Chapter 2
An Historical Overview: From Prehistory to WWII

The only true wisdom is in knowing you know nothing.

– Socrates

2.1 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, increasingly risky health behavior in the general population and the increased presence of carcinogens in consumer products and in the environment. The oldest credible evidence of cancer in mammals consists of tumor masses found in fossilized dinosaurs and human bones from pre-historic times. Perhaps the most compelling evidence of cancer in dinosaurs emanates from a recent large-scale study that screened by fluoroscopy more than 10,000 specimens of dinosaur vertebrae for evidence of tumors and assessed abnormal vertebrae by computerized tomography (CT) [27]. Of the various species of dinosaurs surveyed, only *cretaceous hadrosaurs* (duck-billed dinosaurs) that lived approximately 70 Ma ago exhibited tumors, and although most were benign (hemangiomas,[1] desmoplastic fibromas,[2] and osteoblastomas[3]), malignant metastatic cancers also were detected in 0.2 % of specimens tested.

The earliest written record of what is generally agreed to have been human cancer appeared in ancient Egyptian manuscripts discovered in the nineteenth century, especially the Edwin Smith and George Ebers papyri that describe surgical, pharmacological, and magical treatments. They were written between 1500 and 1600 BCE, possibly based on material from thousands of years earlier. The Smith papyrus, possibly written by the physician-architect Imhotep, who designed and built the step pyramid at Sakkara in the thirtieth century BCE under Pharaoh Djoser, is believed to contain the first reference to breast cancer (case 45) when referring to tumors of the anterior chest. It postulates that when such tumors are cool to touch, bulging, and

[1] Benign vascular tumors.

[2] Benign fibrous tumors of bone.

[3] Rare benign bone tumors.

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have spread over the breast, no treatment can succeed [28]. It also provides the earliest mention of suturing wounds and 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 and practiced by priests and sages, and famous physicians were thought to be gods' intermediaries. For instance, in case 1 of the Edwin Smith papyrus, physicians are called "lay-priests of Sekhmet." Sekhmet, the feared lion-headed "lady of terror" and one of the oldest Egyptian deities, was known as the "lady of life" patron of physicians and healers [29].

The earliest cancerous growths in humans were found in Egyptian and Peruvian mummies dating back to approximately 1500 BC. The oldest scientifically documented case of disseminated cancer was that of a 40–50 year-old Scythian king who lived in the steppes of Southern Siberia approximately 2,700 years ago. Modern microscopic and proteomic techniques confirmed the cancerous nature of the lesions throughout his entire skeleton and their prostatic origin [30]. Half a millennium later and half a world away, a Ptolemaic Egyptian was dying of cancer [31]. 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 favor prostate as the most likely origin.

2.2 From Ancient Egypt to Greece and Rome

Following the decline of Egypt, Greek and Roman medicine became preeminent, especially with Hippocrates of Kos (460–c.360 BC), an island off the coast of Turkey, and Claudius Galenus (AD 129–c.216), better known as Galen of Pergamum (modern-day Bergama, Turkey). Their writings, describing their life-long experience and observations, became the foundation and repository of medical knowledge for the ensuing 1,500 years.

Although little is known with certainty about who he was, what he thought and wrote, and how he practiced medicine, the image we now have of Hippocrates 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" [32]. 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. Much of what we know about Hippocrates we owe to Soranus of Ephesus (a second century AD Greek physician), his first biographer, and to Aristotle (384 BC–322 BC), who mentions him in his writings as *The Great Hippocrates*. The medical legacy associated with 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"[4] of medical writings on a variety of medical topics, including "On air, water, and places", "On ancient medicine", "On epidemics", "On surgery", "On the sacred disease", "On ulcers", "On fractures", "On Hemorrhoids", "Aphorisms" [33], "The oath", and many others of which he might have written only 12–14, according to scholars' best estimates (Fig. 2.1).

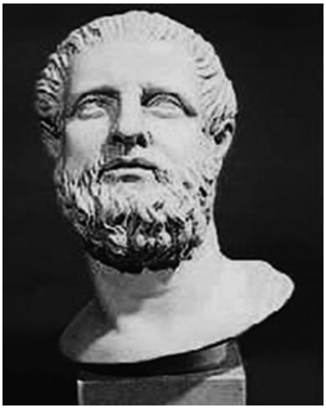

Fig. 2.1 Hippocrates of Kos

The Hippocratic Oath, sworn upon a number of healing gods, required new physicians to be trained and to uphold a number of professional ethical standards. Today, few medical schools adhere to this ancient rite of passage. The Oath:

