

## Cancer Chemotherapy: An Annotated History

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Treating cancer with drugs is an ancient art, but it is from discoveries made during and after the Second World War that real clinical success with cancer chemotherapy has occurred. Human and veterinary cancer chemotherapy have coevolved in the context of fascinating historical, political, and scientific events created by equally fascinating individuals.

**Key words:** Cancer; Chemotherapy; Comparative; History.

The rich historical fabric of science and medicine has been well described in books, manuscripts, classical art, and film. Many fascinating individuals, stories, and events have made small or highly significant contributions to cancer therapy that have culminated in the present standard of care for human and veterinary medicine. Rarely acknowledged are contributions of the cancer patients themselves who willingly submit to randomization in experimental trials and who often have only 2 goals: The first, of course, is to recover and the second is to help someone else by offering themselves as a data point.

It is not my intention to describe and catalog every relevant discovery, every insight of genius, or to chronicle the years of careful scientific investigations of different tumor types or drug category. It is also not my purpose to present the history of any specific drug, although some of them are fascinating and all of them have a story. Finally, it is not my intention to review the entire history of medicine.

My purpose is to introduce a small number of historical figures and events that played a significant role the history of cancer chemotherapy and to present them in the context of their contemporary times. Veterinary cancer chemotherapy has coevolved with human cancer chemotherapy and consequently the larger story is also our story.

### The First 5000 Years

“Those about to study medicine, and the younger physicians, should light their torches at the fires of the ancients.” Baron Carl von Rokitansky (1804–1878), a Bohemian physician and pathologist offered that advice more than a century ago.<sup>1</sup> Like medicine in general, chemotherapy for diseases including cancer is an ancient art. All early drugs were derived from mineral or animal sources, or from plants whose leaves, stems, bark, or roots were used for medicinal purposes.

The earliest written accounts of cancer recognition and treatment were recorded 50 centuries ago by Egyptian physicians. Two of the most famous written sources of ancient Egyptian medicine are known as the Ebers Papyrus and the Edwin Smith Papyrus. Both papyri have unique histories and give hints at the understanding of cancer circa 1600–3000 BC.<sup>1–6</sup>

The Edwin Smith Papyrus is a 5-m-long surviving fragment of a larger ancient Egyptian textbook consisting of 48, primarily surgical, case histories (mostly addressing trauma and wounds inflicted by war).<sup>2,3,5</sup> It is named for an American expatriate farmer at Luxor near Thebes, Egypt, who bought it from an antiquities dealer in 1862. This papyrus records the earliest mention of breast cancer (tumors or ulcers of the breast in 8 individuals).<sup>5</sup> Although Smith realized that the document was probably important, he never fully translated or published it. The historian and archeologist James Henry Breasted, acting on behalf of the New York Historical Society, finished translating it in 1930.<sup>2,3</sup> The document was bequeathed to his daughter after his death in 1935 and she gave it to the Society, where it remains.

The Ebers Papyrus is a much larger scroll of medical information being 20 m long and contains almost 900 medical formulae and an additional 400 descriptions of drugs.<sup>1,4,5</sup> It is chiefly an internal medicine resource, but also is a good reference on ophthalmology, dermatology, and gynecology. It contains descriptions of uterine cancer and breast cancer and treatment with surgery and cautery with a gruesome sounding device called a fire drill.<sup>1,4,5</sup> This papyrus is named for Georg Moritz Ebers, a German Egyptologist who bought it from Edwin Smith during the winter of 1873–1874 and who first had it translated in 1890.<sup>3</sup> This papyrus now is held in the collection of the University of Leipzig.

In much of early recorded medical history, ideas for treatment of cancer emanated from contemporary ideas of what caused cancer. Hippocrates (ca. 460–370 BC), the father of medicine, established the belief that an excess of black bile caused cancer.<sup>5,7–9</sup> He also is credited with substituting the black bile theory for vengeance of the gods as the cause of cancer, thus ending the role of heavenly retribution for sin in individuals who develop tumors. It is clear from his writings that Hippocrates was familiar with cancer because he described different cancers affecting the skin, breast, stomach, cervix, and rectum.<sup>5</sup> The Hippocratic view of the cause of cancer held for the next 19 centuries. The approach to cancer treatment over these long centuries was static and consisted of surgery, cautery, caustic pastes, blood-letting,

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and mineral and herbal medicines, but was dominated by the certainty that those individuals with malignant tumors were without hope.<sup>5,8,9</sup>

However, not all ancient ideas and practices were totally unfounded by modern standards. Some of the compounds used by physicians during ancient times were derived from natural sources that are the same as for compounds developed in the 1950s and 1960s and that are used in modern cancer chemotherapy. For example, in the 1st century AD, Dioscorides, a Greek physician, pharmacologist, and botanist, used a drug made from the autumn crocus plant (*Colchicum autumnale*) that was soaked in wine and used to dissolve tumors and growths “not yet making pus.”<sup>10</sup> The autumn crocus plant was the same plant investigated by the Belgium physician Albert Pierre Dustin as an antitumor agent (colchicine) in 1938 that ultimately led to the discovery of other drugs that inhibit microtubule assembly during mitosis. Dioscorides lists other plants of the genus *Vinca* (later the genus *Catharanthus*) as likely to have antitumor activity, and as we know today drugs derived from them (vincristine and vinblastine) are constituents of many cancer chemotherapy protocols.<sup>a,10–12</sup>

Ancient and medieval physicians used a variety of terms to describe tumors. Hippocrates noted crab leg-like extensions emanating from tumors (probably breast cancers) in some patients and coined the term “carcinosis” in a medical context, which is Greek for crab.<sup>5</sup> The Roman physician Celsus later translated the Greek term *carcinosis* to Latin and the modern word “cancer” was applied to malignancies.<sup>b,5</sup> Celsus also introduced the term *carcinoma* into the Latin language.<sup>5</sup> Galen (129–210 AD), another Roman and the personal physician to Emperor Marcus Aurelius, is a figure of great historical significance to medicine. Galen used the Greek word for swelling (*onkos*) to describe tumors.<sup>5</sup> Obviously these terms and derivations of them are still with us today.

Nonwestern cultures contributed enormously to medicine in general and to cancer medicine specifically. One of the most famous medical textbooks in history is *The Canon of Medicine*. This title is a translation from the Arabic title *Al-Qanun fi al-Tibb* (The Law of Medicine) that was written by the Persian scientist and physician Ibn Sīnā (in the West known as Avicenna).<sup>4,5,8–10,13</sup> He described how cancers progressively increase in size and invade and destroy contiguous tissues.<sup>5</sup> Ibn Sīnā combined his own experiences with the writings of Galen and others to produce the most influential and long-lasting medical opinions since Hippocrates. The Canon of Medicine was translated into many languages and became the basis for medical practice throughout the Islamic world, the Indian subcontinent, Europe, and Asia and remained a respected resource in Europe and the Islamic world through the early 19th century. It has large sections of text devoted to plant sources and compounding of drugs for many purposes. Both Galen and Ibn Sīnā carefully described malignant tumors in patients, and Galen in particular regarded patients as incurable once a diagnosis of cancer was made.<sup>5,8</sup> Galen’s views on the incurability of malignant cancer persisted well into the mid-1900s.

From the time of Hippocrates, through the medieval period and the Dark and Middle Ages in Europe, the practice of medicine and the understanding of cancer changed very little. The use of surgery, cautery, herbal medications, caustic pastes, and blood-letting persisted with little to no innovation, and represented almost 2000 years of relative medical stagnation.<sup>5,8</sup> It was a time when human beings endured more from endless wars, malnutrition, famine, and infectious diseases that episodically devastated the populations of continents than from cancers that killed individuals. Nevertheless, medical knowledge did coevolve with advances in contemporary technology, and a new understanding of medicine and cancer medicine emerged.

