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Mini Review

A brief history of cancer: Age-old milestones underlying our current knowledge database

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This mini-review chronicles the history of cancer ranging from cancerous growths discovered in dinosaur fossils, suggestions of cancer in Ancient Egyptian papyri written in 1500–1600 BC, and the first documented case of human cancer 2,700 years ago, to contributions by pioneers beginning with Hippocrates and ending with the originators of radiation and medical oncology. Fanciful notions that soon fell into oblivion are mentioned such as Paracelsus and van Helmont substituting Galen's *black bile* by mysterious *ens* or *archeus* systems. Likewise, unfortunate episodes such as Virchow claiming Remak's hypotheses as his own remind us that human shortcomings can affect otherwise excellent scientists. However, age-old benchmark observations, hypotheses, and practices of historic and scientific interest are underscored, excerpts included, as precursors of recent discoveries that shaped modern medicine. Examples include: Petit's total mastectomy with excision of axillary *glands* for breast cancer; a now routine practice, Peyrilhe's *ichorous matter* a cancer-causing factor he tested for transmissibility one century before Rous confirmed the virus-cancer link, Hill's warning of the dangers of tobacco snuff; heralding today's cancer pandemic caused by smoking, Pott reporting scrotum cancer in chimney sweepers; the first proven occupational cancer, Velpeau's remarkable foresight that a yet unknown subcellular *element* would have to be discovered in order to define the nature of cancer; a view confirmed by cancer genetics two centuries later, ending with Röntgen and the Curies, and Gilman *et al*. ushering radiation (1896, 1919) and medical oncology (1942), respectively.

From prehistory to ancient Egypt

Cancer has afflicted humanity from pre-historic times though its prevalence has markedly increased in recent decades in unison with rapidly aging populations and, in the last half-century, the increasing risky health behavior in the general population and the increased presence of carcinogens in the environment and in consumer products. The oldest credible evidence of cancer in mammals consists of tumor masses found in fossilized dinosaurs and human bones from prehistoric times. Perhaps the most compelling evidence of cancer in dinosaurs emanates from a recent large-scale study that screened by fluoroscopy over 10,000 specimens of dinosaur vertebrae for evidence of tumors and further assessed abnormalities by computerized tomography (CT).[1] Out of several species of dinosaurs surveyed, only *cretaceous hadrosaurs* (duck-billed dinosaurs), that lived ∼70 million years ago, harbored benign tumors (hemangiomas[*] desmoplastic fibromas,[†] and osteoblastomas,[‡] but 0.2% of specimens exhibited malignant metastatic disease.

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[*]Benign vascular tumors.
[†]Benign fibrous tumors of bone.
[‡]Rare benign bone tumors.

The earliest written record generally regarded as describing human cancer appeared in ancient Egyptian manuscripts discovered in the 19th century, especially the Edwin Smith and George Ebers papyri that describe surgical, pharmacological, and magical treatments. They were written between 1500 and 1600 BC possibly based on material from thousands of years earlier. The Smith papyrus, possibly written by Imhotep the physician-architect who designed and built the step pyramid at Sakkara in the 30th century BC under Pharaoh Djoser, is believed to contain the first reference to breast cancer (case 45) when referring to tumors of the anterior chest. It warns that when such tumors are cool to touch, bulging, and have spread over the breast no treatment can succeed.[2] It also provides the earliest mention of wound suturing and of using a "fire drill" to cauterize open wounds. In ancient times, gods were thought to preside over human destiny, including health and disease, medicine and religion were intertwined, practiced by priests and sages who often were revered as gods' intermediaries. For instance, in case 1 of the Edwin Smith papyrus caregivers are called "lay-priests of Sekhmet;" the feared lion-headed "lady of terror" and one of the oldest Egyptian deities also known as the "lady of life" patron of caregivers and healers.[3]

The earliest cancerous growths in humans were found in Egyptian and Peruvian mummies dating back to ∼1500 BC. The oldest scientifically documented case of disseminated cancer was that of a 40- to 50-year-old Scythian king who lived in the steppes of Southern Siberia ∼2,700 years ago. Modern microscopic and proteomic techniques confirmed the cancerous nature of his disseminated skeletal lesions and their prostatic origin.[4] Half a millennium later and half a world away, a Ptolemaic Egyptian was dying of cancer.[5] Digital radiography and multi-detector CT scans of his mummy, kept at the Museu Nacional de Arqueología in Lisbon, determined that his cancer was disseminated. The morphology and distribution of his lesions (spine, pelvis, and proximal extremities), and the mummy's gender and age suggest prostate as the most likely origin.

From ancient Egypt to Greece and Rome

Following the decline of Egypt and Greece, Roman medicine became preeminent, especially with Hippocrates of Kos (460-c.360BC), an island off the coast of Turkey, and Claudius Galenus (AD129–c.216), better known as Galen of Pergamum (modern-day Bergama, Turkey). Writings attributed to them, describing life-long experiences and observations, became the foundation and repository of medical knowledge for the ensuing 1,500 years.

Hippocrates. Little is known with certainty about who he was, how he practiced medicine, and which writings attributed to him are his. The little we know about Hippocrates we owe to his first biographer Soranus of Ephesus (a 2nd century AD Greek physician) and to Aristotle (384–322BC) who refers to him as *The Great Hippocrates*. His current image emerged in the sixteenth Century after "…[being] constantly invented and reinvented; constructed, deconstructed, and reconstructed; molded and remolded, according to the cultural, philosophical, social, and political context, or the private and moral background…[of interpreters]"[6] According to that image, Hippocrates emerged from a group of illustrious teachers at the famed medical school in the island of Kos in the Aegean Sea, during the Age of Pericles. As a seat of learning and the provincial seat of the museum of Alexandria, Kos was an educational center and a playground for the princes of the Ptolemaic dynasty. Its market place was one of the largest in the ancient world and its well-fortified port gave it prominence in Aegean trade. The medical legacy associated to Hippocrates' name and the imagery it conjures up have become legendary. Hippocrates is called the *Father of Medicine* more for rejecting prevailing views on the supernatural causes of disease and their cure through rituals and offerings, for promoting a rational approach to medicine, and for his famous Oath, than for the so-called Hippocratic Corpus. A collection of 60 "books"[$] of medical writings on a variety of medical topics, the corpus includes "On air, water and places," "On ancient medicine," "On epidemics," "On surgery," "On the sacred disease," "On ulcers," "On fractures," "On Hemorrhoids," "Aphorisms,"[7] "The oath," and many others of which he might have written only 12 to 14, according to scholars' best estimates. The Hippocratic oath, sworn by several healing gods, is remarkable for it promoted a system of accreditation requiring a period of apprenticeship and an ethical code of conduct that differentiated knowledgeable and trustworthy physicians from charlatans. Today, few medical schools adhere to this ancient rite of passage though several principles are still relevant including:

[$]Essay-length. For instance, the "book" of *Aphorisms* is only 14,426 words-long in its English translation.

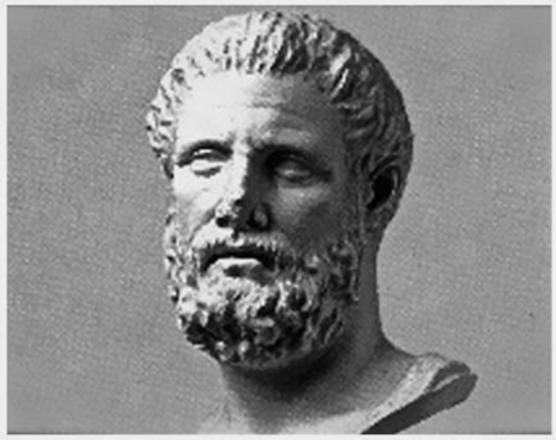

Figure 1. Bust of hippocrates. *150 B.C. Archaeological Museum of Kos*.