> I swear by Apollo the physician, Asclepius, Hygieia, Panacea, and all the gods and goddesses as my witnesses, that, according to my ability and judgment, I will keep this Oath and this contract:
>
> 1. To hold him who taught me this art equally dear to me as my parents, to make my teacher a partner in life, and to fulfill his needs when required; to look upon his offspring as equals to my own siblings, and to teach them this art, if they shall wish to learn it, without fee or contract; and that by the set rules, lectures, and every other mode of instruction, I will impart a knowledge of the art to my own sons, and those of my teachers, and to students bound by this contract and having sworn this Oath to the law of medicine, but to no others.
> 2. I will use those dietary regimens which will benefit my patients according to my greatest ability and judgment, and I will do no harm or injustice to them.
> 3. I will not give a lethal drug to anyone if I am asked, nor will I advise such a plan; and similarly I will not give a woman a pessary to cause an abortion.
> 4. In purity and according to divine law will I carry out my life and my art.
> 5. I will not use the knife, even upon those suffering from stones, but I will leave this to those who are trained in this craft.
> 6. Into whatever homes I go, I will enter them for the benefit of the sick, avoiding any voluntary act of impropriety or corruption, including the seduction of women or men, whether they are free men or slaves.

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

7. Whatever I see or hear in the lives of my patients, whether in connection with my professional practice or not, which ought not to be spoken of outside, I will keep secret, as considering all such things to be private.
8. So long as I maintain this Oath faithfully and without corruption, may it be granted to me to partake of life fully and the practice of my art, gaining the respect of all men for all time. However, should I transgress this Oath and violate it, may the opposite be my fate [34].

The Hippocratic Oath is remarkable for it promotes both a system of accreditation requiring a period of apprenticeship and an ethical professional code of conduct that differentiate knowledgeable and trustworthy physicians from improvised healers, whether this was intended or not.

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. If he looks his usual self this is a good sign. If not, however, 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 the face is like this at the beginning of the illness, the doctor must ask the patient if he has lost sleep, or had diarrhea, or not eaten [35].

In his book "On epidemics", he advises to record patients' symptoms and appearance on a day-to day-basis in order to forecast disease progression or recovery. He believed that health resulted from the balance and disease from the imbalance in the main four body fluids or humors: *black bile*, *yellow bile*, *phlegm*, and *blood*, each originating in a different organ and each corresponding to a personal temperament, a physical earthly element, and a specific season (Table 2.1). However, while Hippocrates subscribed to the theory that was later adopted by Greek, Roman, and Muslim physicians, its true origins are controversial.

Table 2.1 Hippocrates' humoral system of health and disease

Humor	Organ	Temperament	Element	Season
Blood	Heart	Sanguine	Air	Spring
Black bile	Spleen	Melancholic	Earth	Summer
Yellow bile	Liver	Choleric	Fire	Fall
Phlegm	Brain	Phlegmatic	Water	Winter

The relative dominance of one of the humors determined personality traits and their imbalance resulted in a propensity toward certain diseases. Thus, 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. The Hippocratic Corpus deals at length with diseases that produced masses (*onkos*), and coined the word *karkinos* to describe ulcerating and non-healing lumps that in retrospect 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, actual cautery often heals; but when all these fail, the disease is incurable" [36]. To his credit, he recognized the relentless progression of deep-seated karkinomas and the often-negative effect of treatment when he wrote: "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 [37]). Hippocrates died at Larissa, in Thessaly, at the probable age of 100.

Aulus Cornelius Celsus (25 BC–50 AD), a Roman physician and one of Hippocrates' most prominent successors, also held the view that "the excised carcinomas have returned and caused death" [38]. He described the evolution of tumors from *cacoethes* followed by *carcinos* (which he later called *carcinomas*) without ulceration, then fungated ulcers and is credited as the first to have performed reconstruction surgery following excision of cancer [39]. Celsus believed that cacoethes were treatable by surgical resection, whereas more advanced lesions were unresponsive and should be left alone. He wrote,

> 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 to an increase until they cause death [40].

Yet, he acknowledged that only time could differentiate the stage of a particular tumor,

> 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 [41].

He vividly described the invasive nature of advanced cancer,

> 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 [42].

Archigenes of Apamea, Syria (75–129 AD), who practiced in Rome in the time of Trajan, 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 cope with the harshness of the operation, warning, "if it has taken anything into its claws it cannot be easily ripped away." However, Hippocrates' most prominent successor and the one who propelled his legacy for nearly 15 centuries was Galen.