The Renaissance in Europe brought more to the world than legendary art and literature. Science and art were now intertwined. Leonardo Di Vinci made more than 700 detailed anatomical sketches based on dissection. William Harvey defined the fundamentals of circulation. Anton van Leeuwenhoek viewed living cells with a light microscope and began to reveal the submacro world of life. Gaspare Aselli, an Italian physician, discovered the lymphatic system that led to speculation, and later acceptance, that this newly identified vascular network played a role in the spread of cancer. The Renaissance was also the age of Galileo, Sir Thomas More, the Medici family, Marlowe, Shakespeare, Copernicus, Hooke, and thousands of others who advanced Western civilization. The Renaissance made possible and set the stage for the Age of Discovery, which defined, explored, and enlarged the known world. Perhaps the most important achievement of all from the Renaissance was the evolution of the scientific method, a process of thought that changed forever how the human mind would approach science. In a very real sense, the establishment of the scientific method during the Renaissance was the Big Bang of the modern world.

## The Last 200 Years

Cancer chemotherapy did not advance in a scientific and medical vacuum. Science and technology had advanced enormously in the centuries since Hippocrates, Galen, Dioscorides, Celsus, and Ibn Sīnā made their marks on medical history. At any given moment in history, technology and strategies for new cancer treatments reflected the entire scientific and social contemporary world. For example, the 1st hospital devoted exclusively to the care of cancer patients was opened in Rheims, France, in 1740.<sup>5</sup> It was a small hospital with an initial bed complement of 12. At that time, cancer was believed to be contagious and fear of infection was so great that by 1779, the inhabitants of Rheims succeeded in having the cancer patients transferred out of the city to a new hospital under construction named the Hôpital Saint Louis.<sup>5</sup> The 1st hospital to be used exclusively by cancer patients in the United Kingdom opened in London in 1851.<sup>5</sup> This hospital was typical of the times and primarily offered surgery and later radiation-based treatments. For most of the subsequent 150 years, cancer treatment continued to be dominated by surgery and

radiation therapy.<sup>14</sup> Only relatively recently has cancer chemotherapy become established as a legitimate tool of modern medicine.

Advances in cancer chemotherapy sometimes followed advances in chemotherapy for infectious diseases. In 1796, the English physician Thomas Fowler used an arsenic solution to treat a number of maladies, including fevers, malaria, and headaches. To be sure, the use of arsenic for medicinal purposes originated in ancient times, but Fowler appears to be the historical pivot point because his mixture of arsenic trioxide and potassium bicarbonate had become known as “Fowler’s Solution” and became the standard of care in medical practice for many ailments.<sup>15</sup> In 1865, the German neurologist Heinrich Lissauer used Fowler’s Solution to treat human leukemia and a few years later lymphoma.<sup>15</sup> This approach to cancer treatment was not new at all. The use of arsenic for cancer therapy had been described in an ancient Indian medical text that was based on Ibn Sīnā’s writings.<sup>4,15</sup> It appears that Lissauer rediscovered the ancient approach or independently arrived at it. Fowler’s Solution as treatment for leukemia persisted up until the 1930s, when its use for leukemia began to decline.<sup>15</sup> Of great interest is the fact that reports of a high proportion of hematologic responses in patients with acute promyelocytic leukemia who were treated with arsenic trioxide in China led to FDA-approved randomized clinical trials of arsenic trioxide for relapsed or refractory acute promyelocytic leukemia in the United States in 2000.<sup>15</sup> Arsenic trioxide is now considered a first-line treatment for promyelocytic leukemia.<sup>16</sup> This torch was clearly lit by the fires of the ancients.

Meanwhile, by 1763, France had lost its wilderness empire in North America and 13 English colonies, arranged north to south along the coastline of the ocean that separated the new from the old world, formed an independent nation. John Adams, the 2nd President of the United States, signed legislation in 1798 that established the Marine Hospital Service for the “relief of sick and disabled seamen.” The Marine Hospital Service evolved over the next 139 years into the National Institutes of Health (NIH).<sup>17</sup>

Rudolph Virchow (1821–1902), one of the giant figures in medical history and now regarded as the “Father of Pathology,” also contributed to the understanding of cancer that made subsequent chemotherapy developments possible.<sup>5,8</sup> Capitalizing on the work of Theodore Schwann,<sup>c</sup> Robert Remak,<sup>d</sup> Francois-Vincent Raspail,<sup>e</sup> and others, Virchow helped advance what became known as the cell theory, a proposition that all life is composed similar cellular units and that all living cells are derived from the division of a preexisting living cell like it (*Ominis cellula e cellula*).<sup>5,8,18,19</sup> Virchow introduced the terms leukocytosis and leukemia as the designations for increases in what he called “the colorless corpuscles of the blood” while at the same time realizing that they represented distinctly different disease processes.<sup>20</sup>

Paul Ehrlich (1854–1915) was a German physician who was very interested in infectious diseases, but only peripherally interested in cancer. Ehrlich coined the

terms “chemotherapy” and “magic bullets” saying famously: “We must search for magic bullets. We must strike the parasites and the parasites only, if possible, and to do this we must learn to aim with chemical substances.”<sup>5,8,14</sup> He was one of the earliest pioneers in using animals to screen chemicals for use in treating disease. In 1908 Ehrlich used a rabbit model for syphilis that led to routine treatment of this affliction with arsenicals.<sup>12</sup> Ehrlich is known as the “Father of Chemotherapy.”<sup>5,8,14</sup> He died in 1915 having lived just long enough to see his country be the first to use poison gas on the battlefield (Ypres,<sup>f</sup> Belgium), an event upon which the era of modern chemotherapy is founded.

Despite The Hague Conventions of 1899 outlawing the use of poison gas in war, in April 1915 Canadian and French colonial Moroccan and Algerian troops fighting in the 2nd battle of Ypres experienced the effects of 5,700 chlorine gas cylinders (168 tons of chemical) released into their ranks by German troops.<sup>g,21</sup> Chlorine gas was quickly supplanted by mustard sulfur gas that was subsequently used by both sides and made the front an even more barbaric abattoir. Postwar estimates place the number of gas exposures during the Great War at 1.2 million, with 91,000 acute deaths.<sup>21</sup> From all of these casualties, 75 autopsies were performed that indicated that mustard gas exposure could cause severe lymphoid depletion, bone marrow aplasia, and neutropenia.<sup>22</sup> The pathological changes associated with mustard gas exposure were noted, but it took until 1935 before the notion would be advanced of using mustard compounds therapeutically.<sup>14</sup>

In addition to the Great War, the first 4 decades of the 20th century saw significant development in the sophistication and use of animal models in medical research. Society also was changing (Figs 1–3). Building on Ehrlich’s work, the 1st transplantable tumor systems in rodents were developed by Dr George Clowes while at the Roswell Park Memorial Institute, Buffalo, NY.<sup>14</sup> This was a significant achievement because it standardized model systems and allowed for the testing of a large number of chemicals. Much effort over several decades was devoted to developing and identifying the ideal model system in which to study cancer.<sup>14</sup> Most early 20th century physicians treating cancer still relied on surgery and radiation, while some still embraced ancient homeopathic approaches such as treating breast cancer with *Conium* (hemlock), *Phytolacca* (polkweed), *Lycopodium* (clubmoss), and silica, or intestinal cancer with *Ornithogalum umbel* (star of Bethlehem).<sup>14,23</sup>

The years between the Great War and the even greater war yet to come saw the Office of Cancer Investigations of the United States Public Health Service combined with the NIH Laboratory of Pharmacology to become the National Cancer Institute (NCI) in 1937.<sup>14</sup> In the same year, Furth and Kahn<sup>24</sup> published a manuscript describing the transmission of leukemia in mice from a single implanted cell that resulted in the death of the recipient thus echoing Ehrlich’s and Raspail’s *Ominis cellula e cellula*.

