital was Mercers

Hospital, near St. Stephens Green. Doctor Peter Daly, a Medical Oncologist joined the staff. He was a man of dynamic style and character, newly returned from training in the United States. He introduced chemotherapy, to mixed reviews! I remember a ward round with him. The style was impressive, Matron, staff nurses, and the complete medical team from registrar to intimidated medical students. An elderly man was looking wan after chemotherapy for metastatic stomach cancer. He reported nausea and a cough. On sitting forward for chest examination, he retched and brought up his entire stomach contents, over the leg of Peter's sharp suit and shiny leather shoes. Chaos ensued, and an unsympathetic Matron sniffed "Serves you right for giving him that poison!"

Oncologists started to report some success. Larry Einhorn published a trial in 1977 on 50 patients with advanced testicular cancer. Patients received cisplatin in a 3-drug chemotherapy combination and nearly all were cured (75% with chemo alone and a further 20% converted to complete response by surgery). I saw this paper as a medical student, and it really enthused me that chemotherapy and oncology were the future.

As a Consultant, I had a special interest in testicular tumours, and I can give an illustrative example. A teenager had fatigue and a cough for two weeks, His chest X-ray (on the left)¹ shows myriad rounded masses, confirmed as metastases from testicular choriocarcinoma with greatly raised levels of beta-human chorionic gonadotrophin (β HCG) at over 100,000 IU/L (reference range 0-4). He received 4 cycles of platinum-based chemotherapy, with virtually resolution of the lesions, as shown on the X-ray on the right.¹ He remains well 15 years later.

Nowadays, chemotherapy has been refined and contributes to cure in many rapidly growing tumours. It can be combined with radiation for cure, it can improve the cure rate of surgery and can effectively palliate advanced cancer from many sites. Therapeutic index is still an issue, as chemotherapy is a poison. Therefore, research focus has moved on to finding cancer-specific targets and pathways in the cells. Cancer cells often have receptors on the cell membrane or nucleus which can be targeted, or they have mutations causing activation of enzyme pathways influencing cell proliferation and growth. Examples included the EGFR mutations in lung cancer and HER2 receptors in breast cancer. The key principle is that the target is vital to the cancer cell, but is not present, or unimportant, in normal cells,

¹ Not included

giving a huge advantage to targeting it.

The HER2 receptor is on the breast cancer cell membrane in 20% of breast cancers. These HER2-positive tumours had a poor prognosis, having 50% shorter median survival for HER2-positive metastatic tumours. Trastuzumab (Herceptin) is a monoclonal antibody against the HER2 receptor, and it showed moderate activity in metastatic disease, improving response rates and survival, but not achieving cures. To test its value in early breast cancer, three large adjuvant trials, aiming to recruit 12,000 patients, were opened. Recruitment was rapid, including around 50 volunteers from Belfast, to whom we are very grateful. Patients received standard care of surgery, chemotherapy and radiation, and were then randomised to placebo or Herceptin treatment for 1 – 2 years.

I was at the annual meeting of the American Society of Clinical Oncology in Chicago in 2005 when the results of all three trials were released in a plenary session. A massive lecture hall, packed with 5,000 Oncologists, heard the incredibly positive results (relapse rates halved and a 9% improvement in survival with Herceptin). The largely American audience were very excited, culminating in a standing ovation. When the session ended, there was rush to the phones to spread the news, and no doubt order Herceptin for their patients. The UK processes prevented us from using the drug for another year. Of note, one-year course of Herceptin cost about £30K per patient, or £3M for the cohort of 100 eligible patients. Our annual chemotherapy drug budget for Northern Ireland had crossed the landmark £1M only eight years previously. Our annual drug budget now exceeds £30M. Drug costs and value for money are a major issue, with the suggestions that some new therapies may cost over £1m per patient! HER2-positive breast cancer patients now have a better outlook than HER-negative. The role of targeted drugs has expanded exponentially, with many new agents against a multitude of targets throughout Oncology.

