1

History of Breast Cancer

WILLIAM L. DONEGAN

The story of breast cancer is told in the acts and artifacts of the human struggle against disease. It is an epic tale that follows the concepts of illness from the work of evil spirits or of offended gods to the results of identifiable physical causes, and the healing arts from mysticism to the tools of modern science. The following is a brief history of breast cancer in the Western world.

PREHISTORY AND THE ANCIENT WORLD

Prior to recorded history, life was undoubtedly short, and as cancer is predominantly a disease of maturity one suspects that cancer was a poor competitor among causes of mortality. The study of primitive peoples indicates that for the ill, rituals, potions, and recipes at the hands of magicians, witch doctors, and folk healers were the usual recourses. In ancient Babylon (2100–689 BC) it was common practice to place the ailing in public places for the recommendations of passersby, but professional healers were also recognized. The Code of Hammurabi, inscribed on a pillar in Babylon, indicated that healers were paid fees for their services and were penalized for surgical deaths with amputation of their hands.[1]

Before the third millennium BC, physicians had learned the futility of treating certain tumors of the breast. Among the eight extant Egyptian medical papyri, *The Edwin Smith Surgical Papyrus* is believed to contain the first reference to breast cancer (Figure 1–1). This surgical text, penned in hieratic script, is the incomplete and fragmented copy of an original document that probably dates back to the pyramid age of Egypt (3000–2500 BC) and was possibly written by Imhotep, the physician-architect who practiced medicine and designed the step pyramid in Egypt in the 30th century BC.[2] It provides the earliest references to suturing of wounds and to cauterization with fire drills. More pertinently, it includes the diagnosis and treatment of eight cases of ailments of the "breast," meaning of the bones and soft tissues

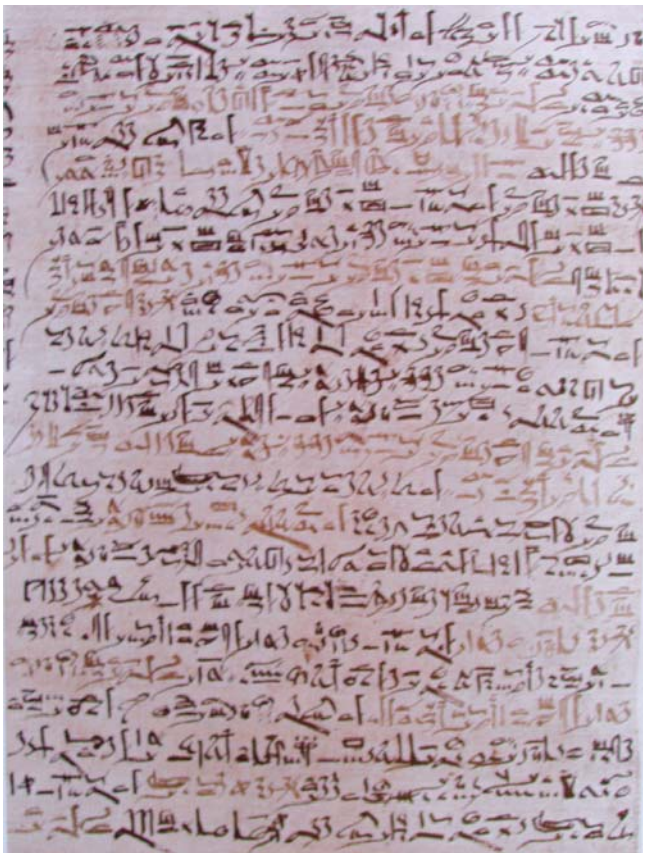

Figure 1–1. Column VIII of *The Edwin Smith Surgical Papyrus*, a copy of the first document believed to describe cancer of the breast, circa 3000 BC. Used with permission from The Classics of Surgery Library.[2]

of the anterior thorax, all in men and most due to injuries. One of the five cases relating to soft tissues (Case 45) describes "bulging tumors" in the breast. The author writes that if the tumors have spread over the breast, are cool to the touch, and are bulging, there is no treatment. Whether this case was a rare cancer of the male breast is conjectural, but in stark contrast to the physician's active recommendations for the other cases, he recognized this one as sinister; and his conviction that no treatment would help appears to have been based on established practice.

GREEK AND ROMAN PERIOD (460 BC–475 AD)

Ancient Greece was pervaded by a rich mythology based on a belief in close associations between humans and gods. Historians speculate that the god of medicine, Aesculapius, may have had origin in a physician who lived around the time of the siege of Troy (≈1300 BC) and to whom were attributed miracles of healing. In the *Iliad*, Homer mentioned Aesculapius' two sons as "good physicians" who had come to join the siege.[3] On the seal of the American College of Surgeons, Aesculapius is pictured seated, holding his staff entwined with a serpent, the symbol of life and wisdom. Early Greeks sought cures by sleeping in the abaton at the temples of Aesculapius and enjoying the associated baths and recreations, forerunners of modern health spas. Votive offerings in the form of breasts found at such sites offer evidence that some came hoping for cure of breast disease (Figure 1–2).

Greek medicine and surgery became the most sophisticated of its time. In the course of his conquests, Alexander the Great of Macedonia (356–323 BC) founded the city of Alexandria on the Nile delta in 332 BC, and a famous medical school arose there around 300 BC. The library at Alexandria was the largest of its time, housing more than 700,000 scrolls. Many prominent Greek and Roman physicians studied, taught, and practiced in Alexandria. The study of anatomy was based on dissection of human bodies and surgery flourished; vascular ligatures were used.

Physicians of the Hellenistic period provide vivid accounts of breast cancer. The Greek term "karkinoma" was used to describe malignant growths and "scirrhous" to describe particularly hard, solid tumors. "Cacoethes" referred to an early or a probable malignancy. A "hidden" cancer was one not ulcerating the skin. In an anecdote, Herodotus (484–425 BC), historian of the wars between Greece and Persia, claimed that Democedes, a Persian physician living in Greece, cured the wife of Persian King Darius of a breast tumor that had ulcerated and spread.

Hippocrates (460–375 BC), whose legacy, the *Corpus Hippocraticum*, may have been the work of more than one person, was the most prominent of Greek physicians. He maintained that every disease was distinctive and arose from natural causes, not from gods or spirits.[4] He also believed in the power of nature to heal and in a humoral origin of disease. In his view, a balance of the four bodily fluids, blood, phlegm, yellow bile, and black bile (later linked to sanguine, phlegmatic, choleric, and melancholy dispositions by Galen) was necessary for good health. Hippocrates described cases of breast cancer in detail. One of his case histories was of a woman of Abdera who had a carcinoma of the breast with bloody discharge from her nipple. Attaching a beneficial effect to the bleeding, he noted that when the discharge stopped, she died. Similarly, Hippocrates associated cessation of menstrual bleeding with breast cancer and sought to restore menstruation in young sufferers. His detailed description of the inexorable course of advancing breast cancer rings true today. He said that

Figure 1–2. Votive offerings from an Etruscan temple include a vagina, a uterus, an ear, an eye, and a breast (lower central). Reproduced with permission from Lyons AS and Petrucelli RJ.[6]

hard tumors appear in the breast, become increasingly firm, contain no pus, and spread to other parts of the body. As the disease progresses, the patient develops bitter taste, refuses food, develops pain that shoots from the breast to the neck and shoulder blades, complains of thirst, and becomes emaciated. From this point death was certain. He advised no treatment for hidden breast cancers because treatment was futile and shortened the patient's life.