- I will do no harm or injustice to…[patients].
- I will not give a lethal drug to anyone…nor will I advise such a plan.
- I will enter [homes] for the benefit of the sick, avoiding any act of impropriety.
- Whatever I see or hear in the lives of my patients…I will keep secret.[8]

Hippocrates' approach to diagnosing diseases was based on careful observations of patients and on monitoring their symptoms. For instance, in "On forecasting diseases," he advises, "First of all the doctor should look at the patient's face… the following are bad signs—sharp nose, hollow eyes, cold ears, dry skin on the forehead, strange face color such as green, black, red or lead colored…[if so] the doctor must ask the patient if he has lost sleep, or had diarrhea, or not eaten."[9]

In his book "On epidemics," he advises to note patients' symptoms and appearance on a daily-basis in order to assess disease progression or recovery. He believed health and disease resulted from the balance and imbalance in the main four body fluids or humors: *blood, black bile*, *yellow bile* and *phlegm*. Each humor was linked to a different organ (*heart, spleen, liver, brain*), a personal temperament (*sanguine, melancholic, choleric, phlegmatic*), a physical earthly element (*air, earth, fire and water*), and a specific season (*spring, summer, fall, winter*). The relative dominance of one of the humors determined personality traits and their imbalance resulted in a propensity toward certain diseases. The aim of treatment was to restore balance through diet, exercise, and the judicious use of herbs, oils, earthly compounds, and occasionally heavy metals or surgery. For instance, a phlegmatic or lethargic individual (one with too much phlegm) could be restored to balance by administering citrus fruit thought to counter phlegm. While credited to Hippocrates, the true origins of this system are controversial. The Hippocratic Corpus deals at length with diseases that produced masses (*onkos*), and includes the word *karkinos* to describe ulcerating and non-healing lumps that included lesions ranging from benign processes to malignant tumors. He advocated diet, rest, and exercise for mild illnesses, followed by purgatives, heavy metals and surgery for more serious diseases, especially *karkinomas*. His stepwise treatment approach is summarized in one of his *Aphorisms*, "That which medicine does not heal, the knife frequently heals; and what the knife does not heal, cautery often heals; but when all these fail, the disease is incurable."[10] To his credit, he recognized the relentless progression of deep-seated karkinomas and the often-negative effect of treatment writing: "Occult cancers should not be molested. Attempting to treat them, they quickly become fatal. When unmolested, they remain in a dormant state for a length of time" (Aphorism 38[11]). Hippocrates died at Larissa, in Thessaly, at the probable age of one hundred.

Aulus Cornelius Celsus (25BC-AD50), was a Roman physician and prominent Hippocrates successor. He described the evolution of tumors from surgically resectable *cacoethes* followed by unresponsive *carcinos* (he later called *carcinomas*) and fungated ulcers he advocated should be left alone[12] because "the excised carcinomas have returned and caused death."[13] He explained, "It is only the cacoethes which can be removed; the other stages are irritated by treatment; and the more so the more vigorous it is. Some have used caustic medicaments, some the cautery, some excision with a scalpel; but no medicament has ever given relief; the parts cauterized are excited immediately and increase until they cause death."

Celsus acknowledged that only time could differentiate cacoethes from carcinomas, "No one, however, except by time and experiment, can have the skill to distinguish a cacoethes which admits of being treated from a carcinoma which does not." He vividly described the invasive nature of carcinomas, "This also is a spreading disease. And all these signs often extend, and there results from them an ulcer which the Greeks call phagedaena because it spreads rapidly and penetrates down to the bones and so devours the flesh." Reportedly, he is the first to attempt reconstructive surgery following excision of cancer.

Archigenes of Apamea, Syria (75–129) practiced in Rome in the time of Trajan. He also stressed the importance of early stage diagnosis when various remedies can be successful but advised surgery for advanced cancer as absolutely necessary but only in strong patients able to survive surgery designed to extirpate the tumor in its entirety, warning, "if it has taken anything into its claws it cannot be easily ripped away."

Galen (c.129–c.216), Hippocrates' most prominent successor and the one who propelled his legacy nearly 15 Centuries, was born of Greek parents in Pergamum, the ancient capital of the Kingdom of Pergamum during the Hellenistic period, under the Attalid dynasty. In Galen's time, Pergamum was a thriving cultural center famous for its library second only to Alexandria's and its statue of Asclepius, the Greek god of medicine and healing. His prosperous patrician architect father, Aelius Nicon, oversaw Galen's broad and eclectic education that included mathematics, grammar, logic, and inquiry into the four major schools of philosophy of the time: the Platonists, the Peripatetics, the Stoics, and the Epicureans. He started medical studies in Smyrna and Corinth at age 16 and later lived in Alexandria for 5 years (AD152–157) where he studied anatomy and learned the practice of autopsy as a means to understanding health and disease. Years later he wrote, "look at the human skeleton with your own eyes. This is very easy in Alexandria, so that the physicians of that area instruct their pupils with the aid of autopsy."[14] His appointment as physician of the gymnasium attached to the Asclepius sanctuary of Pergamum, in 157, brought him back to his hometown where he became surgeon to local gladiators. When civil unrest broke out, Galen moved to Rome where his talents and ambition soon brought him fame but also numerous enemies that forced him to flee the city in 166, the year the plague (possibly smallpox) struck. Two years later, Roman Emperor Marcus Aurelius summoned him to serve as army surgeon during an outbreak among troops stationed at Aquileia (168–169) and when the plague extended to Rome, he was appointed personal physician to the Emperor and his son Commodus adding luster and fame to his fast rising career.

While medical practitioners of the time disagreed on whether experience or established theories should guide treatment, he applied Aristotelian empiricism by ensuring that established theories gave meaning to personal observations and relied on logic to sort out uncertainties and discover medical truths. Galen was the first to recognize the difference between arterial (bright) and venous (dark) blood he postulated to be distinct systems originating from the heart and the liver, respectively. He used vivisections to study body functions. For instance, when he cut the laryngeal nerve of a pig the animal stopped squealing; a nerve now known as *Galen's Nerve*. Likewise, by tying the ureters he showed that urine came from kidneys and that severing spinal cord nerves caused paralysis. He performed audacious and delicate operations, such as removal of the lens to treat cataracts, an operation that would become commonplace 2,000 years later. His pioneering anatomical studies, based on dissecting pigs and primates were only surpassed by Andreas Vesalius' pivotal 1543 work *De humani corporis fabrica* based on human dissections. Galen's prolific writings include 300 titles of which approximately half have survived wholly or in part. Many were destroyed in the fire of the Temple of Peace (AD191). *On My Own Books*, Galen himself indicated which of the many works circulating under his name was genuine though "several indisputably genuine texts fail to appear in them,

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Figure 2. Bust of Galen by Commodus, 2nd Century (photo AKG Images/Dagli Orti).

either because they were written later, or because for whatever reason Galen chose to disown them."[15] A renowned Galen expert called him "The most prolific writer to survive from the ancient world, whose combination of great learning and practical skill imposed his ideas on learned doctors for centuries."[16] The influence of his work in the west went into decline after the collapse of the Roman Empire for no Latin translations were available and few scholars could read Greek. Yet, Greek medical tradition remained alive and well in the Eastern Roman (Byzantine) Empire. Indeed, Muslims' interest in Greek science and medicine during the Abbasid period led to translations of Galen's work into Arabic, many of them by Syrian Christian scholars. Likewise, the limited number of scholars fluent in Greek or Arabic hampered translations into modern languages. Karl Gottlob Kühn of Leipzig assembled the most complete and authoritative compendium of Galen's work between 1821 and 1833. It gathered 122 of Galen's works into 22 volumes (20,000 pages long), translated from the original Greek into Latin and published in both languages. Galen addressed tumors of various types and origins, distinguishing *onkoi* (lumps or masses in general), *karkinos* (included malignant ulcers), and *karkinomas* (included non-ulcerating cancers). His greatest contribution to understanding cancer was by classifying lumps and growths into three categories ranging from the most benign to the most malignant. The *De tumoribus secondum naturam* (tumors according to nature) included benign lumps and physiologic processes such as enlarging pubertal breasts or a pregnant uterus. *De tumoribus supra naturam* (tumors beyond nature) comprised processes such as abscesses and swelling from inflammation he compared to a "soaking-wet sponge" for "if the inflamed part is cut, a large quantity of blood can be seen flowing out." Not surprisingly, bloodletting was his preferred treatment for these conditions. *De tumoribus praeter naturam* (tumors beyond nature) included lesions considered cancer today. Galen's classification of lumps and growths is the first and only written document of antiquity devoted exclusively to tumors both cancerous and non-cancerous. In addition to contributing to a wide range of medical disciplines Galen bridged the Greek and Roman medical worlds by enshrining Hippocratic principles and his own as the foundation of all medical knowledge that would last 1,500 years. Nevertheless, Galen's contributions to understanding the nature and treatment of cancer were essentially nil. He died in Rome at the probable age of 87.[17]

From Rome to the Middle Ages

With the collapse of Greco-Roman civilization after the fall of Rome in AD 476, medical knowledge in the Western Roman Empire stagnated and many ancient medical writings were lost. Nevertheless, prominent physician-scholars emerged during the Eastern Roman (Byzantine) Empire including Oribasius of Pergamum (325–403), Aëtius of Amidenus (502–575), and Paulus Ægineta (625?-690?) all of whom viewed Galen as the source of all medical knowledge.