Galen was born of Greek parents in Pergamum, the ancient capital of the Kingdom of Pergamum during the Hellenistic period, under the Attalid dynasty (281–133 BC). In Galen's time, Pergamum was a thriving cultural center famous for its library second only to Alexandria's and its statue of Asclepius (Aesculapius in Latin), the Greek god of medicine and healing. His prosperous patrician architect father, Aelius Nicon, oversaw Galen's broad and eclectic education, which 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 (152–157 AD), where he studied anatomy and was exposed to 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” [43]. In 157 AD, his appointment as physician of the gymnasium attached to the Asclepius sanctuary of Pergamum 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 (presumably smallpox) struck.

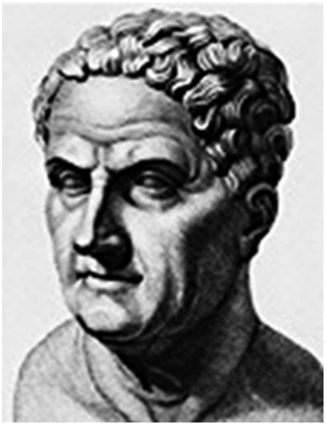

Fig. 2.2 Galen of Pergamum

Two years later, Roman Emperors Marcus Aurelius and Lucius Verus recalled 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 named personal physician to Emperor Marcus Aurelius 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, Galen 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. He viewed himself as the best interpreter of Hippocratic thought. His pioneering anatomical studies, based on dissecting pigs and primates, were only surpassed by Andreas Vesalius’ pivotal 1543-work *De humani corporis fabrica* that described and illustrated human dissections. He was the first to recognize the difference between arterial (bright) and venous (dark) blood, which he postulated to be distinct systems originating from the heart and liver, respectively. He used vivisections to study body functions. For instance, when he cut the laryngeal nerve of a pig, the animal stopped squealing; this nerve is now known as *Galen’s Nerve*. Likewise, he showed that urine came from kidneys by tying the ureters, 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 only 2,000 years later. 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 (AD 191). In *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, either because they were written later, or because for whatever reason Galen chose to disown them" [44].

The influence of Galen's 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, but Greek medical tradition remained alive and well in the Eastern Roman (Byzantine) Empire. This is because interest in Greek science and medicine by Arab Muslims during the Abbasid period led to translations of Galen's work into Arabic, many of them by Syrian Christian scholars. The need to be fluent in Greek or Arabic limited the number of later scholars capable of translating Galen's work into modern languages. Perhaps the most complete and authoritative compendium of Galen's work is the one compiled by Karl Gottlob Kühn of Leipzig between 1821 and 1833. It assembled 122 of Galen's works into 22 volumes (20,000 pages in length), translated from the original Greek into Latin and published in both languages. In addition to contributing to understanding anatomy, physiology, pathology, neurology, pharmacology, and other disciplines, Galen bridged the Greek and Roman medical worlds by enshrining Hippocratic principles and his own as the foundation of all medical knowledge that lasted through the Middle Ages. Indeed, many of the later medical scholars, teachers, and practitioners referred to Galen as the source of all medical knowledge, including Oribasius of Pergamum, Aëtius of Amidenus, Alexander of Tralles, and Paulus Ægineta. Professor Vivian Nutton, 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" [45]. With respect to cancer, Galen addressed tumors of various types and origins, distinguishing *onkoi* (lumps or masses in general), *karkinos* (including malignant ulcers), and *karkinomas* (including non-ulcerating cancers) [46]. His greatest contribution to advancing our understanding of cancer was the classification that graded 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 the growth of breasts during puberty, or even 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 the preferred treatment of 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. Not surprisingly, despite his decisive role in shaping Greek medical tradition and his influence on medical practice lasting nearly 1,500 years, Galen's original contributions to understanding and treating cancer were essentially nil. He died in Rome at the probable age of 87 [47].

2.3 From Rome to the Middle Age

With the collapse of Greco-Roman civilization after the fall of Rome in 476 AD, medical knowledge in the Western Roman Empire stagnated and many ancient medical writings were lost. Nevertheless, prominent physician-scholars emerged during the Eastern Roman or Byzantine Empire by the end of the fourth century, including Oribasius of Pergamum (325–403), Aëtius of Amidenus (502–575), and Paulus Ægineta (625?–690?), all of whom wrote about cancer. 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 (resembling a crab). He believed that surgery for uterine cancer was too risky but advocated that approach for more accessible cancers, such as breast. In his writings, he upheld observations on breast cancer made by Leonides of Alexandria (second 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 [48].

A century later, Paulus Ægineta published seven books 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 [49].

In book IV, section 26, he states that cancer "occurs in every part of the body…but it is more particularly frequent in the breasts of women…". In book VI, section 45, 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 [50].