In the ascendant Roman Empire, physicians were guided largely by Greek medicine. Around 30 AD, the Roman physician Aulus Cornelius Celsus (42 BC–37 AD) noted that the breasts of women were frequent sites of cancer. Celsus described breast cancer in his manuscript, *De Medicina*, and defined four stages. The first was cacoethes, followed by carcinoma without skin ulceration, carcinoma with ulceration, and, finally, "thymium," an advanced exophytic and sometimes bleeding lesion, the appearance of which suggested to him the flowers of thyme. Celsus recommended excision for the cacoethes but no treatment for other stages. In situations of uncertainty, the tumor was treated first with caustics, and if the symptoms improved, it was a cacoethes; if they worsened, it was a carcinoma. Some masses for which treatment was successful might have been fibroadenomas, phyllodes tumors, or even tuberculosis.

Leonides, a surgeon of the Alexandrian school, described surgical removal of breast cancers during this time.[4] Leonides said that with the patient supine he cut into the sound part of the breast and used a technique of alternately cutting and cauterizing with hot irons to control bleeding. The resection was carried through normal tissues wide of the tumor and customized to the extent of involvement. The operation was concluded with a general cauterization to destroy any residual disease. Poultices were then applied to the wound to promote healing. He explained that excision was used selectively for tumors in the upper part of the breast of limited extent, and he specifically advised against surgery if the whole breast was hardened or if the tumor was fixed to the chest wall. Leonides was perhaps the first to record that breast cancers spread to the axilla. Complete and thorough excision of breast malignancies has been a cardinal principle of surgery since the time of Leonides.

The teachings of the Greek physician, Galen of Pergamum (129–200 BC), on the subject of breast cancer reached far beyond his time. Born of a wealthy and educated family in Asia Minor, he traveled and studied widely. Galen became surgeon to gladiators in Pergamum and finally practiced in Rome, attending the emperor Marcus Aurelius. His vast experience, clinical acumen, investigative approach to knowledge, and prolific, authoritative writings (400 treatises) gained Galen enormous respect. For the next 1,500 years, Galen's teachings guided medical practice, and his animal dissections provided the bases for human anatomy and physiology.

Galen revered Hippocrates and adopted his humoral theory of disease. In Galen's view, breast cancer was a systemic disease caused by an excess of black bile in the blood (ie, melancholia). Black bile was formed in the liver from blood elements and absorbed in the spleen; malfunction of either of these organs caused an excess of black bile, which thickened the blood, and where black bile accumulated, carcinoma developed as hard, non-tender tumors that ulcerated if the bile was particularly acrid. Like Hippocrates, he noted that carcinomas were predisposed to accumulate in the breasts of women who had ceased to menstruate, a recurring theme and doubtless a reference to the frequency of cancer in postmenopausal women. This observation supported Galen's belief that menstruation, and the practice of bleeding, served to clear the body of excess black bile. He likened the dilated veins that radiated from carcinomas to the legs of a crab; as a result, the crab became a symbol for cancer. Leonides had also likened cancers to crabs, but rather because the tenacious adherence to surrounding tissues mimicked the crab's pinchers. For early cancers, Galen recommended purging, bleeding, diet, and topicals. Ulcerating cancers were treated with caustics or cleansed and treated with zinc oxide.

In operating for breast cancer, Galen's approach was less modern than that of Leonides before him. Galen condemned the use of ligatures, and although he was aware of the dangers of excessive blood loss, he preferred to let the blood run unchecked and to express the dark, dilated veins in order to rid them of the morbid black bile. The cancer was removed at

the boundary between diseased and healthy parts, sparing the cautery out of concern for destroying too much tissue. After Galen, medicine languished into a contented observance of his teachings, and the Middle Ages intervened, temporarily halting further medical progress.

MIDDLE AGES (476–1500 AD)

The Middle Ages, a period of roughly 1,000 years, began with the collapse of the Roman Empire in 476 and ended with the Renaissance and discovery of the New World in 1492. With the Middle Ages came feudalism, bubonic plague, crusades, and the age of faith. Papal influence spread in the form of the Holy Roman Empire, and human dissection was prohibited by Papal decree; opposition to church doctrine constituted heresy. To save his soul, the astronomer Copernicus (1473–1543 AD) was forced to rescind his thesis that the earth circled the sun rather than the reverse, and the physician Michael Servetus (1511–1553), discoverer of the pulmonary circulation, was burned alive for heresy. Meanwhile, monastic scribes in Christian Europe quietly preserved medical knowledge, principally that of Galen, by copying and illuminating surviving ancient manuscripts, manuscripts that were in little demand during an era of widespread illiteracy. Monks dispensed folk remedies, and surgery was discouraged. Amputation of the breast was depicted by the church as a form of torture in the story of St. Agatha, the patron saint of breast disease[5] (Figure 1–3). Many miraculous cures were attributed to saints. Faith healing by the laying on of hands was among the remedies, a practice that endured to recent times. Folk medicine included application of fresh bisected puppies and cats.

After the death of the prophet Muhammad (570–632 AD), the rise of Islam resulted in the Arab conquest of the southern shores of the Mediterranean from Persia to Spain, bringing to an end the medical center in Alexandria. Medical documents that survived were translated into Arabic for study and preserved; translated later from Arabic into Latin, the language of medicine in Europe, they re-entered the continent. In addition to preserving the past, Arabic medicine was noted for expertise in pharmacy and for establishing fine hospitals. Among the most influential physicians of this period were Avicenna (980–1037 AD), the Jewish physician Maimonides (1135–1204 AD) and Albucasis (936–1013).[6] Avicenna's reputation rivaled that of Galen, but he had no new insights about breast cancer. Albucasis in Moorish Spain favored the cautery and caustic applications for treatment of breast cancer but admitted that he had never cured a case of breast cancer and knew of no one who had. Caustic paste (a mixture of zinc chloride, stibnite, and *Sanguinaria canadensis*) was used for treatment of breast cancer in the United States as late as the 1950s.[7] The paste was applied to the involved breast to cause progressive tissue necrosis, which was then cut away or allowed to slough and to heal by granulation. Continued use of charms, prayers, medicaments, and caustics in conjunction with surgery and modern methods is a reminder that treatments for breast cancer progressed through history not by substitution, but by addition.