Years of research with sulfa mustard followed after the Great War. Yale University studies by Drs Alfred

1920 – The manufacture, sale, transport, importation, or exportation of intoxicating liquors becomes illegal in the United States, starting the era of Prohibition and the Roaring Twenties.  
 1922 – Howard Carter discovers the tomb of the Pharaoh Tutankhamen. The Lincoln Memorial in Washington, DC, is dedicated.  
 1923 – Adolph Hitler is jailed after a failed coup attempt and writes *Mein Kampf*. Clarence Birdseye invents frozen foods with a special quick-freezing process.  
 1924 – The first Winter Olympic Games are held in Chamonix, France. The trial of John T. Scopes for teaching Charles Darwin's theories of evolution begins in Tennessee because it violates state law. He is convicted and fined \$100.  
 1925 – The Grand Ole Opry transmits its first radio broadcast.  
 1926 – Robert Goddard experiments with liquid-fueled rockets. Pilots Floyd Bennett and Richard Byrd become the first humans to fly to the North Pole and return.  
 1927 – Babe Ruth hits 60 home runs in a single season of baseball. Al Jolson stars in the first of the talking picture films, *The Jazz Singer*.  
 1928 – The animated film *Steamboat Willie* is released by Walt Disney and begins an entertainment empire built on a mouse.  
 1929 – Wall Street collapses and starts the Great Depression, the car radio is invented, and the St. Valentine's Day Massacre transpires in Chicago.

**Fig 1.** Other events of the 1920s.

Gilman and Louis Goodman, funded by the US Office of Scientific Research and Development (US OSRD),<sup>h</sup> found that nitrogen mustard (in which a nitrogen atom was substituted for a sulfur atom on mustard gas) had antitumor activity against murine lymphoma.<sup>14,25,26</sup> Nitrogen mustard had activity similar to the parent compound but with less toxicity. The 1st recorded treatment of human cancer with a mustard compound occurred in 1943 in a patient with non-Hodgkin's lymphoma and severe airway obstruction.<sup>14,25,26</sup> The patient was under the care of a thoracic surgeon at Yale named Gustaf Lindskog. Convinced that their work with mice could be translated to help this individual, Goodman and Gilman persuaded Lindskog to administer nitrogen mustard to his patient. Marked, but temporary, regression was observed in this and other lymphoma patients.<sup>14,25,26</sup> Wartime secrecy associated with the war gas program precluded publication of these case reports until 1946.<sup>25</sup> It took another gas catastrophe during the Second World War to bring the Yale work into sharp focus for the medical community and launch the era of modern chemotherapy.

Poison gases were not used during the Second World War, but there was a real fear that as the Allies turned the fortunes of war against the Axis powers Germany might be tempted to again resort to these horrible weapons.<sup>21</sup> Although outlawed by the Geneva Gas Protocol of 1925, all the major powers involved in the European conflict had vigorous research and production programs on gas warfare or accepted gas supplies from their allies.<sup>i,21</sup> No one, but especially Eisenhower and Churchill, wanted to

be unprepared in the event that a desperate enemy would use gas first.

By late 1943, the Allies had pushed the Wehrmacht forces from North Africa and Sicily and were now slowly advancing up the Italian peninsula. The Italian town of Bari fell into Allied hands and was used as a staging area because of its superb harbor on the Adriatic coast. On December 2, 1943, the harbor was stuffed with allied shipping that was being unloaded day and night to supply the enormous material needs of an army at war. In the early evening of that day, a flight of 105 German bombers struck Bari. The raid was devastating, and 15 ships were sunk and another 8 were severely damaged. One ship, the SS John Harvey<sup>j</sup> vaporized in 1 massive explosion that killed everyone on board and produced a shock wave that literally knocked observers over at a distance of 5 miles. The John Harvey was carrying a secret cargo of 100 tons of liquid mustard gas and millions of gallons of gasoline.<sup>21,27</sup> Many seamen on surrounding ships who survived the initial blast found themselves swimming in the harbor, which was now a highly deadly mix of fuel oil and liquid mustard gas that coated their clothing and exposed skin. An American physician named Stewart Francis Alexander realized that mustard gas was responsible for the blistering of epithelial surfaces that was exacerbated by medical responders who wrapped survivors in blankets.<sup>21,27</sup> This mustard gas exposure in the Second World War was officially suppressed to the extent possible. American and British leadership immediately imposed an information blackout and news censorship fearing a negative public

1930 – United States Census:  
 The population is 123,188,000 in 48 states.  
 Life expectancy for males was 58.1 years and for females 61.6 years.  
 Average annual salary was \$1368.00.  
 Unemployment was 25%.  
 There were 21 lynchings.  
 1931 – Japan invades Manchuria and 2 years later walks out of the League of Nations.  
 1932 – Franklin Delano Roosevelt elected 32<sup>nd</sup> President of the United States.  
 1935 – Social Security Act passed by Congress and Elvis Presley is born to Vernon and Gladys Presley in Tupelo, MS.  
 1939 – Germany invades Poland, starting the Second World War in Europe.

**Fig 2.** Other events of the 1930s.

- 1940 – United States Census:  
Population of the United States reaches 132,122,000 in 48 states.
- 1941 – Aaron Copeland composes *Rodeo* and *Fanfare for the Common Man*.
- 1944 – Glenn Miller, musician and composer, at age 40 dies when his plane disappears over the English Channel on his way to give a concert for Allied troops who had recently liberated Paris.
- 1945 – The Atomic Age is born and brings the war in the Pacific to an end.
- 1947 – *Kukla, Fran, and Ollie*, the first television program produced specifically for children, is broadcast from Chicago. After 2 years in the minor leagues, Jackie Robinson breaks the color barrier by playing major league baseball for the Brooklyn Dodgers.
- 1948 – The Berlin Airlift begins.

**Fig 3.** Other events of the 1940s.

reaction to possessing poison gas and also fearing retaliation with gas by the enemy. Churchill ordered that mustard gas burns on surviving British seamen be recorded as “dermatitis” or “due to enemy action.”<sup>21,27</sup> Keeping a disaster that resulted in thousands of casualties secret was impossible.<sup>k</sup> Finally, in April 1945, a press release told of a massive blast of unknown cause occurring in an unidentified American liberty ship that was loaded with munitions in Bari, Italy, but it gave no date or details of the event. In his postwar memoir *Crusade in Europe*, Eisenhower fails to mention that gas was present at the Bari disaster.<sup>21</sup>

By 1946, the medical world was informed that the 1st modern chemotherapy agent, nitrogen mustard, had been developed, and additional drugs derived from nitrogen mustard followed (Fig 4).<sup>25</sup> Parallel developments during the Second World War led to the creation of antifolate compounds (methotrexate) that in 1948 produced temporary, but definite remissions in childhood leukemia.<sup>14,28</sup> Actinomycin D came out of US OSRD programs searching for antibiotics and was found to have antitumor activity. It was heavily used in pediatric tumors in the 1950s and 1960s and later in veterinary patients. The early postwar years also saw the development of the thiopurines (6-mercaptopurine and 6-thioguanine) that were used for acute leukemia and also have been used as immunosuppressive agents.<sup>14</sup>

In the immediate postwar years, most drug development efforts, before the NCI became involved, took place at large centers like the Sloan-Kettering Institute (later known as Memorial Sloan-Kettering Cancer Center [MSKCC]) in New York City, the Chester Beatty Research Institute in London, the Southern Research Institute in Birmingham, Alabama, and the Children’s Cancer Research Foundation in Boston.<sup>14</sup> The largest of these drug development programs was at the Sloan-Kettering Institute and was led by Dr Cornelius Rhoads, who, with almost all of his staff, had served in the Chem-

Mechlorethamine HCL  
Cyclophosphamide  
Ifosfamide  
Chlorambucil  
Melphalan

**Fig 4.** Drugs derived from mustard compounds.

ical Warfare Service during the war. All of these centers used easily transplantable mouse models to screen numerous compounds for antitumor activity.<sup>14</sup>

Despite the Korean and Cold Wars, the 1950s were a time of great American confidence, optimism, and world leadership, but also societal tensions (Fig 5). Confidence and optimism were not, however, prevalent among those who hoped to treat and cure cancer with drugs. Although drugs like the nitrogen mustards could produce impressive remissions, they were short and/or incomplete. Corticosteroids and 5-fluorouracil were introduced in the 1950s and found use in cancer patients, but remissions were short and serious questions about their usefulness were asked. Physicians who prescribed drugs to treat cancer frequently suffered professional ridicule and were ostracized by the powerful of the medical establishment.<sup>14</sup> The drugs they used were routinely referred to as poisons and their use was routinely and openly discouraged. However, a much-needed boost to the morale of those who believed in the potential of chemotherapy for cancer came in 1958 when Hertz and Li used methotrexate to treat choriocarcinoma, a germ cell malignancy that originates in trophoblastic cells of the placenta.<sup>14</sup> This seminal event marked the moment in history when the 1st solid tumor in humans was cured by drug therapy alone.