He called attention to the presence of lymph nodes in the armpits of women with breast cancer and advocated poppy extracts to combat pain. 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. Paulus Ægineta clearly acknowledges its 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…[51].

Greek scientific tradition spread widely, first through Christian Syriac writers, scholars, and scientists reaching Arab lands mainly via translations of Greek texts into Arabic by "Nestorians" [52]. Followers of Nestorius, Patriarchy of Constantinople, Nestorians' teachings were eventually condemned as heretical at the Council of Chalcedon (451 AD). Nestorianism spread throughout Asia Minor through churches, monasteries, and schools where Nestorian monks came into close contact with Arabs. 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" [53] 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… [54].

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 [55].

And he was the first to describe the coronary circulation and its function, "The nourishment of the heart is through the vessels that permeate the body of the heart" [56].

Of greatest interest to us is Avenzoar, who first described the symptoms of esophageal and stomach cancer in his book *Kitab al-Taysir*, and proposed feeding enemas to keep alive patients with stomach cancer [57], a treatment approach unsuccessfully attempted by his predecessors. 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 had become 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, 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 "The Catholic", Queen of Castile and León and her husband Ferdinand II of Aragón, completing the centuries-long recapture of the Iberian Peninsula from the Arabs, marked the decline of the Islamic world that accelerated the demise of traditional Hippocratic and Galenic medicine.

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*[5] 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 [58].

Perhaps the most famous Hospitium was the ninth century *Studium* of Salerno, a coastal town in southern Italy, key to trade with Sicily and other Mediterranean towns. Although this humble dispensary was initially sustained by the needs of thousands of pilgrims en route to the Holy Land, the Studium soon became the first formal association of physicians that eventually grew into the *Schola Medica Salernitana*. Fostered by its Greek past, the dispensary and the town rose in fame with the arrival at a nearby abbey in 1060 of Constantine Africanus, a Benedictine monk and native of 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 of its teachers and scholars, women as well as men, and of their writings still anchored in the Hippocratic-Galenic tradition. Prominent and best known medical writings arising from the Studium in that period include the *Breviary on the Signs, 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 between the eleventh and thirteenth centuries. And although the *Studium* had little direct impact on the progress of medicine, it is noteworthy mainly as the precursor of the *Schola Medica Salernitana*, the first university of medicine in the world, and as a model for the greatly influential and enduring pre-Renaissance medical schools at Montpellier (1150), Bologna (1158), and Paris (1208) that through local and relocated scholars became European meccas for the study and practice of medicine.

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[5] Precursors to today's hospices.

2.4 From Medieval Europe 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 who fled Constantinople after the Turks conquered Byzantium in 1453, thus 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 that culminated in the publication of two revolutionary and immensely influential treatises of that period: "*De Humani Corporis Fabrica Libri Septum*" (*Seven Books on the Fabric of the Human Body*) [59] by Andreas Vessalius (1514–1564), and "*De Revolutionibus orbium coelestium*" (*On the Revolutions of the Celestial Orbs*) by Nicolaus Copernicus (1473–1543) [60]. Likewise, progress was made in surgical techniques and treatment of wounds, thanks to Ambroise Paré (1510–1590), surgeon to the French Armies, private physician to three Kings of France 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 [61]. He is said to have turned butchery into humane surgery. However, this burst of Renaissance knowledge did not extend to cancer, leading Paré to call all cancers *Noli me tangere* (do not touch me) and to declare, "Any kind of cancer is almost incurable and…[if operated]…heals with great difficulty" [62].

Nonetheless, some of the physical attributes of cancer began to emerge. Gabriele Fallopius (1523–1562) is credited with having described the clinical differences between benign and malignant tumors, a distinction largely applicable today. He identified malignant tumors by their woody firmness, irregular shape, multilobulation, adhesion to neighboring tissues (skin, muscles, and bones), and by congested blood vessels often surrounding the lesion. In contrast, benign tumors were said to be softer masses of regular shape (often round) that are movable and do not adhere to adjacent structures. Like his predecessors, he advocated a cautious approach to cancer treatment, "Quiescente cancro, medicum quiescentrum" (If a cancer doesn't bother, leave it alone). More importantly, for the first time in 1,500 years, 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 substituting Galen's black bile with *"ens"* (entities): *ens astrorum* (cosmic entities); *ens veneni* (toxic entities); *ens naturale et spirituale* (physical or mental entities); and *ens deale* (providential entities). Similarly, Johannes Baptista van Helmont (1577–1644) envisioned a mysterious "*Archeus*" system [63]. 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) [64]. 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 chyle (lymph) by Gaspare Aselli (1581–1626) [65] and of its circulation and final drainage into the blood system through the thoracic duct later discovered by Jean Pecquet (1622–1674), and the circulation of blood in a system that included the heart, arteries, and veins, discovered by William Harvey (1578–1657), led scholars to conclude that Galen's black bile implicated in cancer could be found nowhere, whereas lymph was everywhere and was therefore suspect. For instance, 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 [66], 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' [67, 68]. Three and a half centuries later, the practice survives as a prognostic indicator rather than as a preventive measure. Petit's surgical approach to breast cancer surgery is still current today after many modifications made possible by enormous progress achieved in surgical techniques, anesthesia, antibiotics, and general medical support.

