Communication

A Note From History: Landmarks in History of Cancer, Part 4

Steven I. Hajdu, MD

In the second half of the 19th century, most cancer patients were cared for by surgeons who exerted ascesis and limited their operations to 1 or 2 specific areas. To assist surgeons and other physicians in caring for their patients, pathologists described newly discovered entities, refined the microscopic classification of tumors, and introduced the grading of cancers. The discoveries of Rontgen and the Curies revolutionized the diagnosis and treatment of cancers. The search for the cause of cancers extended to infectious organisms, chemicals, and radioactive materials. The 50 years covered in this review formed the groundwork for the coordinated, specialized care of cancer patients at institutions dedicated to render the most promising treatment. ***Cancer* 2012;000:000–000.** © *2012 American Cancer Society.*

KEYWORDS: history of cancer, history of surgical oncology, history of surgical pathology, history of neurosurgery, history of radiology and radiation therapy, history of nuclear medicine, history of chemotherapy, history of hematologic oncology, history of cancer research, history of cancer epidemiology and statistics.

During the first half of the 19th century, the microscopic diagnosis of tumors became routine at select university hospitals. Most surgeons welcomed the assistance of pathologists in the preoperative and postoperative microscopic characterization of tumors. In many instances, because of the scarcity of pathologists, surgeons assumed the role of pathologists and performed the microscopic examination of tumors they excised from their patients. In the mid-1800s, the 3 best known surgeon microscopists were James Paget (1814-1899) of England, Alfred Velpeau (1795-1867) of France, and Samuel D. Gross (1805-1884) of the United States.[1] Their combined knowledge of macroscopic and microscopic pathology and surgery formed the foundation of a new field, surgical pathology. Of the pathologists, Rudolf Virchow (1821-1902) of Germany contributed more to the advancement of the macroscopic and microscopic understanding of tumors than any of his contemporaries. His extensively illustrated book on benign and malignant tumors, *Die krankhaften Geschwulste*,[2] a transcript of his lectures given at the University of Berlin between 1862 and 1863 and published in 3 volumes between 1863 and 1867, is an incomplete work. Regrettably, Virchow never completed the fourth volume, which was intended to be on the genesis and classification of epithelial tumors. Nonetheless, his book remains a great sourcebook on cancer and is regarded as one of the most significant contributions to the oncology literature in the 19th century (Fig. 1).[2]

Everything Virchow knew about tumors he included in his comprehensive treatise, except his theory about the histogenesis of malignant epithelial tumors, carcinomas. He coined the terms "hyperplasia" and "metaplasia" and recognized that both conditions are potential precursors of cancer, and that cancer cells are distinctly different in size and shape from benign cells. He introduced the terms "chromatin," "tumor agenesis," "tumor parenchyma," "tumor thrombus," "tumor embolus," and "leukemia." Virchow believed that the growth of cancer cells in body fluids is due to the presence of a growth-stimulating substance (a chemical growth factor) in the fluids. He provided the first microscopic description and illustration of numerous benign and malignant tumors, including condyloma and carcinoma of the penis; infiltrating cancroid (keratinizing squamous carcinoma) of the lip, uterine cervix, and orbit; microinvasion and mucus secretion by certain carcinomas; and myogenic, lipoid, and fibrous sarcomas.[2] Among his many illustrations, a particularly noteworthy one shows a woman with lymphedema of the left leg, multiple pigmented skin lesions (café-au-lait spots), and numerous cutaneous and soft tissue tumors.[2] The disease was named neurofibromatosis 20 years later by Friedrich Daniel von Recklinghausen.