During the 1950s, a fascinating, wealthy, and politically well-connected woman named Mary Woodward Lasker<sup>1</sup> began to work behind the scenes with her ally Dr Sidney Farber<sup>m</sup> whose data on childhood leukemia treatment with aminopterin and amethopterin (later to be known as methotrexate) had impressed her.<sup>14,28,29</sup> Among her 1st activities was to join and then remake the American Society for the Control of Cancer (ASCC) into an efficient, fund-raising machine based on a business model of advertising, publicity, and promoting the idea of a “cure” by sponsoring cancer research.<sup>14,29</sup> Almost 2000 years after Galen, the idea of curing malignant cancer was suddenly starting to be considered not only possible, but attainable. The ASCC quickly grew into the potent force we know today as the American Cancer Society (ACS) with Mary Lasker having transformed the ASCC with an annual budget of about US\$100,000 into the ACS with a multimillion dollar annual budget.<sup>14,29</sup> By 1948, the ACS was raising US\$14 million annually with 25% of that amount devoted to research.<sup>29</sup> In 1954–1955, Lasker and her political allies persuaded the Appropriations Committee of the US Senate to fund the development of the Cancer

1950 – North Korea invades South Korea.  
 1953 – Julius and Ethel Rosenberg are executed for atomic espionage and the Korean peninsula sees a truce after more than a million casualties on all sides. Senator Joseph McCarthy of Wisconsin holds hearings on communists in the US Army. Televised hearings the following year turn public opinion against him and he is censured by the Senate. James Dewey Watson and Francis Harry Compton Crick correctly interpret the data of Rosalind Franklin and propose the structure of DNA to be that of a double helix.  
 1955 – Rosa Parks decided not to give up her seat in the front of the bus in Montgomery, AL. Dr. Jonas Salk invents the first vaccine for polio.  
 1956 – Elvis Presley gains a national audience with his appearance on the Ed Sullivan Show.  
 1958 – National Airlines starts the first commercial jet passenger service in North America (Miami to New York City). National Airlines merged with Pan American Airlines in 1980.  
 1959 – Hawaii and Alaska become the 49<sup>th</sup> and 50<sup>th</sup> states. Barbie dolls are introduced by the Mattel Toy Company.

**Fig 5.** Other events of the 1950s.

Chemotherapy National Service Center (CCNSC) within the NCI.<sup>14,29</sup>

Among the initial decisions made by the CCNSC was to set up a Cancer Chemotherapy National Committee that included representation by the ACS.<sup>14</sup> This committee established a series of panels to address each of the major questions associated with cancer drug development. One of the successes of this program occurred in 1955 when the Eastern Solid Tumor Group that later became known as the Eastern Cooperative Oncology Group was established as one of the first cooperative groups launched to perform multicenter cancer clinical trials.<sup>14</sup> This concept would serve as the model for the establishment of the highly successful Veterinary Cooperative Oncology Group in 1984.

Mary Lasker and Sidney Farber and their political allies were a genuine political force. It was their mutual belief that cancer was not insurmountable and that medical science was not impotent to cure cancer that bound Sidney Farber and Mary Lasker in common purpose. Their lobbying campaign helped the NIH budget grow from US\$1.57 million to US\$460 million in the 15 years between 1946 and 1961.<sup>14,29</sup> They continued their activism and took advantage of their many political contacts to encourage ever-increasing funding for the NCI, which by 1957 was devoting half of its annual budget to testing of potential chemotherapy drugs. In the decade between 1957 and 1967, NCI funding increased from US\$48 million to US\$176 million.<sup>29</sup>

Mary Lasker was devoted to the idea of curing cancer. Her often-quoted remark, “I am opposed to heart attacks and cancer and strokes the way I am opposed to sin,” gives a sense of her.<sup>29,30</sup> Mary and her husband Albert Lasker established the prestigious Lasker Prize through their foundation that has celebrated and highlighted biomedical advances for more than 50 years.<sup>29–33</sup> Her activism was criticized and belittled by some scientists as “Mary Lasker’s war” out of a concern that she was promising more than science could, at that time, deliver.<sup>14,29</sup> However, she remained highly influential politically, using her contacts to help ensure the passage of the National Cancer Act of 1971 (the national “war on cancer”).<sup>14,29</sup> Although the majority of federal money for this “war on cancer” went to investigator-initiated research projects, substantial funding was available

to expand the Developmental Therapeutics Program that screened drugs for anticancer activity and developed new screening systems.<sup>14</sup> Transplantable mouse systems were abandoned as the primary screening method in favor of a panel of tumors, human xenografts in nude mice matched to transplanted animal tumors of the same tissue that were instead found to be more useful.<sup>14</sup> The idea was to test and compare in vivo the efficacy of human xenografts and murine transplanted tumors in predicting anticancer activity in humans.<sup>14</sup> This approach identified the taxanes as having antitumor effects. The 1st taxane drug, paclitaxel (Taxol) entered clinical trials in 1984 and was soon found to be very useful for human ovarian cancer, breast cancer, lung cancer, and AIDs-related Kaposi’s sarcoma among others.<sup>14</sup>

Throughout the early stages of Mary Lasker’s activism for a cure for cancer there was real debate among physicians as to whether cancer drugs caused more harm than good. The specialty of medical oncology did not yet exist, and cancer chemotherapy drugs frequently were regarded as “poisons” that were administered only by the “lunatic fringe.”<sup>14</sup> Nevertheless, progress was slowly being made, and the early 1960s saw the introduction of the vinca alkaloids (vincristine, vinblastine) by the Eli Lilly Company and also the introduction of procarbazine.<sup>11,14,34,35</sup> During these years, virtually all human cancer chemotherapy was with single agents.<sup>14</sup>

The concept of combination chemotherapy would not arrive until the end of the 1960s, a decade that was marked by political assassinations, deepening United States military involvement in Vietnam, and a human footprint on the moon (Fig 6). By the late 1960s, clinical success with combination chemotherapy had accumulated, beginning with treatment of acute lymphocytic leukemia in children using “VAMP” (vincristine, methotrexate, 6-mercaptopurine, and prednisone), which increased the remission rate from 25 to 60%, with 50% of the remissions being long enough to be considered “cures.”<sup>14</sup> Non-Hodgkin’s lymphoma was being treated with MOMP (melphalan, methotrexate, vincristine, and prednisone) and MOPP, which substituted procarbazine for methotrexate.<sup>14</sup> These protocols took the complete remission rate for non-Hodgkin’s lymphoma from near zero to 80%, with about 60% of those patients achieving a complete remission in the original MOPP study, never

1960 – John Fitzgerald Kennedy is elected the 35<sup>th</sup> President of the United States.  
 1961 – Harper Lee publishes *To Kill A Mockingbird*.  
 1962 – Cuban exiles with backing from the Central Intelligence Agency attempt to overthrow Fidel Castro and invade Cuba at the Bay of Pigs. In October an international crisis over Soviet ballistic missiles in Cuba comes to a head and a potentially catastrophic military clash between the East and West is averted as much by luck as by diplomacy.  
 1963 – John Fitzgerald Kennedy is assassinated in Dallas, Texas.  
 1964 – The United States Surgeon General declares that smoking is a health hazard and within a year all cigarettes sold in the United States require a health warning label. The Beatles appear on the Ed Sullivan Show and forever change popular culture. W.F.H. Jarrett leads a team that discovers the feline leukemia virus (FeLV).  
 1965 – US ground troops are committed in large numbers to the war in South Vietnam.  
 1966 – Nehru jackets become popular.  
 1968 – Dr Martin Luther King, a man who had been awarded the Nobel Prize for Peace and devoted his life to nonviolent protest, is killed in Memphis, Tennessee. Robert Francis Kennedy is murdered moments after declaring victory in the California primary for the nomination of the Democratic Party for President of the United States.  
 1969 – NASA puts men on the moon at Tranquility Base and Woodstock happens in upstate New York.