Oribasius stressed the painful nature of cancer and described cancers of the face, breast, and genitalia. Aëtius is attributed the observation that swollen blood vessels around breast cancer often look like crab legs; hence the term cancroid (crab-like). He believed that uterine cancer surgery was too risky but advocated excision of the more accessible breast cancers. In his writings, he upheld observations on breast cancer made by Leonides of Alexandria in the 2nd century AD, "Breast cancer appears mainly in women and rarely in men. The tumor is painful because of the intense traction of the nipple...[avoid operating when] the tumor has taken over the entire breast and adhered to the thorax...[but] if the scirrhous tumor begins at the edge of the breast and spreads in more than half of it, we must try to amputate the breast without cauterization."[18]

Paulus Ægineta published seven books two centuries later he described as a treatise that, "Contain[s] the description, causes, and cure of all diseases, whether situated in parts of uniform texture, in particular organs, or consisting of solutions of continuity, and that not merely in a summary way, but at as great length as possible."[19]

In book IV, section 26, he states that cancer "occurs in every part of the body"...but it is more frequent in the breasts of women..." In book VI, section XLV, he quotes Galen's surgical treatment for breast cancer, which he advocates as the treatment of choice for all operable cancers, "If ever you attempt to cure cancer by an operation, begin your evacuations by purging the melancholic humor, and having cut away the whole affected part, so that a root of it be left, permit the blood to be discharged, and to not speedily restrain it, but squeeze the surrounding veins so as to force out the thick part of the blood, and then cure the wound like other ulcers."

He called attention to the presence of lymph nodes in the armpits of women with breast cancer and advocated poppy extracts to combat pain. Paulus Ægineta clearly acknowledges Greek-Roman medical tradition dominance over medical practice of his time in the introduction of the preface to his seven books, "It is not because the more ancient writers had omitted anything relative to the Art that I have composed this work, but in order to give a compendious course of instructions; for, on the contrary, everything is handed by them properly, and without any omissions..." Although these authors and their contemporaries contributed little to our knowledge of medicine and cancer, through their writings they ensured the preservation of Greek-Roman medical tradition accumulated by their predecessors.

Greek scientific tradition also spread widely first through Christian Syriac writers, scholars, and scientists reaching Arab lands mainly via translations of Greek texts into Arabic by "Nestorians"; followers of Nestorius, Patriarchy of Constantinople.[20] Nestorianism spread throughout Asia Minor through churches, monasteries, and schools where Nestorian monks intermingled with Arabs until the sect was abolished as heretical at the Council of Chalcedon (AD451). Pivotal to the adoption of Greek thought by the Arabs was the pro-Greek penchant of Ja'far Ibn Barmak, minister of the Caliph of Bagdad, along with like-minded members of the Caliph's entourage. "Thus the Nestorian heritage of Greek scholarship passed from Edessa and Nisibis, through Jundi-Shapur, to Baghdad" Islamic physician-scholars and medical writers became preeminent in the early middle ages, including the illustrious and influential Abu Bakr Muhammad Ibn Sazariya Razi, also known as Rhazes (865?-925?), Abū ʿAlī al-Ḥusayn ibn ʿAbd Allāh ibn Sīnā, known as Avicenna (980–1037), Abū-Marwān 'Abd al-Malik ibn Zuhr or Avenzoar (1094–1162), and Ala-al-din abu Al-Hassan Ali ibn Abi-Hazm al-Qarshi al-Dimashqi known as Ibn Al-Nafis (1213–1288). The latter described the pulmonary circulation in great detail and accuracy, as told in *Commentary on the Anatomy of Canon of Avicenna*, a manuscript discovered in the Prussian State Library of Berlin. Ibn Al-Nafis stated, "The blood from the right chamber of the heart must arrive at the left chamber but there is no direct pathway between them. The thick septum of the heart is not perforated and does not have visible pores as some people thought or invisible pores as Galen thought. The blood from the right chamber must flow through the vena arteriosa [pulmonary artery] to the lungs, spread through its substances, be mingled there with air, pass through the arteria venosa [pulmonary vein] to reach the left chamber of the heart and there form the vital spirit..."[21]

He also understood the anatomy of the lungs explaining, "The lungs are composed of parts, one of which is the bronchi; the second, the branches of the arteria venosa; and the third, the branches of the vena arteriosa, all of them connected by loose porous flesh."[22]
And he was the first to understand the function of the coronary circulation, "The nourishment of the heart is through the vessels that permeate the body of the heart"[21]

However, of greater interest to us is Avenzoar who first described the symptoms of esophageal and stomach cancer, in his book *Kitab al-Taysir fi 'l-Mudawat wa 'l-Tadbir* (Practical Manual of Treatments and Diets), and proposed feeding enemas to keep alive patients with stomach cancer,[23] a treatment approach unsuccessfully attempted by his predecessors. Like Hippocrates, he insisted that the surgeon-to-be receive hands-on training before being allowed to operate on his own. By the end of the fourteenth century, Avenzoar became well known in university circles at Padua, Bologna, and Montpellier where he was considered one of the greatest physicians of all time. Successive publications of his *Kitab al-Taysir* and of translations ensured his influence through the seventeenth century when Paracelsus' new treatment paradigm emphasizing chemical ingredients rather than herbs, disseminated in the vernacular rather than in Greek or Latin, set in motion the decline of Greco-Roman medical tradition. In the meantime, several transcendental events marked the Islamic world decline that accelerated the dwindling of traditional Hippocratic and Galenic medicine. They include the Mongolian capture and sacking of Bagdad, the capital of the Abbasid Caliphate, in 1258, and the defeat of the Emirate of Granada in 1492 by Isabel *La Católica* Queen of Castile and León, and her husband Ferdinand II of Aragón, culminating the centuries-long recapture of the Iberian Peninsula from the Arabs.

Meanwhile, new religious fervor especially in Christian France and the early success of the crusades contributed to the proliferation of Christian monasteries and health centers across Europe becoming the repositories of Greek medicine where monks copied ancient manuscripts and attended the sick, as Nestorian monks had done centuries earlier, giving rise to a network of *hospitiums*¶ throughout Western Europe that, "Flourished during the times of the Christian crusades and pilgrimages that were found mostly in monasteries where monks extended care to the sick and dying, but also to the hungry and weary on their way to the Holy Land, Rome, or other holy places, as well as to the woman in labor, the needy poor, the orphan, and the leper on their journey through life."[24]

Perhaps the most famous Hospitium was the 9th Century *Studium* of Salerno, a coastal town in southern Italy key to trade with Sicily and other Mediterranean towns. Although initially a humble dispensary sustained by the needs of pilgrims en route to the Holy Land, it evolved into the *Schola Medica Salernitana*. The arrival at a nearby abbey in 1060 of Constantine Africanus, a Benedictine monk from Carthage whose medical guide for travelers titled *Viaticum* and his translations and annotations of Greek and Arabic texts led Salerno to be known as *Hippocratica Civitas* (Hippocrates' Town). By the end of the eleventh century, the fame of the Studium had spread across Europe thanks to the erudition and writings of its teachers and scholars still anchored in the Hippocratic-Galenic tradition. Prominent medical writings arising from the Studium include the *Breviary on the Signs,*

¶Precursors to today's hospices.

Causes, and Cures of Diseases by Joannes de Sancto Paulo, the *Liber de Simplici Medicina* by Johannes and Matthaeus Plantearius, and *De Passionibus Mulierum Curandorum,* a compilation of women's health issues attributed to Trotula, the most famous female physician of her time. Given its widespread fame and its eclectic teaching merging Greek, Latin, Jewish, and Arab medical traditions, the Studium became a Mecca for students, teachers, and scholars. Its successor, the *Schola Medica Salernitana*, served as a model to the influential and enduring pre-Renaissance medical schools at Montpellier (1150), Bologna (1158), and Paris (1208) that became meccas for the study and practice of medicine and eventually cancer.