Virchow is also remembered as the only physician whose 80th birthday was celebrated in Germany as a national holiday.[3] It is interesting to note that after Virchow formulated his dictum in 1858 that all cells come from preexisting cells,[1] and in the 1860s conceived the theory that the cell is the ultimate morphologic element in which there is any manifestation of life,[2] he ceased thinking about cells from 1870 onward. He became active in national politics and served 13 years as an orgulous member of the German Reichstag, and devoted his spare time to his lifetime avocation, anthropology.[3] Shortly before his death in 1902, he made the telling observation that no human being can define, even under torture, exactly

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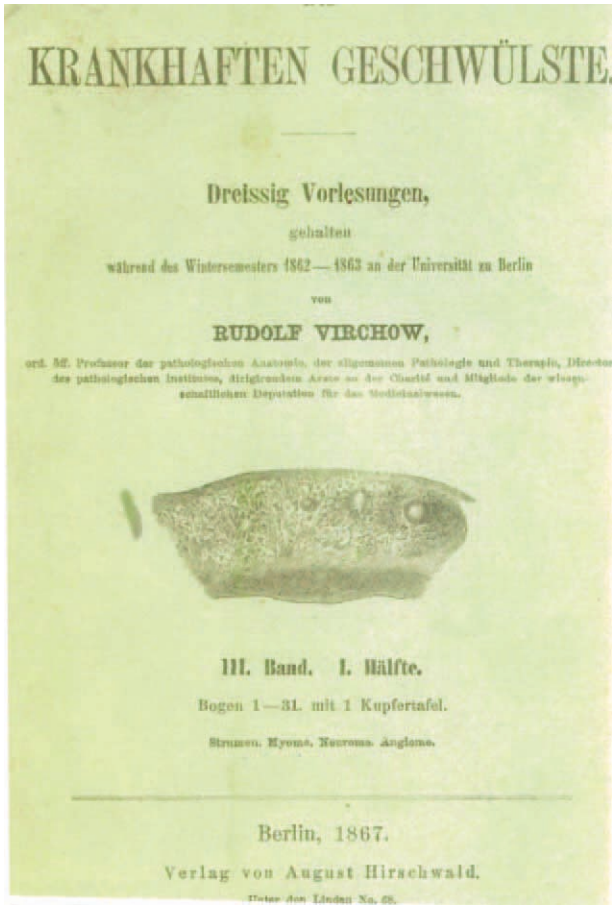

KRANKHAFTEN GESCHWÜLSTE

Dreissig Vorlesungen,

gehalten

während des Wintersemesters 1862—1863 an der Universität zu Berlin

von

RUDOLF VIRCHOW,

III. Band. I. Hälfte.

Bogen 1—31. mit 1 Kupfertafel.

Berlin, 1867.

Verlag von August Hirschwald.

Figure 1. This is the cover of Rudolf Virchow's magnum opus, the first landmark book on tumors.

what a tumor is–a typical Virchowian remark that can perhaps be taken as an erudite summation of the state of the art of oncopathology at the end of the 19th century.

After it had been demonstrated by studying multiple tissue sections of primary tumors that both squamous cell carcinoma and adenocarcinoma were epithelial in origin,[4,5] and not connective tissue as was suggested by Virchow,[2] the origin of breast carcinoma was traced to the terminal acinar (tubulolobular) epithelium,[6] prostate carcinoma was found to originate from the glandular epithelium of the prostate,[7] and cancer of the liver was shown to be from intrahepatic bile duct epithelium.[8] As a continuum of these efforts, it was definitively established that there are only 2 mechanisms for secondary growths (metastases): 1) direct extension by contiguity and 2) by tumor emboli through blood or lymphatic vessels.[5]

In 2 of his lengthy papers,[5] Heinrich Wilhelm Waldeyer-Hartz (1836-1921), a German histopathologist, published his microscopic observations by studying 200 surgically excised cancers in serial sections. By viewing with the microscope the connective tissue stroma of breast carcinomas, he discovered that marked proliferation of epithelial cells in breast acini (hyperplasia and carcinoma in situ) is always accompanied by periacinar proliferation of connective tissue cells. He then added that invasive carcinoma cells can induce such extensive proliferation of connective tissue stromal cells that the carcinoma becomes firm and scar-like. Waldeyer-Hartz, without realizing it, had solved a 2000-year-old enigma. Scirrhous (firm) carcinomas, named by ancient physicians,[9] were firm because of the microscopic build-up of connective tissue cells (fibroblasts and myofibroblasts) around the invading carcinoma cells. As an exception to the rule that carcinoma cells were capable of generating their own stroma, he identified medullary carcinomas (soft carcinomas). Waldeyer-Hartz made a time-honored observation that medullary carcinomas were almost exclusively comprised of epithelial cells without interweaving connective tissue stroma.[5]