Figure 1–3. Saint Agatha, the patron saint of breast disease, was martyred for her Christian beliefs. Her torture included amputation of the breasts shown here in a painting by Anthony Van Dyck.[5]

In the late Middle Ages, Henri de Mondeville (1260–1320 AD), surgeon to the king of France, refined Galen's black bile theory with a distinction between black bile from the liver, which caused a hard tumor in the breast (a sclerosis), and twice combusted black bile derived from breakdown of the other three other body humors, which caused a true cancer. He described true breast cancer as ulcerated with thick margins and having an offensive odor. The treatment: diet and purging, with operation only if the cancer could be completely excised; de Mondeville appreciated that incomplete removal often resulted in a non-healing wound.[8]

RENAISSANCE (SIXTEENTH TO EIGHTEENTH CENTURIES)

The Middle Ages ended with the Renaissance. This period of approximately 200 years, also known as The Enlightenment, saw a rejection of medieval values and a rebirth of interest in secular art, in science, and in exploration of the world and the human body. With the Renaissance came badly needed formal training for physicians. The University of Salerno, founded around 1200 AD, was the first organized medical school in Europe. Free of clerical influence and progressive for its time, Salerno served as the precursor of prominent schools of medicine in France, England, and elsewhere on the continent. The Royal College of Physicians was established in London in 1518, and the first medical journal, the *Ephemerides*, appeared in 1670.

Surgeons became more respectable. Traditionally unlettered craftsmen whose operations were directed by physicians, surgeons became independent practitioners. Incorporated as barber-surgeons in England since 1461, surgeons were officially separated from barber guilds in 1745. The French Academie de Chirurgie, established in 1731, produced the first journal for surgeons, *Memoires*, which in 1757 published Henri LeDran's thesis that breast cancer had a local origin, providing an impetus for surgical cure.[9]

The Renaissance in medicine brought a critical reexamination of anatomy and physiology and a decline of Galen's authority. Publication of Andreas Vesalius's *De Humani Corporis Fabrica* in 1543 marked the beginning. This volume of anatomical drawings, based on the young professor of surgery at Padua's own dissections of human cadavers, illustrated the errors of Galen's anatomy and stimulated further interest in human anatomy.[10] The *Fabrica* provided no useful details of the female breast. However, 300 years later, Sir Astley P. Cooper (1768–1841), surgeon to Guy's Hospital in London, illustrated with desiccated specimens the suspensory ligaments of the breast that bear his name. The Parisian anatomist Marie-Philibert-Constant Sappey (1810–1896) illustrated the lymphatics of the breast, a name that endures as Sappey's subareolar plexus.[11,12]

Each anatomic discovery generated new theories about breast cancer, but to little advantage. John Hunter (1728–1793), the father of investigative surgery, conceived that coagulation of lymph rather than black bile was responsible for carcinoma of the breast and the associated cancerous nodes. Boerhaave of Leyden (1668–1738) postulated that neural fluid "liquor nervorum" might be the instigator of breast cancer, whereas others believed that inspissated milk within the mammary ducts generated cancers. Trauma to the breast was believed to cause leakage into the tissues, which created irritation, induration, and malignant change. Observing the rapid growth of ulcerating breast cancers, Claude-Nicholas le Cat (1700–1768) in Rouen postulated that exposure to air was a stimulant to cancers, a tenacious idea persisting in some laity today. Anecdotes of multiple-affected family members supported the suspicion that breast cancer was infectious long before the hereditary aspect of the disease became known in the twentieth century. The deadly spread of malignancy was attributed to circulating humors or to a general diathesis. The suspicion of a "cancer prone" personality lingers but remains unconfirmed by modern psychological research.[13]

Breast lumps continued to fuel controversy about the nature of a "schirrous," the hard tumor that generated concern for patient and physician. Whether schirrous was benign, a stage of cancer, or a precursor that became cancer by a process of "acrimony" remained in doubt. Observation or immediate treatment divided opinions. Opinions on the worth of surgery varied. Extended survival of

occasional untreated cases, coupled with the considerable risk and poor results of mastectomy, supported a nihilistic attitude among many physicians. Others shared the opinion of Nicolaes Tulp (1593–1674) of Amsterdam, who saw the need for early surgery. "The sole remedy is a timely operation," he said.[4] For the most part, the fearsome prospect of an operation was delayed until bulky growth, pain, or ulceration made obvious both the diagnosis and the need. Informed surgeons recognized tumor attachment to the chest wall, sternal pain due to deep invasion or involvement of the internal mammary nodes (described by Petrus Camper in 1777), poor general health, or a diathesis-revealing "melancholy" appearance as contraindications to mastectomy.

Without anesthesia or antisepsis, mastectomies were a painful and dangerous ordeal customarily carried out in the patient's home. The procedure varied from impalement of the breast with needles and ropes for traction followed by swift amputation through the base, leaving a large open wound as illustrated by Johann Scultetus (1595–1645) in his *Armamentarium Chirurgicum*, to the alternative of incising the skin and enucleating the tumor by hand.[4] The prevailing opinion was to leave the wound open to minimize the risk of infection. From 2 to 10 minutes were required for the operation, depending on the technique. Ligatures, if used, were led out through the wound to be withdrawn later, after necrosis or infection loosened them. Painful re-explorations of the wound on subsequent days were performed to inspect for infection or to remove additional tumor; the major threats were secondary hemorrhage or potentially fatal infection. In various illustrations, the patient's hands were tied behind her back or assistants restrained her while another assistant caught jets of blood in a pan. A cauterizing iron provided hemostasis, and steam issued from the wound where it seared the flesh. The company included a dour, attending physician and often an anguished family standing in witness. Students of breast cancer should not miss the touching account of such an operation in Scotland told by John Brown.[14] The rigors of surgery were such that alternative treatment with compression of the breast using metal plates or strapping, not entirely devoid of pain and occasional necrosis, continued to survive into the nineteenth century.