From the Middle Ages to World War II

The early-Renaissance period witnessed a revival of interest in Greek culture fostered by the arrival in Western Europe of many Greek scholars fleeing Constantinople after the Turkish conquest of Byzantium in 1453, enabling western scholars to abandon Arabic translations of the Greek masters. This and other transcendental events of that time, such as the invention of the printing press, the discovery of America, and the Reformation, brought about a change in direction and outlook; a desire to escape the boundaries of the past and an eagerness to explore new horizons. This inquisitiveness was broad-based, encompassing all areas of human knowledge and endeavor from the study of anatomy to the scrutiny of the skies as witnessed by the publication of two revolutionary and immensely influential treatises. "*De Humani Corporis Fabrica Libri Septum*" (Seven Books on the Fabric of the Human Body)[25] by Andreas Vessalius (1514–1564), and *"De Revolutionibus orbium coelestium* (On the revolutions of the celestial orbs) by Nicolaus Copernicus (1473–1543).[26] Likewise, progress was made in surgical techniques and treatment of wounds, thanks to the Ambroise Paré (1510–1590), surgeon to the French Armies and private physician to three French Kings and the father of modern surgery and forensic pathology, whose extensive experience on the battlefields of France's Armies and ingenious prostheses reduced surgical mortality and accelerated rehabilitation.[27] He is said to have turned butchery into humane surgery. However, this burst of Renaissance knowledge did not extend to cancer. For instance, Paré called cancer *Noli me tangere* (do not touch me) declaring, "Any kind of cancer is almost incurable and...[if operated]...heals with great difficulty."[28]

Nonetheless, some of the physical attributes of cancer began to emerge. Gabriele Fallopius (1523–1562) is credited to having described the clinical differences between benign and malignant tumors, which is largely applicable today. He identified malignant tumors by their woody firmness, irregular shape, multi-lobulation, adhesion to neighboring tissues (skin, muscles and bones), and by congested blood vessels often surrounding the lesion. In contrast, softer masses of regular shape, movable, and not adherent to adjacent structures suggested benign tumors. Like his predecessors, he advocated a cautious approach to cancer treatment, "Quiescente cancro, medicum quiescentrum" (dormant cancer; quiescent doctor). More importantly, for the first time in 1,500 years the Galen's black bile theory of the origin of cancer was challenged and new hypotheses were formulated. For example, Wilhelm Bombast von Hohenheim (1493–1541) best known as Paracelsus proposed to substitute Galen's black bile by several "*ens*" (entities): *astrorum* (cosmic); *veneni* (toxic); *naturale et spirituale* (physical or mental); and *deale* (providential). Similarly, Johannes Baptista van Helmont (1577–1644) envisioned a mysterious "*Archeus*" system.[29] While these hypotheses were throwbacks to pre-Hippocratic beliefs in supernatural forces governing human health and disease, it was at this time that René Descartes (1590–1650) published his "*Discours de la méthode pour bien conduire sa raison et chercher la verité dans les sciences*" (Discourse on rightly conducting one's reason for seeking the truth in the sciences).[30] This seminal philosophical treatise on the method of systematic doubt, beginning with *cogito ergo sum* (I think therefore I exist), was pivotal in guiding thinkers and researchers in their quest for the truth. Then, the discovery of blood circulation through arteries, veins, and the heart by William Harvey (1578–1657), of chyle (lymph) by Gaspare Aselli (1581–1626),[31] and its drainage into the blood circulation through the thoracic duct by Jean Pecquet (1622–1674), led the view that Galen's black bile implicated in cancer could be found nowhere, whereas lymph was everywhere and therefore suspect. French physician Jean Astruc (1684–1766) was key to the demise of the bile-cancer link. In 1759, he compared the flavor of cooked slices of beef and breast cancer, and finding no appreciable difference, concluded breast tissue contained no additional bile or acid. Based on this new lead, Henri François Le Dran (1685–1770), one of the best surgeons of his time, postulated that cancer developed locally but spread through lymphatics becoming inoperable and fatal,[32] an observation as true today as it was then. His contemporary, Jean-Louis Petit (1674–1750), advocated total mastectomy for breast cancer, including resection of axillary glands (lymph nodes), which he correctly judged necessary "to preclude recurrences."[33,34] Three and a half Centuries later, Petit's surgical approach to breast cancer surgery survives after many modifications made possible by enormous progress achieved in surgical techniques, anesthesia, antibiotics, and general medical support.

How did cancer begin and what were its causes remained puzzles and several academic institutions promoted the search for an answer. For example, in 1773, the Academy of Lyon, France offered a prize for the best scientific report on "Qu'est-ce que le cancer" (What is cancer?). It was won by Bernard Peyrilhe's (1735–1804) doctoral thesis; the first investigation to systematically explore the causes, nature, patterns of growth, and treatment of cancer[35] that catapulted Peyrilhe as one of the founders of experimental cancer research. He postulated the presence of an "*Ichorous matter*"; a cancer-promoting factor akin to a virus, emerging from degraded or putrefied lymph. To test whether the *Ichorous* *matter* was contagious, he injected breast cancer extracts under the skin of a dog, which he kept at home under observation. However, the experiment was interrupted when his servants drowned the constantly howling dog. Peyrilhe also subscribed to the notion of the local origin of cancer and called distal disease *consequent* cancer we now call *metastasis*, a term coined in 1829 by Joseph Recamier (1774–1852), a French gynecologist better known for advocating the use of the vaginal speculum to examine female genitalia. Like Petit's, Peyrilhe breast cancer surgery included removal of the axillary lymph nodes but added the pectoralis major muscle; an operation further augmented by William Stewart Halsted (1852–1922), a New York surgeon, who in 1882 popularized "radical" mastectomies, which consisted of removing the breast, the axillary nodes, and the major and minor pectoralis muscles in an *en bloc* procedure.[36] Yet, more aggressive twentieth century surgeons added prophylactic oophorectomy, adrenalectomy, and hypophysectomy**, procedures soon abandoned as ineffectual and mutilating. Meanwhile, Giovanni Battista Morgagni (1682–1771) contributed greatly to understanding cancer pathology through his monumental "*De Sedibus et Causis Morborum per Anatomen Indigatis*"(On the Seats and Causes of Diseases as Investigated by Anatomy), which contains careful descriptions of autopsies carried out on 700 patients who had died from breast, stomach, rectum, and pancreas cancer. On another front, concerned that the special needs of cancer patients were not being met, Jean Godinot (1661–1739), canon of the Rheims cathedral, bequeath a considerable sum of money to the city of Rheims to erect and maintain in perpetuity a cancer hospital for the poor. The *Hôpital des cancers* was inaugurated in 1740 with 8 cancer patients; 5 women and 3 men.[37] However, the fear of cancer presumed contagious among locals forced Rheims' authorities to relocate the hospital outside city limits in 1779.

In the meantime, Bernardino Ramazzini (1633–1714), born in Capri, focused on workers' health problems from his medical school years, visiting workplaces in attempts to determine whether workers' activities and environment impacted their health. After years of painstaking field observations, he published *De morbis artificum diatriba* (Diseases of workers),[38] first in Modena (1700) and later in Padua (1713). His exhaustive workplace surveys produced the first persuasive empiric evidence of a link between work activity and environment and human disease. The inclusion of detailed descriptions of 52 specific occupational illnesses and their link to particular work activities or environment, and treatment suggestions won him the title, father of modern occupational medicine.[39] In 1713 he reported a virtual absence of cervical cancer but a higher incidence of breast cancer in nuns relative to married women suggesting sexual activity as an explanation, a notion challenged two and a half centuries later.[40] Though sexual activity per se is not responsible, promiscuity increases exposure to the sexually transmitted human papillomaviruses (HPV) that cause 90% of cases of cervical cancers worldwide.[41] Hence, life-long celibate women, whether nuns or not, are not exposed to genital HPVs greatly reducing their risk of developing cervical cancer.