How cancer began and what its causes were remained a puzzle, and several scientific 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 explore systematically the causes, nature, patterns of growth, and treatment of cancer [69] 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 degenerated or putrefied lymph. To test whether the *Ichorous matter* was contagious, he injected breast cancer extract under the skin of a dog, which he kept at home under observation. However, his servants drowned the constantly howling dog, thus cutting short the experiment. Peyrilhe also subscribed to the notion of the local origin of cancer and called disease emerging distally as *consequent cancers*. Like Petit's, his surgical approach to breast cancer 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 the "radical mastectomy", which consisted of removing the breast, the axillary nodes, and the major and minor pectoralis muscles in a single *en bloc* procedure [70]. Yet more aggressive twentieth century surgeons added prophylactic oophorectomy, adrenalectomy, and hypophysectomy[6] to breast cancer surgery, procedures

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

that have been abandoned as ineffective and mutilating. The term *metastases* to describe cancer arising distally to the primary lesion was coined in 1829 by Joseph Recamier, a French gynecologist better known for advocating the use of the vaginal speculum to examine female genitalia. 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 died from breast, stomach, rectum, and pancreas cancer. On another front, recognizing that the special needs of cancer patients were not being met, Jean Godinot (1661–1739), canon of the Rheims cathedral, bequeathed 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* became functional in 1740 amidst strong protestations by local inhabitants. It initially welcomed 8 cancer patients; 5 women and 3 men [71]. However, the fear that cancer might be contagious was such that cancer patients were avoided, as were lepers, and the inhabitants of Rheims eventually succeeded in having the hospital relocated outside the city 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) [72], 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 diseases. The inclusion of detailed descriptions of 52 specific occupational illnesses and their link to a particular work activity or work environment, supported by literature surveys, and complemented by suggested remedies won him the title *Father of modern occupational medicine* [73] and, three centuries later, to the Colegium Ramazzini, an international organization dedicated to the advancement of occupational and environmental issues [74]. In 1713, he reported a virtual absence of cervical cancer but a higher incidence of breast cancer in nuns relative to married women and thought there might be a connection to their celibacy, a notion challenged in 1991 [75]. Surprisingly, he suggested a lack of sexual activity as the possible cause for both. Yet, he couldn't have known that refraining from sexual activity lowered nuns' exposure to the virus responsible for the vast majority of cervical cancers. Indeed, we now know from empiric evidence that over 90 % of cases of cervical cancers worldwide are caused by sexually transmitted human papillomaviruses (HPV), especially HPV-16 [76]. Hence, life-long celibate women, whether nuns or not, are not exposed to genital HPVs and should be spared 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" [77], and in 1775, Percivall Pott (1714–1788) called attention to scrotum cancer in chimney sweepers. In his *Chirurgical observations relative to the Cataract, the Polypus of the Nose, and the Cancer of the Scrotum, etc.*, he accurately noted,

> Ramazzini has written a book De morbis artificum; the Colic of Poictou[7] is a well-known distemper, and every body is acquainted with the disorders to which painters, plummers, 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 publickly 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 [78].

Pott was well aware of the progressive nature of the disease, of the benefits of early intervention, and of the questionable outcome of late surgical intervention, for he advised,

> 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 [79].

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…" [80] Two centuries later, scrotal cancer in chemeney sweepers was linked to absorption of polycyclic aromatic hydrocarbons [81]. In his Chirurgical observations book, Pott states not having encountered any case under the age of puberty. Yet, his editor added a footnote regarding an 8-year old 'chimney sweeper apprentice' whose scrotum cancer was confirmed by Pott [82]. A century later (1875), an Act of the British Parliament, passed in 1840, was finally enforced. It provided for chimneysweepers to be licensed and forbade both chimney climbing before age 21 and apprenticeship before age 16 [83].