Expert surgeons operating in major centers during these times enlarged mastectomies to include all morbid parts. In Paris, Jean Louis Petit (1674–1750) removed both the breast and diseased nodes in his operations, and in 1774, Bernhard Perilhe reported removing the pectoralis major muscle as well. A healed wound was the customary end point for declaring a surgeon's success; few bothered with further follow-up. In a report by Richard Wiseman (1622–1676), surgeon to Charles II, among twelve mastectomies, two patients (17%) died from the operation, eight died shortly afterwards from progressive cancer, and two of the 12 were declared "cured" for undisclosed lengths of time.[4]

NINETEENTH CENTURY

From the oncologic standpoint, the nineteenth century was truly a giant step forward. Major advances were made in human pathology and in the safety of surgery. Hand washing was promoted by the Hungarian physician Ignac Semmelweis (1818–1865) and by Oliver Wendell Holmes, MD (1809–1894), Professor of Anatomy and Physiology at Harvard University. Building on Louis Pasteur's (1822–1895) discovery of "putrefying" bacteria, Joseph Lister (1827–1912) in Glasgow introduced surgical antisepsis with carbolic acid spray in 1867.[15] Adoption of aseptic techniques (ie, steam sterilization) first by Ernst von Bergmann of Berlin in 1886, the surgical mask by the Pole Johannes von Mikuliez-Radecki in 1886, and sterile rubber surgical gloves by William S. Halsted in 1890 further reduced contamination.[16] Successful demonstration of general anesthesia by William T. Morton in Boston in 1846 allowed unprecedented development of surgery; operations became more acceptable, and for the first time surgeons could concentrate on precision rather than haste. Blood transfusions became safe after 1900 when Karl Landsteiner in Austria discovered blood groups. All of the current technology for treatment of breast cancer had their beginnings in this century; only chemotherapy remained for development in the years to come.

The microscope was the key to progress in pathology. Building on Anton van Leewenhoek's (1674–1723) work with lenses, perfection of the com-

pound achromatic microscope in Germany opened the world of microscopic anatomy, and Germany was the center of this new science under the leadership of Johannes Müller at the University of Berlin.

Early in the century, the microscopic work of Matthias Schleiden (1804–1881), a botanist at the University of Jena, and of Theodor Schwann (1810–1882), working in Müller's laboratory, established that both plants and animals were composed of living cells with the nucleus as the essential feature. Robert Hooke (1655–1703) earlier had coined the word "cell" from the structure he saw in cork. "The cells are organisms," said Schwann, "and animals as well as plants are aggregates of these organisms…" These two researchers destroyed the existing humoral and the competing solidistic concepts of tissue composition. Johannes Müller (1801–1859) was first to report that cancers also were composed of living cells. In his landmark publication of 1838, *Uber den feinen Bau und die Formen der krankhaften Geschwülste*, Müller noted the similarity of cells in a "scirrhus" of the breast and its metastases in the ribs and noted that cancer cells had lost the proportions of normal cells[17] (Figure 1–4). Rudolph Virchow, also of Berlin, Müller's former student and the founder of cellular pathology, is responsible for the dictum that "all cells come from cells." His lectures, *Die Cellularpathologie*, published in 1858, laid to rest the notion of spontaneous generation of living cells from a liquid "blastema." But Virchow did not make the connection between migrating malignant cells and metastases; he thought that axillary metastases arose from cells in the nodes responding to "hurtful ingredients" or "poisonous matter" from the cancer in the breast.[18] Müller was perhaps the first to suspect that spread of malignant cells constituted the mechanism of metastasis, later confirmed by the microscopic work of Carl Thiersch (1822–1895) and Wilhelm von Waldeyer (1836–1921).[4] These insights supported the concept that breast cancer spread from a local origin.

Noteworthy clinical observations were also being made. Alfred Velpeau was the first to describe breast cancer en cuirasse, the deadly form that spreads across the chest like a breast plate.[19] Velpeau's *Traite des maladies du sein,* published in 1854, was a comprehensive review of breast disease of the time. Across the English Channel in London, Sir James

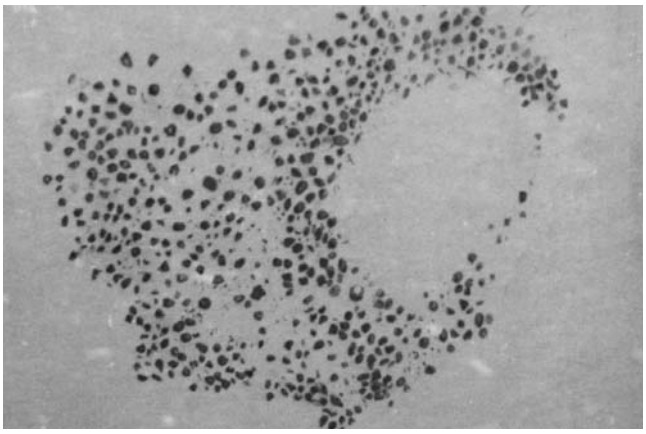

Figure 1–4. Figure 9, Table I, from Johannes Müller's *Uber den feinen Bau und der Formen dei Krankhafte Geschwülste*, 1838, illustrating for the first time the cellular structure of breast cancer. Reproduced from Müller J.[17]

Paget made a brief (1,050 words) but enduring report in 1874 describing changes on the nipple that preceded breast cancer and continue to bear his name. He said, "… certain chronic affections of the skin of the nipple and areola are very often succeeded by the formation of sirrhous cancer in the mammary gland…within at the most two years, and usually within one year."[20] Paget's observation remains as valuable today as when it was first made.

Charles Moore (1821–1870) at the Middlesex Hospital in London deserves credit for the en bloc principle of resection. Moore was convinced that the piecemeal mastectomies of his day spread the "elements" of cancer in the surgical wound and accounted for the local reappearance of cancer in, or adjacent to, the scar. In 1867 he published a strong argument for removal of the whole breast intact in every case.[21] He also recommended removal of axillary nodes and the pectoral muscles if they were involved. William M. Banks in Liverpool carried mastectomy a step further in 1882 by practicing routine removal of axillary lymph nodes.[22]

Similar initiatives were occurring in Germany. Ernst G.F. Küster (1839–1922) in Berlin was performing routine axillary clearance and reported that it virtually eliminated recurrences in the axilla. In 1875 Richard von Volkmann (1830–1889) was routinely removing the pectoralis major fascia, and Küster's assistant Lothar Heidenhain (1860–1940) held the muscle itself suspect. Their microscopic studies of mastectomy specimens showed extension

of cancer to the deep pectoral fascia, and occasionally to the muscle itself, when it had not been suspected. Samuel W. Gross at Jefferson Medical College in Philadelphia (1837–1879) attributed a 3-year survival of 19.4% to routinely removing not only the whole breast but the pectoralis fascia and axillary contents.[4]

The events in Germany influenced William S. Halsted (1852–1922), Professor of Surgery at Johns Hopkins Hospital in Baltimore, to devise what became known as the radical mastectomy. He reported the operation in 1894 almost simultaneously with a similar report by Willy Meyer in New York.[23] Through a large "tear-drop" incision, Halsted removed en bloc the breast complete with its skin, the axillary lymph nodes, "a part, at least" of the pectoralis major muscle (the sternal portion) and "usually" cleared the supraclavicular region. Halsted had adopted this "complete" operation 5 years earlier, and emphasized that the pectoralis major muscle must be removed in all cases to obtain a secure tumor-free deep surgical margin. He explained that von Volkmann had removed the pectoral muscles in 38 cases with reduction in local recurrences. As Moore before him, Halsted wrote that the crux of the operation was "to remove in one piece all of the suspected tissues" lest the wound become infected by the division of tissues or lymphatics invaded by the disease, and lest shreds or pieces of cancerous tissue be overlooked in a piecemeal extirpation. It is clear from Halsted's descriptions that the supraclavicular clearance initially was a removal of tissues superior to the axillary vessels in the course of the axillary dissection, later a formal dissection through a cervical incision and ultimately an excursion that he abandoned. The complete operation resulted in a large open wound left to heal by granulation. Two years later he began to close the wound with a split-thickness skin graft, a technique developed by Thiersch (Figure 1–5). Eventually primary closure of skin became more popular.