**Fig 6.** Other events of the 1960s.

relapsing (40 years plus of follow-up).<sup>14</sup> Supportive medical care also was growing in sophistication and contributed to increased survival.

Furth and Kahn<sup>24</sup> had demonstrated that the implantation of a single leukemic cell was sufficient to result in fatal illness in a mouse. In 1964, Dr Howard Skipper, a mathematical biologist at the Southern Research Institute, and associates suggested that it was therefore necessary to kill every single leukemia cell because even 1 surviving cancer cell was sufficient for a fatal recrudescence.<sup>35–37</sup> Skipper suggested a hypothesis known as the “cell kill” hypothesis (sometimes known as the “log kill” hypothesis) that stated that a given dose of a drug killed a constant fraction of the tumor cells rather than a constant number.<sup>35–37</sup> Success therefore would depend on the number of cells present at the beginning of each treatment. For example, if a dose of drug reduces the cancer cell population from  $10^7$  to  $10^6$  cells, the same dose would be required to reduce a cancer cell population of  $10^5$  to  $10^4$  cells. Skipper’s ideas were highly influential and they led to the more aggressive use of chemotherapy and the combining of drugs in a series of cyclical treatments.<sup>35</sup>

The successes of the 1960s and 1970s led to the more routine use of chemotherapy in earlier stages of cancer and as an adjunct to surgery, radiation therapy, or both.<sup>14</sup> The cell kill hypothesis and the inverse relationship between cancer cell numbers and survival suggested that adjuvant chemotherapy might only work in the context of microscopic, remnant disease. Chemotherapy as an adjuvant to surgery has been proven to be very beneficial for patients with diseases such as human breast cancer and colorectal cancer.<sup>14</sup>

The 1970s brought further evolution in the theory and practice of cancer chemotherapy and a far greater acceptance of its legitimacy as a tool for treating cancer. The 1970s also were a time of profound political and social anxiety (Fig 7). The specialty of medical oncology as a subspecialty of internal medicine was established in 1973. New and more effective antimicrobials became available, platelets could be harvested and transfused to prevent bleeding, and many medical advances in surgery, radiation therapy, and immunotherapy were contributing to prolonged survival of cancer patients. In 1975, the 1st reports of cure of advanced diffuse large B-cell lymphoma

1970 – United States Census:  
 Population is 204,870,000.  
 Milk costs \$0.33/quart.  
 Bread costs \$0.24/loaf.  
 1970 – Four college students are shot dead by Ohio National Guardsmen at Kent State University.  
 1971 – John Fowles writes the *French Lieutenant’s Woman* and Dr Judah Folkman proposes the hypothesis that tumors are angiogenesis dependent.  
 1972 – Eleven Israeli athletes are murdered at the Munich Olympics by Palestinian terrorists. The entire tragic drama is broadcast live on television.  
 1973 – Recombinant DNA technology becomes available and Vice President Spiro Agnew resigns his office over charges of tax fraud, bribery, extortion, and conspiracy.  
 1974 – The first use of a commercial barcode scanner occurs in a Marsh supermarket in Troy, Ohio, and Richard Nixon resigns as 37<sup>th</sup> President of the United States.  
 1978 – Louise Brown, the first human being to be conceived in a test tube, is born.  
 1979 – Alex Haley publishes *Roots*, the bestselling biography of his family, a nuclear reactor at Three Mile Island, Pennsylvania, melts down, and the US Embassy in Iran is taken over by militant students during the Iranian Revolution.

**Fig 7.** Other events in the 1970s.

1980 – Mt St. Helens erupts in Washington State.  
 1981 – The space shuttle Columbia is launched from the Kennedy Space Center in Florida, becoming the first spaceship to land on planet earth (really). Sandra Day O'Connor becomes the first woman to serve on the Supreme Court.  
 1982 – *Gandhi* is voted best motion picture film.  
 1983 – Researchers at the Pasteur Institute in France isolate a new virus they suspect is responsible for acquired immunodeficiency syndrome (AIDS) occurring predominantly in gay men. Sally Ride becomes the first American woman in space.  
 1984 – Peter Ueberroth is voted Man of the Year for his successful planning of the Olympic Games in Los Angeles.  
 1985 – Oceanographer Robert Ballard finds the HMS Titanic wreck site.  
 1986 – The nuclear disaster at Chernobyl, Ukraine, USSR kills 56 people directly with an estimated additional 4,000 deaths from exposure to fallout.  
 1987 – Dr. Niels Pederson leads a team that publishes the first report of what became known as the feline immunodeficiency virus (FIV) that had been isolated from a cattery in California the previous year.  
 1988 – Pan Am flight 103 is deliberately bombed over Lockerbie, Scotland, killing 259 passengers and 11 residents of the town. Pan Am dissolves as a company in 1991.  
 1989 – The Berlin Wall falls and Germany is reunited, effectively ending one of the last territorial constructs remaining from the Second World War.

**Fig 8.** Other events of the 1980s.

with C-MOPP (cyclophosphamide substituted for nitrogen mustard) was reported.<sup>14</sup>

In 1976, Norton and Simon published the Gompertzian view of tumor growth.<sup>n,38,39</sup> Their mathematical model was used to create new approaches to chemotherapy in which it was proposed that small tumors grow faster than large ones and that the rate of cell killing is proportional to the rate of growth. Therefore, smaller tumors are more easily killed than larger tumors and tumors given less time between treatments are more likely to be destroyed. The Norton-Simon hypothesis was fundamentally different than the log kill hypothesis. Their view of tumor growth led to the idea of high-density dosing that improved survival in many patients.<sup>38</sup>

In 1979, Goldie and Coldman published another influential model of tumor growth and response to chemotherapy. Their model predicted that within a tumor cell population, mutations to a resistant phenotype occur spontaneously and at a constant rate, and that the probability for resistant clones depends on the tumor cell population size and the mutation rate, and that even the smallest tumor will have at least 1 drug-resistant clone.<sup>35,40,41</sup> Because of these predictions, they advocated a strategy of using all effective drugs having differing mechanisms of action simultaneously. Toxicity associated with combining all effective drugs simultaneously precludes this approach, so alternative

approaches evolved from their ideas in which 2 programs of a smaller number of effective drugs were used in alternating cycles and starting as soon as practical.<sup>40,41</sup> Although they used 2 drug models, their work became the basis for many of the current multidrug alternating protocols used today.

The sophistication of cancer medicine and chemotherapy accelerated during the 1980s and 1990s amid human triumphs and catastrophes (Figs 8 and 9). In 1986, Roger Day addressed treatment sequencing in chemotherapy protocols with a unique view of the issue.<sup>41</sup> Day is a biostatistician who relaxed the rigid symmetrical assumptions of Goldie and Coldman. He realized and assumed that within a given tumor cell population there would be cells of differing sensitivity to any drug(s). His idea, which became known as “Days Worst Drug Rule,” was if 2 drugs were effective against a tumor, and one was more effective than the other, one should use the least effective drug first. Day’s hypothesis was that, by using the least effective drug first, survival would be improved by controlling the cells that were resistant to the more effective drug.<sup>41</sup> The clinical application of this model requires that one can actually predict a better and a worse drug. This usually is not possible. It also means that the distinction between induction and maintenance found in some chemotherapy protocols is artificial and counterproductive.<sup>41</sup> Day’s analysis predicted that sequential

1990 – Human cancer mortality begins to decline in the United States. Nelson Mandela is released from prison after 30 years for opposing apartheid in South Africa.  
 1991 – First monoclonal antibody for clinical use is approved for use in combination with chemotherapy. Iraq invades Kuwait but is soon ousted by an international military coalition led by the United States.  
 1994 – Tribalism-inspired genocide in Rwanda results in hundreds of thousands of deaths.  
 1995 – The Alfred P. Murrah Federal Building is bombed in Oklahoma City and kills 168 and injures hundreds more.  
 1995 – Yitzhak Rabin, Prime Minister of Israel, is assassinated at a peace rally by an Israeli.  
 1997 – Great Britain relinquishes sovereignty of Hong Kong to the Peoples Republic of China, honoring the end of its 99-year lease of the territory.  
 1998 – The 4 largest tobacco companies and the Attorneys General of 46 states settle their medical lawsuits to recover tobacco-related health care costs.