By the end of the 1860s, it was recognized that primary malignant tumors can arise in every organ and the majority of them are clinically and microscopically distinct. Simultaneously with organ-specific studies of malignant tumors, new instruments and techniques were described to facilitate clinical and pathologic diagnoses. Sputa were collected for cytologic examination.[10] Clinical use of the laryngoscope,[11] cystoscope,[12] and pneumatic aspirator,[13] as well as transcutaneous needle biopsy, were introduced.[14]

The realization that malignant tumors were organ-specific growths did not stop the search by cell biologists for that elusive first cell that gives rise to tumors. The most plausible theory that was met with nearly universal acceptance was introduced by Julius Cohnheim (1839-1884), a Berlin pathologist, with the publication of his *Vorlesungen uber allgemeine Pathologie* in 1877.[15] He proposed that tumors develop either from nests of cells that are misplaced during embryonal development or cells that have retained embryonal characteristics. He believed that these cells are distributed throughout the body and are capable of developing into neoplasms through changes in vascularity (angiogenesis) or by virtue of bioplastic energy (genetic predisposition). Two decades later, Moritz Wilhelm Hugo Ribbert (1855-1920), a Zurich pathologist, modified Cohnheim's embryonal theory by adding to it that mechanical irritation (chronic inflammation and trauma) also predisposed epithelial and connective tissue cells to proliferate to cause cancer.[16] It should be perhaps noted that Cohnheim's and Ribbert's theories are accepted as valid, with some minor modifications, even today.

In the 19th century, very few clinicians and pathologists had acquired substantial experience in the diagnosis

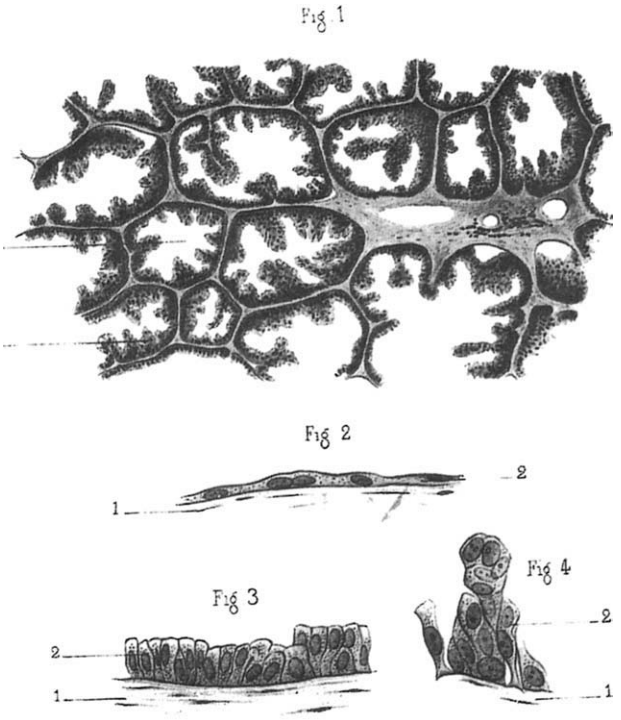
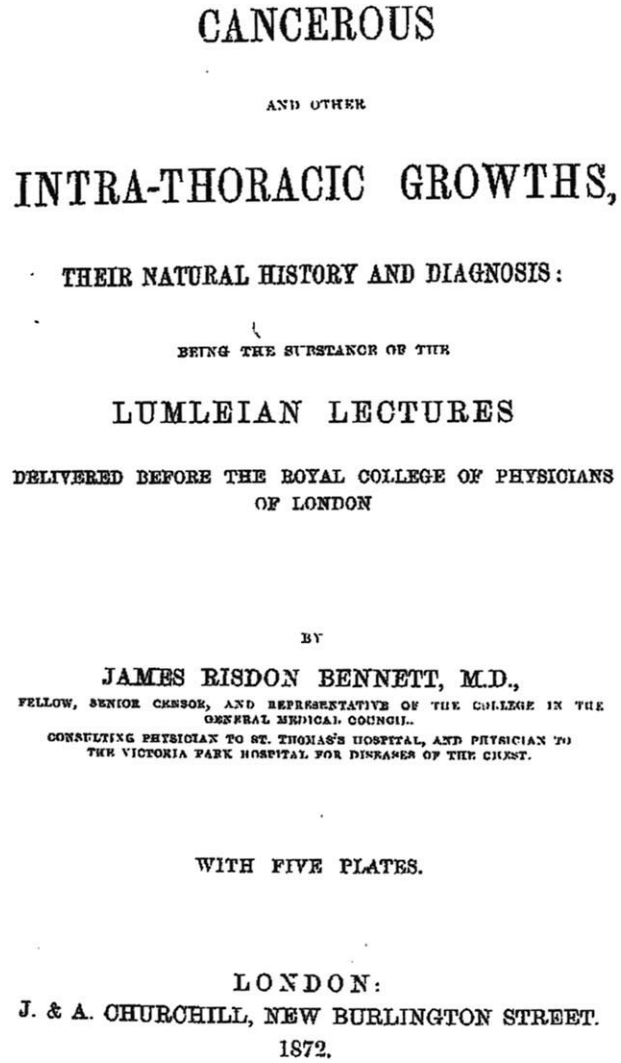