Years later (1761), John Hill (1716?-1775?) warned of the dangers of the then popular tobacco snuff stating "No man should venture upon Snuff who is not sure that he is not so far liable to a cancer: and no man can be sure of that,"[42] and in 1775 Percivall Pott (1714–1788) called attention to scrotum cancer in chimney sweeps. In his "*Chirurgical observations relative to the Cataract, the Polypus of the Nose, and the Cancer of the Scrotum, etc*.," he accurately noted, "The Colic of Poictou†† is a well-known distemper, and everybody is acquainted with the disorders to which painters, plumbers, glaziers, and the workers in white lead are liable; but there is disease as peculiar to a certain set of people, which has not, at least to my knowledge, been publicly noticed; I mean chimney-sweepers' cancer. It is a disease which always makes its first attack on, and its first appearance in, the inferior part of the scrotum; where it produces a superficial, painful, ragged, ill-looking sore, with hard and rising edges. The trade call[s] it soot-wart."[43] Pott was well aware of the progressive nature of the disease, the benefits of early intervention, and of the fatal outcome of late surgical intervention. He described, "If there is any chance of putting a stop to, or prevent this mischief, it must be the immediate removal of the part affected…for if it be suffered to remain until the virus has seized the testicle, it is generally too late for even castration. I have many times made the experiment; but though the sores…have healed kindly, and the patients have gone from the hospital seemingly well yet, in the space of a few months…they have returned either with the same disease in the other testicle, or glands of the groin, or with…a disease state of some of the viscera, and which have soon been followed by a painful death."

Interestingly, he also suspected the chemical origin of scrotum cancer noting, "The disease, in these people, seems to derive its origin from a lodgment of soot in the rugae of the scrotum…" Two centuries later scrotal cancer in chimney sweeps was linked to absorption of polycyclic aromatic hydrocarbons.[44] In his book, Pott states not having encountered any case under the age of puberty. Yet, his editor added a footnote regarding an 8-year old "chimneysweeper apprentice" whose scrotum cancer was confirmed by Pott.[43] In fact, chimney climbing was entrusted to boys while their master sweep employers pulled bundles of rags up and down the chimney instead. In the UK, legislation pasted in 1788 and 1840 remained unenforced but the Chimney Sweepers act of 1875 provided for chimney sweeps to be licensed and forbade chimney climbing before age 21 and apprenticeship

**Removal of the ovaries, adrenal glands, and hypophysis (or pituitary) gland, respectively.

††Chronic lead poisoning by lead-containing wine first diagnosed in the Poitou region of France.

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before age 16.[43] Eventually, several chimney sweep guilds suggested daily bathing; a well thought out measure that sharply reduced this occupational risk.

Notwithstanding a better understanding of certain aspects of cancer, other baffling observations of that time included recurrences distal to the original cancer, multiple cancers in a single individual, and families with a high incidence of cancer. Such occurrences were explained by a certain cancer predisposition or diathesis as first invoked by Jacques Delpech (1772–1835) and Gaspard Laurent Bayle (1774–1816),[45] later re-energized throughout Europe by Pierre Paul Broca (1824–1880), Sir James Paget (1814–1899) and Carl von Rokitansky (1804–1878). Believers in the diathesis hypothesis viewed cancer as a clinical manifestation of an underlying constitutional defect. Pathologist Jean Cruveilhier (1791–1874) considered cancer diathesis and cancer cachexia as different manifestations of the same process caused by cancerous impregnation of venous blood. Consequently, there was a generally nihilistic attitude regarding therapy, as cancer relapses were nearly inevitable unless resected very early. Peyrilhe refined the concept suggesting that cancer was a local disease and that post-surgical relapses were either local re-growth of remnant disease or unrecognized dissemination through lymphatic or blood vessels. This view was widely embraced by prominent physicians and scholars of the time. They include anatomist Heinrich von Waldeyer–Hartz (1836–1931), famous for his work on the pharyngeal lymphoid tissue or *Waldeyer's ring* and for coining the words *chromosome* and *neuron*, surgeon Franz König (1832–1910) who is credited for first using X-rays to visualize a sarcoma in an amputated leg,[46] and Pierre Paul Broca whose *Mémoire sur l'anatomie pathologique du cancer* (Essay on the pathologic anatomy of cancer)[47] provided an empiric foundation for cancer staging and hence prognostic assessment that endures today.

Zacharias Jansen (c. 1580-c. 1638) is credited as the inventor of the microscope but scholars believe his father Hans played a key role for they worked together as spectacle makers in Middleburg, the Netherlands for Zacharias was just an adolescent at the time of the invention, circa 1590.[48] Two centuries later, Vincent Chevalier (1771–1841) and his son Charles (1804–1859) developed the first achromatic (distortion-free) objectives that Charles commercialized in France and abroad in 1842. In Chevalier's catalogue, the instrument, item No. 238, is described as a, "Vertical achromatic microscope, small model, simple and compound with three achromatic lenses, two Huygens oculars, two doublets, accessories, mahogany case, from 180 to 250 [francs]."[49]

As the resolution of microscopes improved, cells were recognized as the fundamental structural and functional units of plants and animals, setting the stage for new hypotheses about cancer to emerge, with some dissenters. For example, Johannes Müller (1801–1858) devoted his efforts to the microscopic study of tumors and, in 1839, published *On the fine structure and forms of morbid tumors* where he postulated that cancer originated, not from normal tissue, but from "*budding elements*," which his 500-fold magnifying microscope failed to identify. Alternatively, Adolf Hannover (1814–1894) fancied that cancer arose from a mysterious "*cellula cancrosa*" that was different to a normal cell in size and appearance. However, Rudolph Virchow (1821–1902), a famous pathologist and politician was unable to confirm the existence of such a cell,[50] a view first articulated by Alfred Armand Louis Marie Velpeau (1795–1867). After examining 400 malignant and 100 benign tumors under the microscope, Velpeau clairvoyantly anticipated the genetics bases of cancer writing, "The so-called cancer cell is merely a secondary product rather than the essential element in the disease. Beneath it, there must exist some more intimate element which science would need in order to define the nature of cancer."[51]

Robert Remak (1815–1865), best known for his studies on the link between embryonic germ layers and mature organs, took another step forward by postulating that all cells derive from binary fusion of pre-existing cells, and that cancer was not a *new formation* but a *transformation* of normal tissues, which resembles or, if degeneration ensues, differs from the tissue of origin. He wrote, "These findings are as relevant to pathology as they are to physiology.I make bold to assert that pathological tissues are not, any more than normal tissues, formed in an extracellular cytoblastem, but are the progeny or products of normal tissues in the organism."[52] Curiously, he dedicated much of his clinical practice to galvano-therapy considered unscientific by the medical establishment leading the medical faculty and the Cultural Ministry to refuse his application for a position at the Charité clinic in Berlin.[53] Unable to practice at the Charité and his unpaid University post as a Jew forced him to rely on income generated from patients he attended at his home where he also conducted research. It is of interest that Virchow, who in his three-volume work, *Die Krankhaften Geschwulste* postulated that cancer originated in changes in connective tissues rejecting Remak's binary fusion hypothesis but after a quick about-face claimed it as his own.[54] He is attributed the phrase *omnis cellula e cellula* (every cell derives from another cell) previously coined by François Vincent Raspail (1794–1878), a French chemist and politician as well as President of the Human Rights Society.

Louis Bard (1829–1894) expanded Remak's observations on cell division proposing, also correctly, that normal cells are capable of developing into a mature differentiated state, whereas cancer cells suffer from developmental defects that result in tumor formation.[55] Remak's and Bard's notions on cell division are significant in providing clues on the genetic origin of cancer and serving as precursors to today's histologic classification of many cancers into well differentiated, moderately differentiated and poorly differentiated subtypes; a stratification useful to plan treatment and to gage prognosis. Another notable scientist, who bridged Velpeau's views on the probable cause of cancer to our present knowledge, was Theodor Boveri (1862–1915). In an essay entitled *Zur*

Frage der Entstehung maligner Tumoren (The Origin of malignant tumors),[56] Boveri first proposed a role for somatic mutations in cancer development based on his observations in sea urchins. He found that fertilizing a single egg with two sperm cells often led to anomalous progenitor cell growth and division, chromosomal imbalance, and the emergence of tissue masses. Thus, it had taken 50 years of progress for Boveri to validate Velpeau's intuition, and it would take another half a century for the emergence of molecular biology and molecular genetics to confirm Boveri's initially ignored views on the nature of cancer.