**Fig 9.** Other events of the 1990s.

combinations of drugs should outperform alternating combinations of the same programs because no 2 combinations are likely to have equal cell-killing capacity or be strictly non-cross-resistant.<sup>41</sup>

Strategic changes in the approach to cancer drug development began in the early 1980s.<sup>14,26</sup> Each marginal gain against solid tumors required large and lengthy clinical trials, and mouse models, which were the mainstay of drug screening systems, were poor predictors of clinical outcomes.<sup>26</sup>

Starting in 1984, the NCI began investing in a Program of Molecular Biology that had grown out of a Special Virus Cancer Program that had been established at the urging of Mary Lasker.<sup>14</sup> The signaling pathways that regulate normal cellular activities such as proliferation and survival were subsequently uncovered during the biotech revolution and many of these were found to be radically altered in cancer cells. Insights into these molecular signaling defects provided the potential for a new approach to chemotherapy. The path to future success would be no less arduous than that of the past advances.

By the 1990s, the age of targeted therapy had arrived. In 1996, the 1st tyrosine kinase inhibitor imatinib mesylate<sup>o</sup> was released for general use.<sup>14,42</sup> Imatinib is a drug designed to fit into the ATP binding site of the Bcr-Abl protein created by translocation, thus blocking the function of this aberrant kinase.<sup>42</sup> The treatment and outcome for human myelogenous leukemia have been dramatically changed as a result. A focal point for much current drug development research comes from data from genome sequencing, which suggests that many of the abnormalities of cancer cells are derived from abnormal function of protein kinases.<sup>26</sup> Protein kinase and *kit* inhibitors like imatinib have revolutionized treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors, and they also have been used in veterinary patients.<sup>42</sup>

Introduced in the 1990s, monoclonal antibodies (MAbs) when combined with chemotherapy enhanced the efficacy of treatment by allowing for targeting of specific cancer cell receptors. Rituximab<sup>p</sup> was the 1st MAb to be released.<sup>14</sup> Rituximab was intended for use in refractory or relapsed B-cell non-Hodgkin's lymphomas by targeting the transmembrane antigen CD-20. Concurrent with the approval of the 1st MAb for human use, the US Department of Agriculture approved licensing of a murine-derived MAb 231 for use in dogs with lymphoma after durable remission has been achieved with anthracycline-based combination chemotherapy.<sup>43</sup> This product was available to veterinarians from Synbiotics Corporation from 1992 to 1994, but for a variety of reasons did not find market success at that time.<sup>43</sup>

In many similar ways, veterinary medical oncology has closely followed the advances in human medical oncology, with both fields gaining new abilities at an ever-increasing tempo. Some of the very many "firsts" in veterinary chemotherapy should be evaluated in the context of human chemotherapy at the same time. The 1st reported use of chemotherapy in a veterinary cancer patient was in 1946 in the British publication, *The Veterinary Journal*.<sup>44</sup> This case report described a dog

with lymphoma and lymphocytic leukemia treated with urethane that responded with a clinical remission and overall survival of 82 days from the start of treatment. Interestingly, urethane, like nitrogen mustard, grew out of wartime research and was a byproduct of the German war effort to find a substitute for rubber. Although considered a carcinogen today, urethane was for a short time used to treat cancer in humans and it has also been widely used as an anesthetic in laboratory animals.<sup>45,46</sup>

Another early report of chemotherapy for cancer in a veterinary patient was published in the *Proceedings of the Society for Experimental Biology and Medicine* in 1952.<sup>47</sup> The very brief report describes a dog with mast cell tumors treated with cortisone (prednisone and prednisolone would not be introduced until 1955).<sup>9</sup> A 1 paragraph abstract subsequently was published in the *Journal of the American Veterinary Medical Association (JAVMA)* the next year, where it gained the attention of our profession.<sup>48,49</sup>

The 1st facility devoted exclusively to the treatment of cancer in dogs was founded by Dr John R. McCoy, a visionary veterinarian who began to study chemotherapy for cancer in dogs and therapeutic diets while associated with Dr Mark L. Morris at the Raritan Hospital for Animals, in Edison, NJ.<sup>50</sup> In October 1950, he worked cooperatively with basic research scientists at Rutgers University as he began to direct the newly established Canine Cancer Clinic, where among other things he investigated the effects of phosphoramides (a family of phosphorus-nitrogen compounds that includes ifosfamide) on cancer in dogs.<sup>50</sup> In 1956, McCoy and his coinvestigators found that an experimental phosphoramidate, *N*-(3-oxapentamethylene)-*N'*,*N''*-diethylenephosphoramidate (MEPA), in what was essentially a combined phase I and phase II clinical trial caused severe leukopenia and thrombocytopenia, but inhibited tumor growth and produced remissions in dogs with a variety of malignancies including lymphoma (6 of 7 dogs in remission with longest survival of 8 months).<sup>51</sup>

In 1958, publication of data in the *Irish Veterinary Journal* summarized the clinical characteristics of 53 dogs with "lymphatic leukosis" (lymphosarcoma) of which 8 individuals were treated with chlorambucil, 1 with prednisolone, and 1 with trillekamin (a nitrogen mustard similar to chlorambucil).<sup>52</sup> Subjective clinical improvement with decreases in circulating lymphocytes for up to 178 days was noted in some patients.<sup>52</sup> In a review of chemotherapy of dogs with spontaneously occurring tumors published in 1958, John McCoy cited his 1953 abstract of treatment of a dog with 2,4,6-triethylenimine-s-triazine and his 1956 report on MEPA as being capable of producing survival in dogs with lymphoma in excess of 14 months.<sup>53</sup> Dr Hans Meier, who contributed some of the important early oncology literature in veterinary medicine, wrote unequivocally in 1962 that treatment of animal cancer patients, especially dogs and cats, had become an obligation of the veterinarian to his or her community.<sup>54</sup> Cyclophosphamide was first reported as treatment of lymphoma in a dog in 1963, and the use of asparaginase for treatment of the same disease was reported in 1967.<sup>55-57</sup> During these early years of development of veterinary chemotherapy, single agent

chemotherapy was still the standard of care in human oncology.

The 1st use of combination chemotherapy for canine lymphoma using chlorambucil plus prednisone was published in the *JAVMA* in 1968.<sup>58</sup> A far more sophisticated combination chemotherapy protocol for canine lymphoma using vincristine, prednisone, and cyclophosphamide for induction, and either 6-mercaptopurine, methotrexate, and cyclophosphamide or prednisone plus cyclophosphamide for maintenance, was reported in 1975.<sup>59</sup> The evolution in sophistication of the drug protocols used in dogs mirrored what was transpiring in human medical oncology at about the same time. The growing interest in veterinary oncology prompted the 1st meeting of the Veterinary Cancer Society in 1976, with incorporation as a legal entity the next year.

Additional innovation in veterinary chemotherapy followed. The 1st report of doxorubicin use in dogs was published in the veterinary literature in 1976. Doxorubicin is a second-generation anthracycline (after daunorubicin) that had been in clinical trials in the United States since the early 1970s.<sup>60</sup> Interestingly, the authors of the initial report in the veterinary literature were not veterinarians, and the work was a toxicity study in normal dogs that was published in a prestigious clinical journal. Reports of doxorubicin use in animal cancer patients quickly followed.<sup>61-63</sup> In time, this drug became the backbone of many multidrug protocols for a wide variety of canine and feline tumors.