Figure 2. Louis-Charles Malassez's (1842-1909) illustration from 1876 of a newly discovered lung carcinoma that was later named "bronchioloalveolar carcinoma" in 1960 is shown.

and treatment of malignant tumors. The exceptions were breast carcinoma and uterine cervical carcinoma.[1] The new tendency toward subspecialization in medicine and surgery contributed to the publication of cases of unusual tumors, often labeled with new names. Contemporary readers learned about benign and malignant myeloplax tumors of bone (giant cell tumors),[17] primary squamous carcinoma of the lung, carcinoma of the sigmoid colon as the most common intestinal carcinoma, primary brain cancer (malignant glioma),[18] primary encephaloid carcinoma of the lung (which became known 85 years later as bronchioloalveolar carcinoma)[19] (Fig. 2), bilateral renal myosarcomatoid tumor of the kidney of a newborn (later known as Wilms tumor),[20] mucinous carcinoma of the ovary with malignant ascites (pseudomyxoma peritonei),[21] Krukenberg tumor of the ovary,[22] fibro-cancerous tumor of the pleura (malignant fibrous mesothelioma)[23] (Fig. 3), paratesticular myoma (embryonal rhabdomyosarcoma),[24] extraskeletal osteosarcoma[25] and chondrosarcoma,[26] chordoma,[27] hydatidiform mole with peritoneal and distant extension (metastatic choriocarcinoma),[28] cystosarcoma of the breast (cystosarcoma phyllodes),[29] sarcoma botryoides of the uterus,[30] embryonal[31] and pleomorphic[32] rhabdomyosarcoma, angiosarcoma,[33] abdominal-desmoid[34] hemangioendothelioma, lymphangioendothelioma (lymphangiosarcoma), and perithelioma (hemangiopericytoma).[35] Simultaneously, improved tissue techniques led to the discoveries of additional entities; the introduction of new terms such as "myelogenous leukemia,"[36] "lymphosarcoma,"[37] and "pheochromocytema,"[38] anaplasia and asymmetric mitosis as characteristic features of cancer cells (Fig. 4).[39] New laboratory techniques confirmed the connection between neurofibromas and the endo- and epineurium of nerves in neurofibromatosis (a disease known since then as von Recklinghausen disease),[40] and resulted in the discovery of nucleotin,[41] nucleoprotein, (now known as DNA) in every living cell.