Whether radical mastectomy resulted in improved local control is unclear. Halsted recognized "local" as recurrences in the surgical area within 3 years of operation (6% in his cases); "regionary" recurrences, by his definition, appeared after 3 years or in the skin away from the scar. The German literature did not distinguish local from regionary recurrences. By counting both, and making the unlikely assumptions that cases were comparable and had equal periods of follow-up, his recurrence rate was 20% compared to 55 to 82% for his German counterparts. Halsted disregarded that local and/or regionary recurrences totaled 58% when von Volkmann had removed the pectoralis major muscle and 60% when he had not, a negligible difference.

Halsted had no surgical deaths despite having "old" patients. "Their average age is nearly 55 years," he said. "They are no longer very active members of society." This comment is strange to modern ears, but the average life span at the time was 47 years. For fear of spreading cancer with a biopsy, diagnosis was almost always clinical, established histologically after the operation. In doubtful cases Halsted said, "The excision of a specimen for

Figure 1–5. William S. Halsted's radical mastectomy. A case pictured in 1912. The operation resulted in a large wound closed with skin grafts. Reproduced with permission from the Classics of surgery library. Surgical papers. William Stewart Halsted. Vol. 2. Special Edition. Birmingham (AB): L. B. Adams Jr. 1984; Figure 2, Plate LX. p. 82.

macroscopic or microscopic is never resorted to except just before operation."[24]

Radical surgery had intellectual support from W.S. Handley's theory of permeation, which held that breast cancer spread centrifugally in continuity, and lymph nodes provided mechanical barriers. Blood vascular spread was insignificant; tumor emboli were destroyed by clot.[25] Halsted's operation was used, with mixed results, for the next 80 years.

Cushman D. Haagensen (d 1990) was both a staunch supporter and a critic of radical mastectomy.[19] His book *Diseases of the Breast,* published in 1956, is a classic. Haagensen's careful analysis of cases treated at Presbyterian Hospital in New York City resulted in eight "criteria of inoperability" to discourage inappropriate use of the operation. He also standardized physical breast examination and originated the Columbia Clinical Classification (CCC) staging system. After the CCC, staging systems became increasingly sophisticated and eventuated in the current Tumor, Node, Metastasis system initially adopted in 1954 by the International Union Against Cancer. Prior to randomized clinical trials, staging provided the principal means for comparing different methods of treatment.

As the nineteenth century came to a close, mastectomy appeared better than no treatment but still cured less often than not. The actuarial survival of Halsted's first fifty cases 5 years from the first symptom (40.4%) was greater than twice that of untreated patients in the Middlesex Hospital Charity Ward in London admitted between 1805 and 1933, which was 18%.[26,27]

Two events of this time were momentous for the future treatment of breast cancer. The first was the discovery of x-rays, and the second was the discovery that breast cancer was hormone dependent. Discovery of x-rays by Wilhelm Conrad Röntgen in Würzburg in 1895 provided the basis for radiotherapy and mammography. The mysterious ray, designated "x," not only penetrated tissues but also killed cancers. One year after Röntgen's discovery, x-rays were used to treat three cases of breast cancer, two by Hermann Goeht in Hamburg and one by Emile Herman Grubbé in Chicago.[4] All three had advanced, inoperable cancers and died shortly afterwards. With the development of dosimetry, improvements in instrumentation and appropriate safeguards, radiation therapy became an effective local treatment of inoperable cancers, and a postoperative (and sometimes preoperative) supplement to mastectomy that ultimately enabled breast-conserving surgery. The discovery of radium in 1898 by Pierre and Marie Curie added interstitial radiation to therapeutic options. Geoffrey Langdon Keynes in London (1932) used radium as the sole treatment of operable cases.[28] The obvious benefit of ionizing irradiation was in reducing the bulk of large cancers and in reducing recurrence in treated fields. An inferred influence on survival proved elusive.

The hormonal treatment of breast cancer began with oophorectomy. In 1899 Albert Schinzinger (1827–1911) in Freiburg commented on the poor prognosis of young women with breast cancer and proposed castration to age them and slow down the malignant growth. Independent of this suggestion, George Thomas Beatson (1848–1933) of Glasgow performed the first castration for breast cancer 7 years later. Beatson knew by his studies of lactation that castration or rebreeding of cows shortly after they calved prolonged milk production, both measures having in common the interruption of ovarian function. Since the hyperplastic cells of lactation decomposed into milk, he reasoned that castration might make the hyperplastic cells of breast malignancy do so as well. The reasoning was wrong, but the result was gratifying. In 1896 he reported temporary tumor regression after oophorectomy in three cases of advanced breast cancer. Beatson's discovery established the palliative value of oophorectomy, and for a period it became a regular adjuvant to mastectomy by some surgeons.[29] Secondary endocrine surgery with adrenalectomy and hypophysectomy developed as sequels to oophorectomy, but in time endocrine surgery was replaced by hormone therapy (Henry Starling described hormones in 1905) and, ultimately, by pharmacologic methods of reducing estrogen production or its effects with luteinizing hormone-releasing hormone agonists, estrogen receptor modulators and aromatase inhibitors. Discovery of intracellular estrogen receptors (ER) in breast cancers by Elwood Jensen in Chicago in 1967 was another milestone in hormone therapy, permitting patients who could benefit from hormone therapy to be distinguished from those who could not.[30]

TWENTIETH CENTURY

The next 100 years resulted in a retreat from radical surgery and the introduction of mammography and chemotherapy. Research confirmed a hereditary component of breast cancer. As important as all else came a demand for scientific evidence to support claims of efficacy and to supplant the anecdotes and polemics of the past. Cooperative groups of clinician investigators amassed large numbers of patients for study, and randomized, controlled clinical trials with sophisticated statistical analysis of data became commonplace. Breast cancer was recognized as a major health problem in the Western world, stimulating a concerted effort against it.