An early attempt at chemoimmunotherapy for lymphoma in dogs was published in 1977 and combined a multidrug chemotherapy protocol with a crude autologous vaccine.<sup>64</sup> Combination chemotherapy followed by total body irradiation and bone marrow transplantation for dogs with lymphoma was reported in 1979.<sup>65</sup> The next 35 years in veterinary medical oncology saw the establishment of the specialty of veterinary medical oncology in 1988, the evolution and proliferation of complex combination chemotherapy protocols for many tumor types, and the adoption of newly approved drugs (intended for human use) as they became available. Veterinary clinicians also introduced other advances from human oncology such as the use of vascular access ports for chemotherapy administration, far more aggressive surgery such as limb-sparing techniques, and the general adoption of linear accelerators, 3D conformal radiation therapy treatment planning, and intensity-modulated radiation therapy.

Following the example and experiences from human chemotherapy has not always been a direct or cost-free transfer of ideas, principles, and technology. For example, most drugs are prescribed to patients based on body weight. Oddly perhaps, many cancer chemotherapy drugs have been prescribed on the basis of body surface area (BSA). The relationship between BSA and various physiological parameters had been observed and noted long before 1910 when Dreyer and Ray reported that the ratio of blood volume to body weight in rabbits, guinea pigs, and mice decreased with increasing body weight, but the relation of blood volume to BSA was constant.<sup>66,67</sup> In 1958, Donald Pinkel first outlined the rationale for the use of BSA as the criterion for dose

determination in anticancer chemotherapy.<sup>66</sup> The use of BSA then became standard for dose prescription for many drugs in human and veterinary oncology. In 1998, Price and Frazier reexamined the use of the BSA concept to normalize drug dose in dogs because there were some chemotherapy trials that reported increased toxicities in small dogs.<sup>67</sup> This problem was very noticeable when anthracycline-based protocols began to be used and evaluated. Price and Frazier concluded that the formula for BSA determination was inappropriate for dogs because either the constant ( $K$ ) or the exponent ( $a$ ) in the formula  $BSA = K \cdot W^a$  is incorrect for dogs or because a linear parameter such as body length is lacking from the formula.<sup>67</sup> Although BSA still is used to calculate the dose of some chemotherapy drugs in veterinary patients, highly toxic drugs given to small dogs and cats tend now to be prescribed on a body weight basis.

Some products destined for the human market were found not to have adequate activity in dogs when given at tolerable doses or resulted in unexpected adverse events. For example, in the late 1980s when etoposide was given IV to dogs it was found to be marginally effective as a rescue agent for lymphoma, and it also was associated with an acute pruritic cutaneous reaction and hypotension that were linked to the drug vehicle, polysorbate 80.<sup>68,69</sup>

When did the modern era of cancer chemotherapy begin? Some historians argue that it began with Thomas Fowler. Other medical historians cite Dustin's report of the antimitotic properties of colchicine as the beginning. Still others date the origins of the modern era with the use of sulfa mustards in the Great War or the Bari explosion in the Second World War. It really does not matter. We have come through a modern era in which chemotherapy drugs were ridiculed as poisons and only advocated by the lunatic fringe. Sixty years ago cancer was considered "incurable." Forty years ago, only hematological malignancies were considered curable. Today, there are 14 categories of chemotherapy drugs representing over 50 different agents.<sup>14</sup> Today, 70% of childhood leukemia is potentially curable and most cases of human testicular cancer are curable.<sup>14</sup> In 2007 human cancer mortality was 50% of what it was in 1990 (half of that decline is attributed to prevention and early diagnosis and 50% is attributed to advances in treatment).<sup>14</sup> As rewarding as these medical advances are, they occurred in a complicated decade (Fig 10).

Veterinary medicine has also come of age with respect to cancer chemotherapy. Median survival for many malignancies of dogs and cats has increased from weeks to many months or more, and in some cases long-term remissions can be considered cures. The most recent and exciting development in veterinary chemotherapy is the introduction of toceranib phosphate<sup>7</sup> by Pfizer for the treatment of mast cell tumor in dogs in 2009. This drug is the 1st targeted (tyrosine kinase inhibitor) chemotherapy agent developed specifically for dogs.

The transition from cytotoxic chemotherapy drugs to targeted therapies is an enormous advance, but certain enduring principles that became apparent during the entire history of modern chemotherapy remain. The first

2001 – Human genome is sequenced.  
 2001 – World Trade Center in New York City is destroyed by Islamic terrorists.  
 2003 – The space shuttle Columbia disintegrates during reentry and the United States is again at war in Iraq.  
 2004 – The canine genome is sequenced.  
 2004 – Avastin, the first angiogenesis inhibitor approved for clinical use in humans, becomes available. Avastin is the first commercial angiogenesis inhibitor to emanate from the original hypothesis proposed by Dr Judah Folkman 33 years earlier. An earthquake in the ocean just off Indonesia triggers a tsunami that kills at least 230,000 people in eight countries.  
 2006 – North Korea successfully tests a nuclear device.  
 2007 – The feline genome is sequenced.  
 2008 – Gasoline price is in excess of \$5.00/gallon in some cities in the United States. Barack Obama is elected the 44<sup>th</sup> President of the United States.  
 2009 – A US Airways jet is disabled by striking at least one bird during take-off and lands in the Hudson River in New York City. Miraculously, all on board survive. The H1N1 virus becomes a world-wide pandemic, but with less impact than originally feared.  
 2010 – A volcanic eruption in Iceland paralyzes air travel for much of northern Europe intermittently, and a BP-operated oil drilling platform explodes, killing 11, and results in an oil spill in the Gulf of Mexico of unprecedented size, creating an environmental, engineering, and political nightmare.

**Fig 10.** Other events in the 2000s.

of these is that murine models, although instructive, are unreliable predictors of success against human cancers.<sup>26</sup> Naturally occurring cancers, regardless of histological type, possess great genetic variability so that only a subset of patients is likely to prove responsive to any new agent.<sup>26</sup> Laboratory animals also poorly reflect the pharmacokinetics of drugs in humans because of profound differences in metabolism, tolerance for adverse effects, and differences in protein binding.<sup>26</sup> In addition, the basic biology of murine cells can differ substantially from that of human cells and have uncertain relevance to the human counterpart.<sup>26</sup> A more comparative approach to cancer treatment and chemotherapy is now under way.

The idea of comparative medicine dates back to the time of Aristotle (384–322 BC).<sup>13</sup> Comparative medicine, or perhaps more accurately collaborative medicine or “one medicine,” has made critically important contributions to animal and human health. For example, in early 1966, Drs E. Donnal Thomas, Ranier Strobe, and Robert Epstein of the Division of Hematology and Transplantation (later Oncology) at the University of Washington (later Fred Hutchinson Cancer Research Center) solicited dogs with lymphoma from veterinarians in the Pacific Northwest for bone marrow transplantation (S.R., personal communication, 2010). Their pioneering experiments built on previous work with rodents and normal dogs earned Thomas a Nobel Prize in 1990. Thomas’ Nobel Lecture acknowledged that marrow grafting would not have reached clinical application without dogs.<sup>70</sup>

As a young veterinarian, Dr William Hardy Jr<sup>s</sup> joined the staff of MSKCC.<sup>70</sup> Hardy together with Dr Lloyd J. Old, a physician at MSKCC, established the Donaldson-Atwood Cancer Clinic at the Animal Medical Center (AMC) in New York City in 1975 with funding from the Donaldson Charitable Trust and Mrs Helen C. Nauts.<sup>1,71,72</sup> The Donaldson-Atwood Cancer Clinic was the source of much of the early and best modern literature regarding veterinary cancer chemotherapy. One of the pioneers of veterinary oncology, Dr E. Gregory MacEwan, met Hardy and Olds in the early 1970s and agreed to come to the AMC as a medical resident hoping to specialize in

oncology even before the Donaldson-Atwood Cancer Clinic was officially established (H.A.E., personal communication). A recent partnership led by Dr Phillip Bergman between the animal health company Merial, the AMC, and MSKCC led to the approval and introduction of a vaccine for malignant melanoma in dogs.<sup>73</sup>

Other early pioneers of veterinary oncology such as Drs Robert Brodey, Susan Cotter, Edward L. Gillette, Ann Jeglum, Dennis Macy, Robert Matus, John McCoy, Bruce Madewell, Gordon Theilen, Ted Valli, Stephen Withrow, and many others recognized the parallels between human and veterinary cancers and had the same attitude as Mary Lasker and Helen Nauts—they wanted to cure cancer but their approach to the problem was to use veterinary cancer patients as models of human disease. Their trainees and subsequent generations of veterinary oncologists still carry on in that belief and continue to rely on much of what they established. Outstanding veterinary pathologists, epidemiologists, immunologists, and other specialists as well as referring veterinarians have supported or led clinical investigations.