Notwithstanding a better understanding of certain aspects of cancer, other baffling observations of that time included recurrence at sites 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) [84], 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. Yet, different medical writers often used the terms diathesis, predisposition, and even cachexia interchangeably. For instance, 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 considered nearly inevitable unless resected very early. However, the observation that at least some cancers were surgically curable

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

convinced Peyrilhe and followers that cancer was a local disease, and that relapses after surgery were either local re-growth of remnant disease or unrecognized early dissemination through lymphatic or blood vessels. This view was widely embraced by prominent physicians and medical writers of the time, including 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 [85], and Broca, whose *Mémoire sur l'anatomie pathologique du cancer* (Essay on the pathologic anatomy of cancer) [86] provided an empiric foundation for cancer staging and hence prognostic assessment that endures today.

Zacharias Jansen (c. 1580–c. 1638) is credited as inventor of a prototype to the microscope but scholars believe his father Hans must have played a key role, for they worked together as spectacle makers in Middleburg, the Netherlands, and Zacharias was just an adolescent at the time of the invention, circa 1590 [87]. Three centuries later, Vincent Chevalier (1771–1841) and his son Charles (1804–1859) developed the first distortion-free (achromatic) objectives that served as a basis for the younger Chevalier to introduce, in 1842, the first commercially achromatic microscope with great success in France and abroad. In Chevalier's catalogue, the instrument, item No. 238, is described as,

> 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] [88].

As microscopes improved in power and resolution, cells were recognized as the fundamental structural and functional unit 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*. 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 from a normal cell in size and appearance. However, Rudolph Virchow (1821–1902) and his followers were unable to confirm the existence of such a cell [89], a view first articulated by Alfred Armand Louis Marie Velpeau (1795–1867). After examining 400 malignant and 100 benign tumors under the microscope, Velpeau concluded, as if he had correctly anticipated the genetic bases of cancer,

> 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 [90].

Robert Remak (1815–1865), best known for his embryological studies that determined which organ derives from each embryonic germ layer, 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 [91].

On the other hand, he dedicated much of his clinical practice to galvano-therapy that was considered unscientific by the medical establishment and led the medical faculty and the Cultural Ministry to refuse his application for a position at the Charité clinic in Berlin [92]. Barred from practicing at the Charité, and his post at the University being, as a Jew, unpaid, he was forced to rely on income generated from patients he attended at his home, where he also conducted research. It is of interest that the famous Rudolf Virchow, a German physician, pathologist, and politician, who in his three-volume work, *Die Krankhaften Geschwulste* had postulated that cancer originated in changes in connective tissues, initially rejected Remak's work, but soon changed his mind and published it as his own [93]. 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, politician, and President of the Human Rights Society. Remak's cell division observations were expanded by Louis Bard (1829–1894), who proposed 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 [94]. 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 still useful today 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) [95], 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 and the code governing its development, growth, and dissemination remained a mystery and remedies continued whimsical and inefficacious. Indeed, Oliver Wendell Holmes (1809–1894), addressing the Massachusetts Medical Society in 1860, 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 [96].

As this statement resonated in America, progress in bacteriology and parasitology was having a profound impact on cancer theory and cancer therapeutics of the nineteenth century. Interest in a possible bacterial or parasitic link to cancer, first raised in the seventeenth and eighteenth centuries, 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, polimorphous microorganisms, and filtrable viruses. It was like fishing in a well-stocked pond. Most fishermen became victims of self-deception… [97].

The zenith of this particular saga was reached 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 [98].

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 false lead. While the determined pursuit of a worthy goal by many is often necessary, overly enthusiastic adherence to a single hypothesis by many is self-reinforcing and can obfuscate good judgment while dismissing the unwelcome views of isolated dissenters. As our knowledge about both the causes of cancer and cancer genetics improved, 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. In turn, this has lead to the development of ever more powerful cytotoxic drugs and increasingly aggressive anti-cancer treatment approaches but few cures. As will be described in Chap. 7, cancer drug development remained hostage, at least initially, to the bacteria-cancer link hypothesis. Indeed, some early unacceptably toxic agents, developed as antimicrobials, were thought suitable for treating cancer and some demonstrated anti-cancer activity. This was the case of the antibiotic agent *daunarubicin*, isolated concomitantly by a French and an Italian laboratory in the 1950s from a new strain of *Streptomyces peucetius* that exhibited good activity against murine tumors. The name daunarubicin derives from *Dauni*, a pre-Roman tribe that lived in the region of Italy where the bacteria were obtained, and *Ruby*, the French word describing the red pigment produced by the bacterium. Daunarubicin is a prototype anthracycline antibiotic from which over 500 derived analogs have been evaluated in the NCI's anti-cancer screening program [99]. The hydroxy derivative of daunarubicin, Doxorubicin, is sold under the trade names of Adriamycin® and Doxil®. The former is an intravenous preparation effective in the treatment of several cancers, especially leukemia and lymphoma, alone or in combination chemotherapy. The latter is a liposome-encapsulated formulation available in the US in limited supplies. Another legacy of this period is a drug development strategy by trial and error, pioneered by Ehrlich in his 7-year quest for antimicrobials, a simplistic approach not suited for cancer drug development that unfortunately persists today, as discussed in Chap. 7. Finally, after 150 years of inconclusive evidence on the bacteria-cancer link, inflammation and mutagenic bacterial metabolites are now invoked as causing several cancers. Examples of the former are gastric carcinoma [100] and MALT[8] [101] that have been linked to the bacterium *Helicobacter pylori*, leading the International Agency for Research on Cancer to classify *H. pylori* as a Group 1 human carcinogen in 1994, and many physicians to attempt its eradication. However, recent data suggest that MALT might straddle between malignancy and inflammation [102]. Moreover,