In the early decades, many sought to improve the results of radical surgery with "extended" radical mastectomies. Margottini and Veronesi in Milan, Caseres in Peru, and Urban and Sugarbaker in the United States removed the internal mammary nodes. Dahl-Iverson in Copenhagen removed the supraclavicular and internal mammary nodes and Wangenstein in Minnesota added removal of mediastinal nodes. Other than showing that extra-axillary nodes often contained metastases and that their removal improved regional tumor control, cures were not increased, and these extensions were eventually abandoned in favor of chest wall and regional irradiation. As Handley's permeation theory lost credence, D. H. Patey and R. S. Handley in London felt justified in preserving the pectoralis major muscle unless it was directly involved by cancer, an operation they called the "conservative" radical mastectomy. With the support of surgeons in the United States such as Hugh Auchincloss Jr. in New York, this operation eventually prevailed in 1979 as the "modified" radical mastectomy.[31]

Mammography, unarguably the most important advance to date in the detection of breast cancer, developed in parallel with surgery. Even early physicians had recognized that small breast cancers were the most curable. Mammography allowed many breast cancers to be detected when clinically occult, including ductal carcinoma in situ, which was regularly curable. Film-screen mammography involved penetrating the breast with x-rays to activate a rare earth screen that glowed in response. This screen exposed a transparent, photosensitive film in the same cassette which, when developed, provided an image in various shades of gray for interpretation. In Robert Egan's *History of Mammography,* he gives Stafford L. Warren at Rochester Memorial Hospital in Rochester, New York, credit for early explorations of mammography beginning in 1926 but also mentioned that the German surgeon, Albert Salomon, performed studies with radiographs of breasts resected for carcinoma as early as 1913 before his work was apparently interrupted by World War I.[32] The technique met resistance despite such advocates as Jacob Gershon-Cohen in Philadelphia and Charles M. Gros in Strasbourg until Egan, while a radiologist at M. D. Anderson Hospital in Houston, Texas, developed the soft tissue technique that allowed mammography to move forward.

An early randomized trial of screening with mammography and physical examination in New York by Sam Shapiro and Philip Strax in 1963 demonstrated that 30% of cancers could be detected by mammography alone, and deaths from cancers among screened women were reduced 30% compared with unscreened. After a host of radiologists was trained in the technique of mammography, a demonstration project, the Breast Cancer Detection Demonstration Project (BCDDP), begun in 1973 and sponsored by the National Cancer Institute and the American Cancer Society (ACS), screened 283,222 asymptomatic women. The BCDDP established the feasibility of mass population screening. Multiple randomized clinical trials of screening followed, showing that regular mammograms could detect 85 to 90% of asymptomatic breast cancers with a reduction of breast cancer mortality. Periodic mammograms and physical examinations for detection of breast cancer in asymptomatic women 40 years of age and older received endorsement by the NCI, ACS, and numerous professional groups.[33]

Mammography was followed by a number of innovative means for imaging the breast. Xeromammography appeared briefly.[34] This dry-process technique recorded all structures in the breast with equally good detail and could be examined without view boxes, but it disappeared from use after further improvements in film-screen mammography. Enduring adjuncts to mammography were ultrasonography

and magnetic resonance imaging (MRI). Ultrasonography came into use in the 1950s. As well as allowing for the distinction between cysts and solid masses, it could characterize solid masses and permitted irradiation-free, real-time, guided needle biopsy of suspicious lesions. Malignant lesions detected by other means were not always visible on ultrasonography, and results were highly operator-dependent, making it unsuited for population screening. MRI proved valuable in special situations.

As the twentieth century advanced, opposition to radical surgery grew. Kaae and Johansen in Denmark and Robert McWhirter in Scotland maintained that simple mastectomy with regional irradiation was the equal of radical mastectomy, and preferable.[35] McWhirter protested that the selective use of radical mastectomy made the results look better but offered no overall increase in cures. George Crile Jr. in Cleveland argued for conservative surgical treatment based on a biological view of breast cancer, largely immunologic.[36] Most compelling, however, was that radical surgical removal of tissues had reached its limits with no decrease in mortality rates. In 1939 Gray showed that early lymphatic spread to axillary nodes was by embolism rather than by permeation, and blood vascular spread was increasingly accepted as the mechanism of general dissemination.[37,38]

Bernard Fisher, Professor of Surgery at the University of Pittsburgh and a researcher in the biology of metastasis, became the intellectual leader and the most compelling spokesman for the need to critically re-evaluate the treatment of breast cancer. Fisher's laboratory investigations indicated that lymph nodes were not effective barriers to cancer spread. Referring to Halsted's rationale for radical mastectomy, Fisher wrote in 1970 that, "…either the original surgical principles have become anachronistic or, if they are still valid, they were conceived originally for the wrong reasons."[39] Much like a modern Galen, Fisher asserted that breast cancer was a systemic disease and that its course was determined by a biologic struggle between tumor and host. Fisher implied that viable cancer cells always, or almost always, disseminated before diagnosis. His thesis presented two testable hypotheses: (1) variations in local treatment were unlikely to influence cure, and (2) effective systemic treatment was necessary to improve cure rates. As Chairman of the National Surgical Adjuvant Breast and Bowel Project (NSABP), Fisher was able to implement large, randomized, controlled clinical trials to test these concepts and to stimulate others to do the same (Figure 1–6). The results confirmed the observations of Moore, Küster, and Halsted, namely, that limited operations resulted in poor local and regional control, and that patients with recurrence fared poorly.[40–42] As predicted, they also confirmed that whether the regional nodes or the whole breast were removed, overall cure rates among different

Figure 1–6. Bernard Fisher MD, modern researcher in the biology of breast cancer who revised Halstedian concepts, (fourth from the right in the front row) with early members of the NSABP at a group meeting in Florida, May 1978.

treatment groups proved similar. The explanation offered was that failure of local control indicated incurability at the outset. But the need to retreat ("salvage") was distressing for all, and as local or regional recurrence might jeopardize cure for some, optimum tumor control at the outset remained a priority.

The greatest impact of these trials was on management of the breast itself. As confidence grew in irradiation for controlling occult regional metastases, the question was whether irradiation could do the same for occult tumor in the breast. Selected cases so treated by F. Baclesse in France, Ruth Guttman in the United States, Sakan Mustakallio in Finland, and others had suggested this was the case as early as 1965.[43] After an initial but unsatisfactory beginning at Guy's Hospital in London, controlled trials of breast conservation started in Milan, Italy, in 1973 by Umberto Veronesi and by the NSABP in 1976.[44,45] These trials established that excision of the primary tumor, "lumpectomy," followed by whole breast irradiation was as effective as total mastectomy for both local and ultimate disease control of most early-stage cases and was an obvious cosmetic improvement. Based on these outcomes, in 1990 the NCI sanctioned breast-conserving surgery as the preferred treatment of stage I and II breast cancers.[46]

Axillary sentinel lymph node biopsy (SLNB) was rapidly adopted after it was introduced in 1997, making routine axillary lymph node dissection unnecessary. Axillary dissection could be reserved instead for cases in which the SLNB showed nodal metastases, thereby sparing many the morbidity of this operation.[47] Surgical treatment of the breast and the regional nodes could be customized to individual needs, and with the combination of SLNB and breast conservation, the surgical component of multidisciplinary treatment reached a minimum.