While small pieces of the cancer puzzle were slowly falling into place, the true nature of cancer, the code governing its development, growth, and dissemination remained a mystery, and its treatment continued whimsical and inefficacious. Addressing the Massachusetts Medical Society in 1860, Oliver Wendell Holmes (1809–1894) summed up the status of drugs at the time as follows, "If the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind—and all the worse for the fishes."[57] As this statement resonated in America, progress in bacteriology and parasitology was having a profound impact on cancer theory and cancer therapeutics of the 19th century. Interest in a possible bacterial or parasitic link to cancer, first raised in the 17th and 18th century, led to equating cancer invasion to bacterial infections and to adopting the bacteria-eradication concept as a model for treating cancer, a notion that still prevails today. Between the 1880s and the 1920s, the hunt for cancer-causing microorganisms was obstinate and relentless as summed up by Sigismund Peller (1890–1980), "In the first period, every conceivable group of microorganisms was the search target: worms, bacilli, cocci, spirochetes; molds, fungi, coccidiae; sporozoa, ameba, trypanosomas, polymorphous microorganisms and filterable viruses. It was like fishing in a well-stocked pond. Most fishermen became victims of self-deception. . .".[58]

This particular saga reached a zenith when Johannes Andreas Grib Fibiger (1867–1928) was awarded the 1926 Nobel Prize in Physiology or Medicine *for his discovery of the Spiroptera carcinoma*. In the presentation speech, the Dean of the Royal Caroline Institute stated, "By feeding healthy mice with cockroaches containing the larvae of the spiroptera, Fibiger succeeded in producing cancerous growths in the stomachs of a large number of animals. It was therefore possible, for the first time, to change by experiment normal cells into cells having all the terrible properties of cancer."[59]

The long-held hypothesis of a link between microorganisms and cancer is of historic significance as it exemplifies how generations of scientists, researchers, and scholars, misguided by flawed hypotheses, often commit their talents and energy, as well as considerable human and financial resources to the unproductive pursuit of a dubious lead. While a resolute pursuit of a worthy goal by many is often necessary, overly enthusiastic adherence to a single hypothesis by many is self-reinforcing and often obfuscates good judgment while dismissing the unwelcome views of few dissenters. As our knowledge about both the causes of cancer and cancer genetics progressed, the hypothesis of the bacteriological basis of cancer eventually lost much of its luster, but not before it had established another, more pervasive and counterproductive, parallel with infectious diseases: that cancer cells, like bacteria, are foreign invaders that must be eradicated at any cost. Consequently, drug development remained hostage to the bacteria-cancer link hypothesis and unacceptably toxic antimicrobials were thought suitable to treat cancer and a few demonstrated anti-cancer activity as was the case of *daunarubicin*, a prototype anthracycline antibiotic from which anti-cancer Adriamycin® and Doxil® derive.[60] Another legacy of that period is a drug development strategy by trial and error, pioneered by Ehrlich in his 7-year quest for antimicrobials, a simplistic time- and resource-consuming approach to cancer drug development that has contributed little to improving cancer treatment after 50-years of trying. Finally, after 150 years of inconclusive evidence on the bacteria-cancer link, inflammation and mutagenic bacterial metabolites are invoked as causing several cancers. Gastric carcinoma[61] and MALT,[62] linked to the bacterium *Helicobacter pylori*, and colon cancer are cited as examples of the former and latter, respectively. A corollary of the bacteria-cancer link hypothesis is the suggestion that bacteria or their products could be used to treat cancer, a concept that goes back more than a century when William B. Coley (1862–1936) inoculated a cancer patient with erysipelas.[63] Eventually, he treated more than 1,000 patients with various bacteria and bacterial products claiming excellent results, but doubts and criticism led him to abandon of the practice.[64] Today, BCG[‡‡] administered intravesically, with or without percutaneous boosting, is the only FDA-approved[§§] bacterial agent for the non-surgical treatment of carcinoma *in situ* of the bladder. It modestly reduces tumor progression and recurrences, and prolongs survival.[65]

The discovery of anesthesia in 1842 by Crawford W. Long (1815–1878)[66] and of asepsis in 1867 by Joseph Lister (1827–1912),[67] along with refinements in surgical techniques, the advent of antibiotics, anesthetic agents, and improved medical support propelled surgery to the forefront of early-stage cancer management and increased cure rates. Likewise, the discovery of X-rays in 1895 by Wilhelm Conrad Röntgen (1845–1923),[68] uranium by Henri Becquerel (1852–1908), and radium and polonium by Marie Sklodowska-Curie (1867–1934) and her husband Pierre Curie (1859–1906),[69] marked the dawn of modern diagnostic and therapeutic radiology and of nuclear medicine, raising expectations that the successful treatment of cancer was at hand. Soon found to cause skin irritation and hair fall, X-rays were used to treat several skin conditions. J. Voigt is often credited with the use of X-rays in January 1896 to treat a patient with nasopharyngeal cancer, though I was unable to find convincing

[‡‡]Bacillus Calmette Guérin; an attenuated Bacillus Bovis.
[§§]Food and Drug Administration

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Figure 3. Pierre and Marie Curie, circa 1903.

documentation. V. Despeignes ((1866–1937) of Lyon, France deserves that credit given his July 1896 report of using X-rays to treat a patient with stomach cancer,[70] followed by H. Gocht of Hamburg-Eppendorf, Germany a few months later.[71] On the other hand, Emil H. Grubbé, a contentious Chicago physician made that claim in 1933 regarding a cancer patient presumably referred to him for treatment in January 1896 while he was a peripatetic medical student traveling the world. His often-cited claim is highly suspect.[72]

In the same timeframe, Pierre Curie developed skin burns from handling radioactive samples, the evolution of which he carefully recorded and reported, leading to collaborating with eminent physicians to further delineate the power of radioactivity in experimental animals. Their results showed that radium could cure growths including some cancers; a therapeutic method that became known as *Curietherapy*. Several clinicians applied the method to diseased individuals with "encouraging results."[73] No longer restricted to research, radioactivity would become central to an entire industry.

Röntgen was awarded the 1901 Nobel Prize in Physics for his discovery. In 1903, it was Marie and Pierre's turn to receive the same Prize, "in recognition of the extraordinary services they have rendered by their joint researches on the radiation phenomena discovered by Professor Henri Becquerel" who shared the Prize.[74] Eager to exploit radioactivity for the treatment of disease and facing inertia from her university and the French state, Marie decided to spearhead the efforts herself by providing radium samples to hospitals for therapeutic purposes and establishing a program, at the Radium Institute she founded in 1911, to train technicians and physicians in their safe use. After an entirely altruistic dedication to science, Pierre died on April 19, 1906 ran over by a horse-drawn wagon. Although sexism and xenophobia prevented her admission to the French Academy of Science in 1911, Marie was awarded that year's Nobel Prize in Chemistry for the discovery of radium and polonium. She was the first woman to win a Nobel Prize, the only woman to win two Nobel Prizes, and one of only two persons to win Nobel Prizes in more than one scientific discipline; the other being Linus Pauling (Chemistry and Peace). Marie's major and unparalleled achievements include techniques to isolate radioactive elements from pitchblende[¶¶] the discovery of Radium and Polonium, and formulating the theory of radioactivity (a term she coined). She also inspired her daughter, Irène Joliot-Curie who along with her husband Frédéric Joliot was awarded the 1935 Nobel Prize in chemistry for the synthesis of new radioactive elements, rounding up the only family awarded 5 Nobel prizes. On July 4, 1934, Marie died of aplastic anemia from exposure to unshielded x-ray equipment she operated while serving as a volunteer radiologist in field hospitals during WWI and to the very radioactivity that brought her fame.[69]

During the early part of the 20th century, the introduction of innovative research tools enabled medical investigators to systematically explore old and new hypothesis on the origin and nature of cancer, leading to incremental progress on many fronts. For example, Percivall Pott's conviction of a tar-cancer link in chimney sweeps was confirmed in 1915 by Katsusaburo Yamagiwa (1863–1930) and his assistant Koichi Ichikawa who were able to induce squamous cell carcinoma in rabbits' ears chronically painted with coal tar. Likewise, Peyton Rous (1879–1970) confirmed the virus-cancer link by inducing cancer in healthy chickens injected with a cell- and bacteria-free filtrate of a tumor from a cancer-stricken fowl, an experiment reminiscent of Peyrilhe's more than a century earlier. In his 1910 report, Rous makes no claims about the nature of the transmissible oncogenic agent.[75] His findings were rejected by much of the medical establishment for they challenged the prevailing view of the genetic heredity of cancer, and he was ostracized for many years. His momentous discovery, now known as the *Rous sarcoma virus*, was acknowledged 50 years later when he won the 1966 Nobel Prize for Physiology or Medicine. Likewise, the carcinogenicity of ionizing, solar and ultraviolet radiation and of numerous environmental agents (*e.g.*, radon), industrial products (*e.g.*, asbestos), and of a growing list of consumer products (*e.g.*, tobacco) was established.