> Evidence links the lack of *H pylori* with gastro-oesophageal reflux disease, Barrett's oesophagus, and the risk of adenocarcinoma of the oesophagus and gastric cardia. In particular, it seems that cag+strains exert a protective effect whereas cag−strains have essentially no effect… suggest[ing] that clinicians should not eliminate *H pylori* from everyone [103].

In fact,

> …screening for and treatment of *H. pylori* infection as a strategy for secondary prevention of gastric cancer remains controversial. The controversy is amplified by data indicating benefits by preventing esophageal adenocarcinoma, asthma, diarrhoea, and even tuberculosis [104].

Colon cancer is cited as possibly being linked to mutagenic bacterial metabolites. A corollary of the bacteria-cancer link hypothesis is the suggestion that cancer could be treated with bacteria or their products, a concept that goes back more than a century when William B. Coley (1862–1936) inoculated a cancer patient with erysipelas [105]. Eventually, he treated more than 1,000 patients with various bacteria and bacterial products, claiming excellent results, raising doubts and criticism, and leading to the abandonment of the practice [106]. Today, BCG[9] 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 has been reported to reduce tumor progression and recurrences, and to prolong survival [107].

The discovery of anesthesia in 1842 by Crawford W. Long (1815–1878) [108] and of asepsis in 1867 by Joseph Lister (1827–1912) [109] propelled surgery to the forefront of early stage cancer management with slowly increasing cure rates paralleling progress in fields underlying surgical success, including effective antibiotics, new powerful and safe anesthetic agents, refinements in surgical techniques, and general medical support. Likewise, the discovery of X-rays in 1895 by Wilhelm

[8] Mucosal-Associated Lymphoid Tissue that can lead to a low-grade non-Hodgkin's Lymphoma.

[9] Bacillus Calmette Guerin; and attenuated Bacillus Bovis.

Conrad Röentgen (1845–1923) [110], uranium by Henri Becquerel, and radium and polonium by Marie Sklodowska-Curie (1867–1934) and her husband Pierre Curie (1859–1906) [111] marked the dawn of modern diagnostic and therapeutic radiology and of nuclear medicine, raising expectations that the successful treatment of cancer was at hand.