Chemotherapy developed in parallel with changes in local treatment. Its beginnings can be traced to the use of mustard gas in World War I. Exposure caused depression of bone marrow and lymphoid tissue followed by death from pneumonia. The effects on tissues were similar to those of ionizing radiation and suggested usefulness against lymphomas. Experiments with animals followed, and, indeed, nitrogen mustard produced regression of implanted lymphoma in mice. In 1942 it was first used to treat human lymphoma at Yale University; the results of which were not reported by Goodman and Philips until 1946, a delay necessitated by the need for wartime secrecy. Reference is sometimes made in texts to events surrounding explosion of mustard agent (dichloroethyl sulfide) bombs aboard the S.S. John Harvey on December 2, 1943, in Bari Harbor, Italy, during WW II as the stimulus for research into chemotherapy, but this event followed the clinical investigations at Yale University.[48] Continued development produced such therapeutically useful alkylating agents as busulfan, cyclophosphamide and chlorambucil. Additional agents with various mechanisms of cytotoxicity followed. None proved toxic specifically for cancer cells or free of undesirable side effects, and none cured overt breast cancers, but their judicious use proved clinically useful. Systemic "chemotherapy," a word coined by the researcher Paul Erlich, often produced temporary regression and occasionally complete disappearance of advanced breast cancers.[49] Initial trials of intravenous, perioperative triethlylene-thiophosphoramide (Thio-TEPA) in the late 1950s, intended to destroy tumor cells released during mastectomy, were failures, but extended adjuvant treatment with L-phenylalanine mustard directed against occult micrometastases improved the survival of patients with early stage breast cancer.[50,51] A similar approach using combinations of drugs with different mechanisms of action (eg, cyclophosphamide, fluorouracil, and methotrexate (CMF), and doxorubicin combinations) proved more effective, securing adjuvant chemotherapy an established place in multidisciplinary treatment. With the addition of chemotherapy, treatment of breast cancer truly became a coordinated effort of specialists, bringing to bear a medley of surgery, radiation therapy, and systemic chemohormonal therapy on the local and systemic components of the disease.

As the twentieth century closed, breast cancer was recognized as a disorder of unrestrained cell growth, but its instigation remained an enigma. A virus caused the disease in mice, but apparently not in humans; ingestion of aromatic hydrocarbons (dimethylbenzanthracene) produced it in rats. In humans, exposure to ionizing radiation increased risk, as evidenced in survivors of the atomic bombing of Hiroshima during WW II and the recipients of multiple fluoroscopies incident to treatment of pulmonary tuberculosis, information spurring closer regulation of mammography

and other radiological procedures. Hormone replacement therapy to alleviate menopausal symptoms also increased risk, prompting cautions about exposure to exogenous estrogens.[52] The discovery of predisposing mutations in *BRCA1* and *BRCA2* genes of families prone to breast cancer confirmed genetic transmission and provided a means to identify individuals at great risk.[53,54] Among preventive strategies, early castration was effective but unacceptable; in 1998 tamoxifen, a synthetic estrogen receptor modulator, became the first drug proven to lower risk and the first approved for this use.[55] Prophylactic mastectomies offered almost total protection, and became an option for women especially in need.[56]

Breast cancer remained a daunting problem as science and medicine reached the third millennium AD, but a problem more accurately defined than ever before and upon which all the tools of modern science were brought to bear. Research explored cellular growth factors and intracellular signaling pathways that might be exploited against it. For practicing physicians radiotherapy, medical oncology, surgical oncology, and even breast surgery had become specialties. Cancer institutes dotted the country. For the record, in the United States in 2004 an estimated 217,000 women continued to develop breast cancer each year and 40,000 died of it annually. With screening and modern therapy, the death rate had begun to decline and overall relative survival 5 years after diagnosis, cured and uncured, was 86.6%.[57]

COMMENT

The sometimes heroic, often tragic, and always poignant story of breast cancer is incomplete; happy will be the day when the final chapter is written. When that day comes, it may not get the attention it deserves. It will come in familiar voices on the nightly news: "Today doctors at (some) medical center announced that a (vaccine?) prepared from the (prions?) of breast cancer resulted in immediate and total disappearance of all signs of the disease in eleven advanced cases. Further studies are planned to follow up this promising development. In international news…" Reactions will be mixed. Most will notice without comment. Skeptics will quip, "Yeah, another breakthrough!" But it will be true. Others, robbed of loved ones, will hesitate in melancholy reflection. More than suspected will reap the rewards, and after more than 5,000 years of telling, the story of breast cancer will have been told.

ACKNOWLEDGMENT

The author wishes to thank Judith H. Donegan, MD, PhD, for constructive criticism of the manuscript.

REFERENCES

1. Encyclopedia Britannica, 15th ed. Encyclopedia Britannica, Inc. Chicago: Encyclopedia Britannica Inc.; 1978. Macropedia. Vol 11 p. 823.
2. Breasted JH, editor. The Edwin Smith Surgical Papyrus. Chicago, IL: The University of Chicago Press; 1930, Special Edition. 1984. The Classics of Surgery Library. Division of Gryphon Editions, Ltd. Birmingham (AB). Frontispiece.
3. Homer. Iliad. Translated by WHD Rouse. New York: A Signet Classic. New American Library; 1966. p. 36.
4. De Moulin D. A short history of breast cancer. Boston: Martinus Nijhoff; 1983. p. 1–107.
5. Lewison EF. Saint Agatha the patron saint of diseases of the breast in legend and art. Bull History of Medicine 1950;24:409–20.
6. Lyons AS, Petrucelli RJ. Medicine. An illustrated history. New York: Harry N. Abrams Publishers; 1978. p. 294–317.
7. Hoxey HM. You don't have to die. New York: Milestone Books Inc; 1956. p. 47.
8. Yalom M. A history of the breast. New York: Alfred A. Knopf; 1997. p. 211.
9. LeDran HF. Memoires avec un précis de plusieurs observations sur le cancer. Memories de l'academie royale de chirurgie 1757;3:1–54.
10. Saunders JB deC M, O'Malley CD. The anatomical drawings of Andreas Vesalius. New York: Bonanza Books; 1982. p. 172–3.
11. Cooper AP. The anatomy and diseases of the breast. Philadelphia: Lea and Blanchard; 1845.
12. Sappey MPC. Anatomie, physiologie, pathologie des vaisseaux lymphatique considérés chez l'homme et les vertébrés. Paris: A Delahaye and E Lecrosnier; 1874.
13. Lillberg K, Verkasalo PK, Kaprio J, et al. Personality characteristics and the risk of breast cancer: a prospective cohort study. Int J Cancer 2002;100 361–6.
14. Robbins G, editor. Silvergirl's surgery—the breast. Austin: Silvergirl Inc.; 1984. p. 25–9.
15. Garrison FH. An introduction to the history of medicine. 4th ed. Philadelphia: WB Saunders, Co.; 1929. p. 588–9.
16. Encyclopedia Britannica, 15th ed. Chicago: Encyclopedia Britannica Inc.; 1978. Macropedia Vol 11 p. 837.
17. Müller J. Uber den feinen Bau und der Formen dei Krankhafte Geschwülste. Berlin: G Reimer; 1838.
18. Virchow R. Cellular pathology. Birmingham; The Classics of Medicine Library, Division of Gryphon Editions, Ltd.; 1978. p. 66.
19. Haagensen CD. Diseases of the breast, 2nd ed. Philadelphia: W. B. Saunders Co; 1971. p. 394–5.