As these health risks became known, growing public awareness and interest triggered a response by policy makers, which eventually prompted the US Congress to enact the National Cancer Act of 1937, the first major attempt to address cancer at the national level. However, the first reports demonstrating the efficacy of an anticancer drug in humans, albeit modest, took place towards the end of World War II.[76,77] Ironically, that drug was derived from mustard gas, a

[¶¶]A uranium-rich mineral and ore also called uraninite.

blistering agent first introduced as a chemical warfare agent by the Imperial German Army but widely used in WWI by both Germany and the Allies. It was know as *Yellow Cross* by the Germans (name inscribed on shells containing the gas), *HS* (Hun Stuff) by the British, and *Yperite* (after Ypres the Belgian town where the gas was first used in 1915) by the French. Despite its widespread use during WWI, countermeasures limited the death rate from mustard gas to 7.5% of 1.2 million total deaths.[78] Remarkably, mustard gas would set in motion the era of cytotoxic chemotherapy that, along with X-ray and to a lesser extent radium, was to become the bases of today's treatment of advanced cancer.

While surgery is most adept and successful at managing early stage cancer, today's treatment of inoperable cancer relies on a variety of agents administered orally or intravenously with or without surgery, radiotherapy or biological agents as adjuvants. Cancer chemotherapy is a recent development with its historical origins in observations of the toxic effects of mustard gas (sulfur mustard) in WWI, on soldiers and civilians accidentally exposed during the Bari raid during WWII, and on animal and human experimental studies preceding and during WWII. Mustard gas is the common name for 1,1-thiobis(2-chloroethane), a vesicant chemical warfare agent synthesized in 1860 by Frederick Guthrie (1833–1886)[79] and first used on July 12, 1917 near Ypres (Flanders); hence its alternate name: Yperite. Because it could penetrate masks and other protective equipment available during WWI and given its widespread use by both sides of the conflict, its effects were particularly horrific and deadly.[80] Out of 1,205,655 soldiers and civilians exposed to Mustard gas during WWI, 91,198 died.[81] In 1919, a captain in the US Medical Corps reported decreased white blood cell counts and depletion of the bone marrow and of lymphoid tissues in survivors of mustard gas exposure he treated in France.[82] Shortly thereafter, military researchers from the US Chemical Warfare Service reported similar effects in rabbits injected intravenously with dichloroethylsulfide contaminated with mustard gas.[83] Other reports between 1919 and 1921 described various properties of dichloroethylsulfide *in vitro* and in laboratory animals[84–86] previously developed for screening thousands of potential anti-cancer compounds.[87,88] Fifteen years later the anti-cancer activity of mustard gas in experimental animal models was reported for the first time.[89]

Soon after, mustard gas was brought to the world's attention by a WWII incident where servicemen and civilians were accidentally exposed to the agent, contributing to launching the era of cancer chemotherapy.[90] A 10-centuries old town of ~65,000 people, Bari was both the main supply center for British General Montgomery's Army and headquarters of the American Fifteenth Air Force division. In the afternoon of December 2, 1943 a German Messerschmitt Me-210 reconnaissance plane made two undisturbed high altitude passes over the city, followed a few hours later by a major air raid by a squadron of 105 twin-engine Junkers Ju-88 A-4 bombers that became known as "second Pearl Harbor." In a mere twenty minutes, twenty-eight merchant ships and eight allied ships were sunk or destroyed including the U.S.S. *John Harvey*, a 7,176-ton Liberty-type American ship, carrying a secret load of 2,000 M47A1 60–70 pound mustard gas bombs.[91,92] Some of the bombs were damaged, "...causing liquid mustard to spill out into water already heavily contaminated with an oily slick from other damaged ships...[Men pulled from the water] were covered with this oily mixture...[By day's end] symptoms of mustard poisoning appeared in [rescued, rescuers, and in] hundreds of civilians ... [exposed to] a cloud of sulfur mustard vapor...[emanating from exploded] bombs...." Informed of the mysterious malady, Deputy Surgeon General Fred Blesse dispatched Lt. Col. Stewart Francis Alexander, a military physician whose WWI experience quickly led him to suspect mustard gas. Carefully tallying the location of the victims at the time of the attack he was able to trace the epicenter to the John Harvey, confirming his suspicion when he located a fragment of an M47A1 bomb he knew contained mustard gas. By the end of the month, 83 of the 628 hospitalized military mustard gas victims had died. Civilian casualties were much higher but the exact number is uncertain because most had sought refuge with relatives out of town. This was the only episode of exposure to a chemical warfare agent during WWII.

In the meantime, the Office of Scientific Research and Development (OSRD), an agency of the US War Department, funded Milton Winternitz of Yale University to conduct secret chemical warfare research in search of antidotes to mustard gas.[93] Winternitz asked Alfred Gilman Sr. (1908–1984) and Louis S. Goodman (1906–2000) to assess the therapeutic potential of its derivative, nitrogen mustard (where the sulfur atom on the mustard gas is substituted by a nitrogen atom). Their initial studies confirmed the latter's toxicity to rabbits' blood cells and its anti-tumor activity in mice xenotransplanted with a lymphoid tumor. These encouraging results led to the first experimental use of nitrogen mustard on JD, a 48-year-old Polish immigrant with refractory lymphosarcoma. Given the secrecy surrounding mustard gas studies, which remained in place well after WWII had ended, JD's records were "lost" until May 2010 when, through persistence and luck, two Yale surgeons found their off-site location and revealed their content at a Yale Bicentennial Lecture on January 19, 2011.[94] Unsurprisingly, JD's record nowhere mentioned nitrogen mustard, referring instead to a "lymphocidal" agent or "substance X." Given its historical significance as the first patient ever treated with an anti-cancer agent, a synopsis of JD's clinical case is warranted.

In August 1940, JD developed rapidly enlarging tonsillar, submandibular, and neck lymph nodes. A node biopsy revealed lymphosarcoma. Referred to Yale Medical Center in February 1941, "He underwent external beam radiation for 16 consecutive days with considerable reduction in tumor size and amelioration of his symptoms. However...by June 1941, he required additional surgery to remove cervical tumors...[and] underwent several more cycles of radiation to reduce the size of the tumors, but by the end of the year they became unresponsive and had spread to the axilla. By August 1942 . . . he suffered from respiratory distress, dysphagia, and weight loss, and his prognosis appeared hopeless."

Having exhausted what was then standard lymphoma treatment, Drs. Gilman, Goodman and Gustaf Lindskog (1903–2002), a Yale surgeon, offered JD Nitrogen Mustard as experimental treatment. "At 10 a.m. on August 27, 1942, JD received his first dose of chemotherapy recorded as 0.1 mg kg^{-1} of synthetic "*lymphocidal chemical*." This dosage was based on toxicology studies performed in rabbits. He received 10 daily intravenous injections, with symptomatic improvement noted after the fifth treatment. Biopsy following completion of the treatment course remarkably revealed no tumor tissue, and he was able to eat and move his head without difficulty. However, by the following week, his white blood cell count and platelet count began to decrease, resulting in gingival bleeding and requiring blood transfusions. One week later, he was noted to have considerable sputum production with recurrence of petechiae,*** necessitating an additional transfusion. By day 49, his tumors had recurred, and chemotherapy was resumed with a 3-day course of "*lymphocidin*." The response was short-lived, and he was administered another 6-day course of substance "*X*." Unfortunately, he began experiencing intraoral bleeding and multiple peripheral hematomas and died peacefully on December 1, 1942 (day 96). Autopsy revealed erosion and hemorrhage of the buccal mucosa, emaciation, and extreme aplasia of the bone marrow with replacement by fat."

Given the cloak of secrecy involving war gas research, all experimental studies were kept secret until 1946 when the Yale researchers were allowed to begin publishing their wartime clinical experiments; the first of which included the following disclosure, "This article was prepared as a background for forthcoming articles on the clinical application of the 3-chloroethyl amines with the approval of the following agencies: Medical Division, Chemical Warfare Service, United States Army; Division 9, NDRC, and Division 5, Committee on Medical Research, OSRD; Committee on Treatment of Gas Casualties, Division of Medical Sciences, NRC††† and Chemical Warfare Representative, British Commonwealth Scientific Office."[95]

For good or for evil, the chemotherapy era had begun.