Rather than being somewhat behind human medical oncology, these investigators began the effort to colead. For example, an important advance in the concept of comparative medicine (One Health) was the establishment of the Comparative Oncology Trials Consortium (COTC). The COTC was conceived by Dr Chand Khanna and is an NIH/NCI-managed program that assesses novel therapies in client-owned pet animals through 19 university-based veterinary cancer centers.<sup>74</sup> The COTC provides an effective interface between the NIH, industry, and the veterinary profession and represents a fundamental paradigm shift by funding agencies toward acknowledging the utility of dogs and cats with spontaneously occurring cancer as useful models of human disease.

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## Footnotes

<sup>a</sup>The plant *Catharanthus roseus* was formally known as *Vinca rosea* and is the origin of the drugs vinblastine and vincristine. Extracts

of this plant have been used medicinally to stop hemorrhage, heal scurvy, relieve toothache, heal wounds and diabetic ulcers, and lower blood sugar.<sup>10</sup> Because *C. roseus* was known in much of the world for its medicinal properties for many centuries, it was a natural suspect for study. Investigations published in 1957 by Dr Robert L. Nobel into its alleged ability to help control blood glucose concentrations in diabetics that drank a tea made from the leaves found that a certain extract of this plant (to become vinblastine in 1958) could cause peripheral granulocytopenia in rats. Further refinement of the various plant alkaloids by Eli Lilly and Company led to vincristine commercialization in 1962 under the original name of leurocristine.<sup>11,12</sup>

<sup>b</sup>The word “cancer” occurs in old English medical terminology and was reintroduced into middle English vocabulary to denote the celestial constellation that is located between Leo to the east and Gemini to the west.<sup>5</sup>

<sup>c</sup>Theodor Schwann (1810–1882) was a German physician who discovered glial cells in the peripheral nervous system that bear his name, contributed to the development of the cell theory, discovered pepsin, and coined the term “metabolism,” among many more achievements.<sup>8</sup>

<sup>d</sup>Robert Remark (1815–1865) was a Jewish Polish/German neurohistologist and embryologist. Remark established the role of the cell membrane in cell division, which contributed greatly to the cell theory.<sup>8,18</sup> His grandson, a mathematician, had the same name and died in Auschwitz in 1942.

<sup>e</sup>Francois-Vincent Raspail (1794–1878) was a French naturalist and physiologist. He was also a revolutionary political figure during the turbulent years of France’s Second and Third Republics.<sup>8,19</sup> Raspail also coined the phrase *Ominis cellula e cellula* that was popularized by Virchow.

<sup>f</sup>The city of Ypres was reduced to red smudges of brick dust when seen from the air by 3 enormous battles between 1914 and 1917. It is also where John McCrae (*In Flanders Fields*), one of the most well-known “war poets” of the 1914–1918 conflict, experienced war and suffering in a war like no other. In 1985, a plaque remembering the 16 British War Poets of the Great War was dedicated in what became known as Poets’ Corner of Westminster Abbey, London.

<sup>g</sup>Germany took advantage of a loophole in the Hague Conventions and released chlorine gas from cylinders along a 5 mile front on the ground with a favorable wind rather than shooting the gas as projectiles into enemy formations with artillery. Germany had previously used tear gas on the Russian Front in January 1915.<sup>21</sup>

<sup>h</sup>US ORD also funded research leading to radar, proximity fuses, and the early phases of the Manhattan project during the years of its existence, 1941–1947.

<sup>i</sup>The US Chemical Warfare Service developed incendiary bombs, white phosphorus projectiles, and flame throwers in addition to liquid mustard gas.<sup>21</sup>

<sup>j</sup>The namesake of the SS John Harvey was a member of the Continental Congress who was also one of signers of the Articles of Confederation. It was a class of cargo ships known as Liberty Ships that were launched in great numbers during the war with a remarkably short average construction time of just 42 days.<sup>21,27</sup>

<sup>k</sup>Dr Alexander relentlessly sought confirmation of his suspicions, and his analysis of the events at Bari identified the John Harvey as the epicenter of the gas disaster. Although his official report earned him a commendation letter from Medical Division Chief Major Cornelius Rhodes, it had strictly limited circulation during the war and remained secret until years after the war.<sup>21</sup>

<sup>l</sup>Among Mary Lasker’s personal friends and many contacts in high places were President Lyndon Johnson, First Lady Lady Bird Johnson, Senator Hubert Humphrey, and heart surgeon Michael DeBakey.<sup>29</sup> In 2009, the US Postal Service honored Mary Lasker with a 79-cent stamp with the simple but hopelessly incomplete and totally inadequate title of “philanthropist.”

<sup>m</sup>Sidney Farber (1908–1973) was a pathologist working at Children’s Hospital in Boston who specialized in childhood cancers.

He was a rare and true visionary who advanced the concept of total care (supporting the emotional, spiritual, and nutritional needs of the patient in addition to the medical needs).<sup>14,28,29</sup> He and Mary Lasker were astonishingly successful in using their main political allies, Senators, Lister Hill of Alabama and John Fogarty of Rhode Island, to dramatically expand NCI funding.<sup>29</sup>

<sup>n</sup>Benjamin Gompertz was a British mathematician who noted that a law of geometrical progression pervades human mortality tables, and he derived a simple formula that described the exponential rise in mortality rates observed in humans between the years of sexual maturity and old age.<sup>39</sup>

<sup>o</sup>Gleevec, Novartis Oncology, Florham Park, NJ

<sup>p</sup>Rituxan, Genentech, Roche Group, Basel, Switzerland

<sup>q</sup>Cortisone was first isolated in 1935 by Edward Calvin Kendall. During the Second World War, Germany imported huge quantities of bovine adrenal glands from Argentina so extracts containing cortisone could be given to Luftwaffe pilots to enhance their performance.<sup>49</sup> Rheumatoid arthritis was the first disorder to be treated with cortisone (1948) that by now was being isolated from wild yams and within another year from soy beans. In 1955, Glaxo introduced prednisone and prednisolone.<sup>14</sup>

<sup>r</sup>Palladia, Pfizer Animal Health, Pfizer Inc, New York, NY

<sup>s</sup>William D. Hardy Jr, VMD, invested most of his adult life studying human and feline retroviruses and later *Bartonella*. In 1970 he developed the first commercial test for feline leukemia virus (FeLV) in cats and using his immunofluorescent antibody test proved that FeLV spreads contagiously among cats.<sup>71</sup>

<sup>t</sup>Helen Coley Nauts was the daughter of the cancer specialist and surgeon Dr William B. Coley, who practiced at what was to become the Memorial Sloan-Kettering Cancer Center. Coley founded the entire field of cancer immunotherapy with his use of bacterial toxins to treat cancer patients, which he first published in 1891. The use of bacterial toxins in cancer patients was controversial and was eventually overshadowed by radiation and chemotherapy. After his death in 1936, his daughter Helen became acquainted with his work and singlehandedly brought it to the attention of contemporary oncologists by organizing over 15,000 letters and records of her father’s that she had found stored in a barn. From these she produced 1,000 carefully researched case histories of individuals treated with bacterial toxins. Nauts also used her considerable wealth to establish the Cancer Research Institute in New York City in 1953 and devoted her life to supporting cancer research. As her long time friend, Dr Lloyd J. Old, said: “She was inflamed. She was absolutely inflamed by a grand idea.” In a memorial tribute published in 2001 after her death, her daughter remembered that her children thought she spent too much time working and when asked by her daughter “Mommy let’s play,” she answered, “I can’t play, because people are dying when I’m not working.”<sup>71</sup>

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