20. Paget J. On disease of the mammary areola preceding cancer of the mammary gland. St. Bartholomew Hospital Reports;1874:vol. 10; p. 75–8.
21. Moore C. On the influence of inadequate operations on the theory of cancer. Royal Medical and Chirugical Society. London. Med Chir Trans 1867;32:245–80.
22. Banks WM. Free removal of mammary cancer with extirpation of the axillary glands as a necessary accompaniment. Paper read before the British Medical Association at Worcester. 1882.
23. Halsted WS. The results of operations for the cure of cancer of the breast performed at the Johns Hopkins Hospital from June 1889 to January 1894. Johns Hopkins Hospital Reports. Baltimore 1894–95;4:297–350.
24. Halsted WS. The results of radical operations for the cure of cancer of the breast. Trans Am Surg Assoc 1907;25:61–79. Reprinted in: Surgical papers of William Stuart Halsted Birmingham (AL): Gryphon Editions; 1984. p 80.
25. Handley WS. Cancer of the breast and its operative treatment. London: John Murray; 1906.
26. Bloom, HJG, Richardson WW, Harries EJ. Natural history of untreated breast cancer (1805-1933). Comparison of untreated and treated cases according to histological grade of malignancy. Brit Med J 1962;I:213–21.
27. Donegan WL. Staging and prognosis. In: Donegan WL, Spratt JS, editors. Cancer of the breast, 5th ed. Philadelphia: W.B. Saunders Co; 2002. p. 478.
28. Keynes GL. The radium treatment of carcinoma of the breast. Brit J Surg 1942;19:415–80
29. Horsley JS III, Horsley GW. Twenty years experience with prophylactic bilateral oophorectomy in the treatment of carcinoma of the breast. Ann Surg 1962;155:935.
30. Jensen EV, DeSombre ER, Jungblut PW. Estrogen receptors in hormone responsive tissues and tumors. In: Wissler RW, Dao TL, Wood S Jr., editors. Endogenous factors influencing host-tumor balance. Chicago: University of Chicago Press; 1967.
31. Special Report: Treatment of primary breast cancer. N Engl J Med 1979;301:340.
32. Egan RL. Mammography, 2nd ed. Springfield: Charles C Thomas; 1972. p. 3–22.
33. NCI statement on mammography screening. Available at: http://www.cancer.gov/newscenter/mammstatement31jan02 (accessed Jan 4, 2005).
34. Wolfe JN. Xeroradiography of the breast. Springfield: Charles C Thomas; 1972. p. 3–5.
35. McWhirter R. Simple mastectomy and radiotherapy in the treatment of breast cancer. Br J Radiol 1955;28:128.
36. Crile G Jr. A biological consideration of treatment of breast cancer. Springfield, IL: Charles C. Thomas;1967.
37. Gray JH. The relation of lymphatic vessels to the spread of cancer. Br J Surg 1939;26:462.
38. Ewing J. Neoplastic diseases, 4th ed. Philadelphia: W. B. Saunders Co; 1940. p. 63–74.
39. Fisher B. The surgical dilemma in the primary therapy of invasive breast cancer: a critical appraisal. Current problems in surgery. Chicago: Year Book Medical Publishers Inc.;1970.
40. Fisher B, Montague E, Redmond C, et al. Comparison of radical mastectomy with alternative treatments for primary breast cancer. Cancer 1977;39:2827–39.
41. Veronesi U, Valagussa P. Inefficacy of internal mammary node dissection in breast cancer surgery. Cancer 1981;47:170–5.
42. Fisher B, Redmond D, Poisson R, et al. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med 1989;320:822–8.
43. Baclesse F. Five-year results in 431 breast cancers treated solely by roentgen rays. Ann Surg 1965;61:103–4.
44. Veronesi U, Volterrani F, Luini A, et al. Quadrantectomy versus lumpectomy for small size breast cancer. Eur J Cancer 1990;26:671–3.
45. Fisher B, Anderson S, Redmond CK, et al. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med. 1995;333:1456–61.
46. Treatment of Early-Stage Breast Cancer. NIH Consens Statement Online 1990 Jun 18–21 [cited 2005 October 26];8: 1–19.
47. Guilliano AE, Jones RC, Brennan M, Statman R. Sentinel lymphadenectomy in breast cancer. J Clin Oncol 1997; 15:2245–50.
48. Papac RJ. Origins of cancer therapy. Yale J Biol and Med 2002;74:391–8.
49. DeVita VT. Principles of chemotherapy. In: DeVita VT Jr, Hellman S, Rosenberg SA, editors. Cancer—principles and practice of oncology. Philadelphia: J. B. Lippincott Co; 1982. p. 132–3.
50. Noer RJ. Adjuvant chemotherapy. Thio-tepa with radical mastectomy in the treatment of breast cancer. Am J Surg 1963;106:405–12.
51. Fisher B, Fisher ER, Redmond C. Ten-year results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trial evaluating the use of L-phenylalanine mustard (L-PAM) in the management of primary breast cancer. J Clin Oncol 1986;4:929–41.
52. Chlebowski RY, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 2003;289:3243–53.
53. Friedman LS, Ostermeyer EA, Szabo CI, et al. Confirmation of *BRCA1* by analysis of germline mutations linked to breast and ovarian cancer in ten families. Nat Genet 1994;8:399–404.
54. Futreal PA, Liu Q, Shattuck-Eidens D, et al. *BRCA1* mutations in primary breast and ovarian carcinomas. Science 1994;266:120–2.
55. Fisher B, Constantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90:1371–88.
56. Hartmann LC, Schaid DJ, Woods JE, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med 1999;340:77–84.
57. American Cancer Society 2004 statistics. Available at: http://www.cancer.org/downloads/MED/Page4.pdf (accessed Jan 11, 2005).