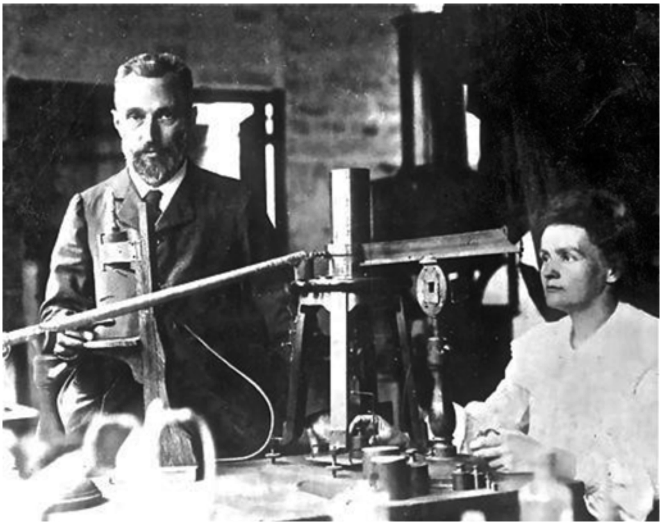

Fig. 2.3 Pierre and Marie Curie in their dilapidated laboratory, circa 1903

It began when Pierre's skin burns from handling radioactive samples, the evolution of which he carefully recorded and reported, led him to seek the collaboration of eminent physicians to further delineate the power of radioactivity in experimental animals. Their results showed that radium could cure growths, tumors, and some cancers; a therapeutic method that became known as *Curietherapy*. Several clinicians applied the method to diseased individuals with "encouraging results" [112]. No longer restricted to research, radioactivity would become central to an entire industry. In 1903, Marie and Pierre were awarded the Nobel Prize in Physics, "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 [113]. At his award address, Pierre questioned whether new discoveries such as theirs in the wrong hands would be harmful to the world, but concluded, "I am one of those who believe with Nobel that mankind will derive more good than harm from the new discoveries." Eager to exploit radioactivity for the treatment of disease and facing inertia from the French state and her university, Marie decided to spearhead the efforts herself by sending gas emanations from radium to hospitals for therapeutic purposes and established a program at the Radium Institute, 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, run over by a horse-drawn wagon. Although sexism and xenophobia had prevented her from being admitted to the French Academy of Science in 1911, Marie received that year's Nobel Prize in Chemistry "in recognition of her services to the advancement of chemistry by the discovery of the elements radium and polonium, by the isolation of radium and the study of the nature and compounds of this remarkable element" [114]. She was the first woman to win a Nobel Prize, the only woman to win two Nobel Prizes, and one of two persons to win Nobel Prizes in more than one scientific discipline; the other being Linus Pauling (Chemistry and Peace). Indeed, Marie's major and unparalleled achievements include formulating the theory of radioactivity (a term she coined), techniques for isolating radioactive elements from pitchblende,[10] and the discovery of Radium and Polonium. The couple's daughter, Iréne Joliot-Curie, and her husband, Frédéric Joliot, were awarded the 1935 Nobel Prize in chemistry for the synthesis of new radioactive elements. On July 4, 1934, Marie died of aplastic anemia from exposure to the very radioactivity that brought her fame. Indeed, she had been exposed to the then unknown damaging effects of ionizing radiation in her ramshackle laboratory (compared to a stable or potato cellar by a visiting colleague) from test tubes containing radioactive pellets she carried in her pockets and kept in her desk drawer and from unshielded x-ray equipment she used while serving as a volunteer radiologist in field hospitals during WWI [115]. She had admitted, "one of our pleasures was to enter our workshop at night; then, all around us, we would see the luminous silhouettes of the beakers and capsules that contained our products."

During the early part of the twentieth century, the introduction of innovative research tools enabled medical investigators to systematically explore old and new hypotheses on the origin and nature of cancer, leading to incremental progress on many fronts. For example, John Hill's suspicion in 1761 that tobacco induced cancer in heavy snuffers and Percivall Pott's 1775 suggestion of a tar-cancer link in chimney sweepers were 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 exposed to coal tar. Likewise, the virus-cancer link was confirmed in 1910 by Peyton Rous (1879–1970) who succeeded in inducing cancer in healthy chickens injected with a cell-free filtrate of a tumor from a cancer-stricken fowl. Because the filtrate had been put through filters of small size pores that removed bacteria, Rous correctly concluded the cancer-causing agent must be a virus. In his 1910 report, Rous stated,

> In this paper is reported the first avian tumor that has proved transplantable to other individuals. It is a spindle-celled sarcoma of a hen, which has thus far been propagated to the fourth generation… [116].

Rous' findings were initially rejected by much of the medical establishment for they challenged the prevailing view of the genetic heredity of cancer, and he was

[10] A uranium-rich mineral and ore.

ostracized for many years. Fifty years later, he was awarded the 1966 Nobel Prize for Physiology or Medicine for his momentous discovery, now known as the *Rous sarcoma virus*. Likewise, the carcinogenicity of radiation and of numerous non-radioactive agents found in the environment (e.g., radon), in industrial products (e.g., asbestos), and in consumer products (e.g., tobacco), was established, and the list keeps growing As these health risks and other aspects of cancer 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 [117, 118]. Ironically, that drug was derived from mustard gas, a blistering agent first introduced as a chemical warfare agent by the Imperial German Army that was widely utilized by both Germany and the Allies as a standard weapon in WWI. It was know as *Yellow Cross* by the Germans (the 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. Although effective countermeasures limited the death rate from mustard gas to 7.5 % of 1.3 million total WWI deaths [119], it was the most-feared weapon of the war, for it caused slow and agonizing death, as witnessed by a British nurse. She reported,

> They cannot be bandaged or touched. We cover them with a tent of propped-up sheets. Gas burns must be agonizing because usually the other cases do not complain, even with the worst wounds, but gas cases are invariably beyond endurance and they cannot help crying out [120].

Remarkably, mustard gas would launch 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, as described in Chap. 7.

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