Cancer milestones through WWII

- Cancer documented in 70 million-old dinosaur fossils. Pg 1.
- Hints of human cancer are found in Egyptian papyri (1500–1600 BCE). Pg 1.
- Oldest proven case of disseminated human cancer, ~2,700 years ago. Pg 1.

***Tiny, flat, and red cutaneous spots caused by capillary hemorrhage.
†††National Research Council

- Hippocrates (c.460–360 BC) describes diseases that produce masses (*onkos*) and coins the words *karkinos* and *karkinomas* referring to benign and malignant processes. Pg 4.
- Aulus Cornelius Celsus (25BC-50AD) describes the evolution of tumors from resectable *cacoethes* to untreatable invasive *carcinos* or *carcinomas*. He is credited to having performed the first reconstruction surgery following excision of cancer. Pg 4.
- Galen of Pergamum (c.129–200) classified tumors according to nature and gravity in the first ever written document of antiquity devoted exclusively to tumors. Pg 6.
- Oribasius of Pergamum (325–403) stressed the painful nature of cancer especially of the face, breast, and genitalia. Pg 7.
- Aëtius of Amidenus (502–575) described swollen blood vessels around breast cancer that look like crab legs. Pg 7.
- Paulus Ægineta (c.625–690) called attention to axillary lymph nodes in breast cancer and advocates poppy extracts to combat pain. Pg 7.
- Avenzoar (1094–1162) first described the symptoms of esophageal and stomach cancer and proposed feeding enemas to keep patients alive. Pg 8.
- Ibn Al-Nafis (1213–1288) described the pulmonary circulation and the anatomy of the lung and the function of the coronary circulation. Pg 9.
- Paracelsus (1493–1541) and Johannes Baptista van Helmont (1577–1644) proposed to substitute Galen's black bile by supernatural forces that govern health and disease, called "*ens*" and "*Archeus*," respectively. Pg 10.
- Ambroise Paré (1510–1590) referred to cancer as *Noli me tangere* (do not touch me) declaring, "Any kind of cancer is almost incurable and. . .[if operated] heals with great difficulty." Pg 10.
- Gabriele Fallopius (1523–1562) accurately described the clinical differences between benign and malignant tumors. Pg 10.
- Zacharias Jansen (c.1580–1638) invented a prototype to the microscope. Pg 16.
- Gaspare Aselli (1581–1626) discovered lymph, Jean Pecquet (1622–1674) its circulation and drainage into the thoracic. Pg 11.
- Bernardino Ramazzini (1633–1714) reported a virtual absence of cervical cancer but a higher incidence of breast cancer in nuns compared to married women he thought possibly related to sexual activity. Pg 12.
- Jean-Louis Petit (1674–1750) advocated total mastectomy for breast cancer, including resection of axillary "glands" to preclude recurrences. Pg 11.
- Henri François Le Dran (1685–1770) postulated the local origin of cancer and its spread via lymphatic channels becoming inoperable and fatal. Pg 10.

- Giovanni Battista Morgagni (1682–1771) reported on 700 autopsies of patients who died of breast, stomach, rectum, and pancreas cancer. Pg 11.
- The first cancer hospital (at Rheims, France) welcomed 8 cancer patients in 1740. Pg 11.
- Joseph Recamier (1774–1852) coined the term *metastases* to describe distal cancer and advocated the use of the vaginal speculum to examine female genitalia. Pg 11.
- John Hill (1716?–1775?) warned of the dangers of tobacco snuff. Pg 12.
- Percival Pott (1714–1788) called attention to scrotum cancer in chimney sweeps. Pg 12.
- Bernard Peyrilhe (1735–1804) postulated a cancer-promoting factor (*Ichorous matter*) akin to a virus and tested its transmissibility by injecting breast cancer extracts under the skin of a dog one century before Rous' proved the virus-cancer. He adopted Petit's surgical approach to breast cancer but added resection of the pectoralis major muscle. Pgs 13–14.
- Vincent Chevalier (1771–1841) and his son Charles (1804–1859) developed the first distortion-free (achromatic) objectives. Pg 13.
- Jacques Delpech (1772–1835) invoked a cancer predisposition or *diathesis* soon adopted by Bayle (1774–1816) and later by Broca (1824–1880), Paget (1814–1899) and Rokitansky (1804–1878). Pg 12.
- François Vincent Raspail (1794–1878) postulated *omnis cellula e cellula* (every cell derives from another cell). Pg 14.
- Louis Marie Velpeau (1795–1867) anticipated that science will eventually discover an element within each cell necessary to define the nature of cancer. Pg 13.
- Adolf Hannover (1814–1894) postulated a mysterious *cellula cancrosa* that was different to a normal cell in size and appearance. Pg 13.
- Robert Remak (1815–1865) believed all cells derive from binary fusion of pre-existing cells and that cancer was not a *new formation* but a *transformation* of normal tissues. Pg 14.
- Crawford W. Long (1815–1878) discovered anesthesia and Joseph Lister (1827–1912) emphasized asepsis, propelling surgery to the forefront of early stage cancer management. Pg 17.
- Pierre Paul Broca (1824–1880) provided an empiric base for cancer staging and prognosis. Pg 13.
- Louis Bard (1829–1894) proposed that normal cells mature by differentiation whereas cancer cells suffer from developmental defects. Pg 14.
- Wilhelm Conrad Röntgen (1845–1923) discovered X-rays in 1895. Pg 19.
- Franz König (1832–1910) first used X-rays to visualize cancer. Pg 13.
- von Waldeyer-Hartz (1836–1931) described the pharyngeal lymphoid *Waldeyer's ring* and coins the words *chromosome* and *neuron*. Pg 13.
- William Stewart Halsted (1852–1922) popularized "radical mastectomy" practiced by Peyrilhe a century earlier. Pg 11.
- Theodor Boveri (1862–1915 first proposed a role for somatic mutations in cancer development based on his observations in sea urchins. Pg 14.
- Johannes Andreas Grib Fibiger (1867–1928) was awarded the 1926 Nobel Prize in Physiology or Medicine *for his discovery of the Spiroptera carcinoma* that causes cancer in cockroaches. Pg 15.
- William B. Coley (1862–1936) inoculated a cancer patient with erysipelas in attempts to prove the bacteria-cancer link. Pg 16.
- Henri Becquerel (1852–1908) discovered uranium. Pg 19.
- Marie Sklodowska-Curie (1867–1934) and Pierre Curie (1859–1906) were awarded the 1903 Nobel Prize in Physics for their joint research on radiation phenomena. Pg 16.
- Marie Sklodowska-Curie (1867–1934) was awarded the 1911 Nobel Prize in Chemistry for discovering radium and polonium. Pg 16.
- Victor Despeignes (1866–1937) was the first to use X-rays to treat a patient with cancer in July 1896. Pg 19
- Marie Sklodowska-Curie (1867–1934) recruited clinicians to use radium to treat growths, tumors, and some cancers, and in 1911 founded the Radium Institute for that purpose. Pg 19.
- Katsusaburo Yamagiwa (1863–1930) induced squamous cell carcinoma in rabbits' ears chronically exposed to coal tar. Pg 17.
- Irène Joliot-Curie and Frédéric Joliot, were awarded the 1935 Nobel Prize in chemistry for the synthesis of new radioactive elements. Pg 18.
- Peyton Rous (1879–1970) demonstrated the virus origin of cancer in chickens and was awarded the 1966 Nobel Prize for Physiology or Medicine for the momentous discovery. Pg 18.
- The US Congress enacted the *National Cancer Act of 1937*, the first major attempt to address cancer at the national level. Pg 18.
- Frederick Guthrie (1833–1886) discovered mustard gas, a vesicant chemical warfare agent that caused 91,198 deaths in WWI, but was precursor to nitrogen mustard the first anticancer agent. Pg 18.
- Alfred Gilman (1908–1984), Louis Goodman (1906–2000) and Gustaf Lindskog (1903–2002) induced a partial and short-lived tumor response in a patient with lymphosarcoma treated with nitrogen mustard. Pgs 22–23.

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