Immunotherapy is also a promising “new” therapy. Basically, if the immune system recognises the cancer cells as foreign, then it will strive (usually unsuccessfully) to attack and kill the cancer cells. Immunotherapy aims to boost this reaction but with the risk that the patient may develop autoimmune disease causing potentially serious disease in organs such as pituitary, adrenal, liver, and colon. William Coley, a US Surgeon in the late 19th century, observed a patient with cancer who got infection, with a high fever. When he recovered from the infection the tumour had undergone “spontaneous”

regression. Coley postulated that the infection stimulated the immune system which then cleared the cancer. He sought to recreate this in the clinic. He developed an infected potion, modified to reduce the sepsis risk and injected his cancer patients with this “Coley’s toxin”. He did achieve high pyrexia, but with no antibiotics available there were some fatal infections. It caused cancer remission in some patients, but the infections were a major issue, especially when others were making the toxin, as effective quality control was lacking. “Coley’s toxin” was eventually abandoned, when more effective and safer options emerged.

Modern immunotherapy using interferon and interleukin-2 emerged in the 1990’s. These gave a broad-based boost to immune activity, causing significant acute toxicity with vascular leak syndrome. Long term remissions were achieved in 5-10% of patients but the acute toxicity, often requiring Intensive Care Unit input, was challenging. Current immunotherapy targets parts of the immune cascade and is more specifically geared towards cancer. It is less toxic and much more effective. Bulky metastatic malignant melanoma, which was almost universally fatal, now yields more than 50% long term complete remissions.

The buzz words now in Oncology are “personalised medicine”. This approach evaluates mutations in the patient’s germline and tumour DNA and targets therapy accordingly. Not every tumour can have a biopsy and the use of “liquid biopsy” where tumour DNA is harvested from peripheral blood is likely to help these patients. Before giving a patient capecitabine chemotherapy, we routinely test them for germline mutations in Dihydropyrimidine dehydrogenase (DPYD), as those mutations put patients at risk of severe toxicity from capecitabine. At the higher level tumour DNA mutation burden can be analysed to determine the likelihood of benefit from chemotherapy. The OncotypeDX gene panel is widely used to assess the likelihood of benefit from adjuvant chemotherapy in breast cancer, often sparing the patient futile and toxic therapy if benefit is unlikely to accrue. Many modern therapies are designed to be effective against specific mutations, and mutation screening can identify those most likely to benefit. The developmental challenge for molecular oncology is to identify, from all the mutations found in a tumour, those critical mutations to target for cure.

A word of caution is that patients can currently avail of commercial mutation testing of a panel of over 200 genes, costing up to £3,000. The interpre-

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tation of the results is particularly challenging, as a mutation which is important in one cancer site may have little importance in another. This is a major area for research. I see the future as involving mutation analysis of the patient and their tumour, thereby getting the personalised specific best and least toxic treatment cocktail for them, with the drug chosen based on mutational status, and not on the organ of origin of the cancer. If you want to delve deeper into the history of cancer, I strongly recommend “The Emperor of all maladies” by Siddhartha Mukherjee which gave me inspiration for this address.

When I entered Oncology in 1985, the 10-year survival rate for cancer in the United Kingdom was 25% and Oncology was not a “trendy” speciality. As a Medical Trainee in Altnagelvin Hospital, I stated my intention to enter Clinical Oncology training. A senior Consultant counselled “You have done well in postgraduate examinations, and you could change to a more interesting speciality”. To me my chosen speciality was the most interesting, given its exciting potential and I hoped to see a big boost in cancer outcomes in my career. Indeed, 10-year cancer survival has doubled to reach over 50% by 2020. Early diagnosis and screening played a large part in that as, by the time cancer has metastasised, options for cure are still somewhat limited.

I believe that the next generation will make huge strides through the molecular maze and, by the time they are getting back to their bicycle in 30 years, they will see the 10-year survival rate push above 85%. People with cancer will expect to be diagnosed early and cured unless they cannot have treatment due to other major medical illnesses or to frailty.

Clinical Oncology has been an exciting and rewarding career for me and there is much more excitement to come. I trust that the next generation will have as much satisfaction from Oncology as I have had, and that they will gain as much reward from changing the outlook for people with cancer.