CANCEROUS

AND OTHER

INTRA-THORACIC GROWTHS,

THEIR NATURAL HISTORY AND DIAGNOSIS:

BEING THE SUBSTANCE OF THE

LUMLEIAN LECTURES

DELIVERED BEFORE THE ROYAL COLLEGE OF PHYSICIANS OF LONDON

BY

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WITH FIVE PLATES.

LONDON:
J. & A. CHURCHILL, NEW BURLINGTON STREET.
1872.

Figure 3. The title page of James R. Bennett's book in which he described malignant pulmonary and pleural neoplasms is shown.

The trend in specialization in Vienna, Austria produced a prestigious school of clinical dermatology that was established in the mid-1800s. There, in 1872, Moritz

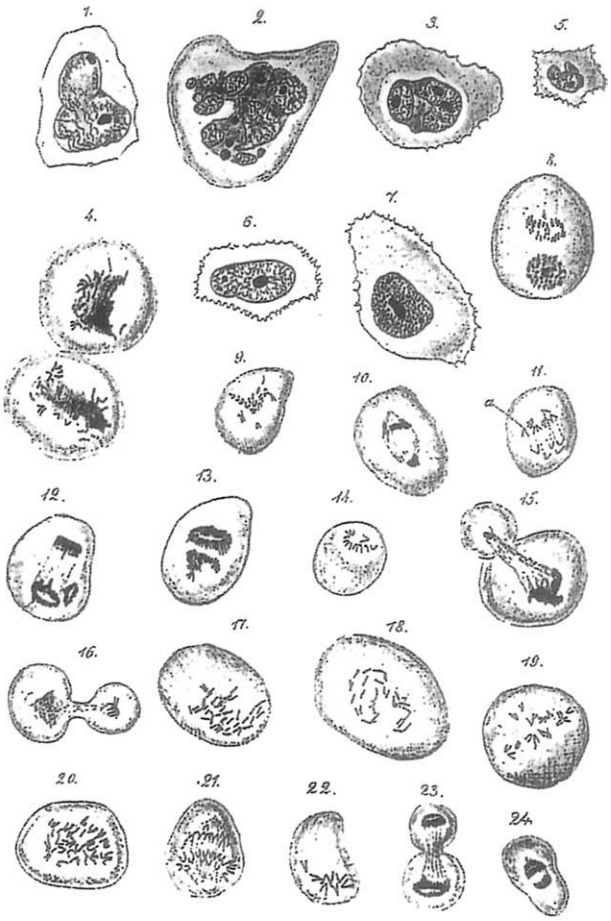
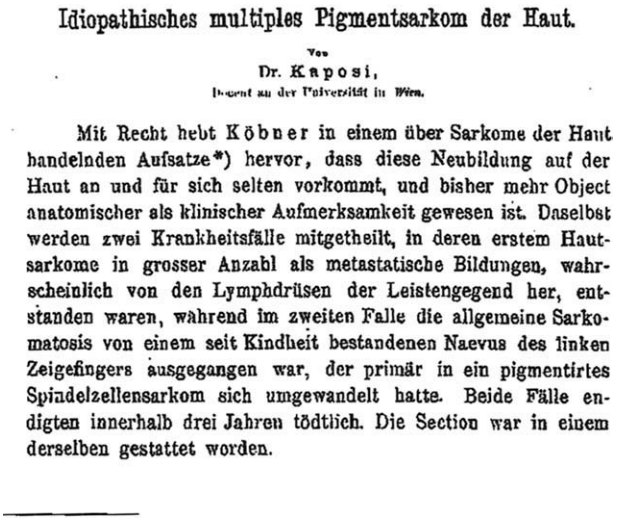


Figure 4. David Paul von Hansemann's 1890 illustration of mononuclear and multinuclear cancer cells with enlarged nuclei and nucleoli is shown, demonstrating various forms of atypical mitosis of malignant epithelial tumor cells.



Idiopathisches multiples Pigmentsarkom der Haut.

Von

Dr. Kaposi,

Docent an der Universität in Wien.

Mit Recht hebt Köbner in einem über Sarkome der Haut handelnden Aufsatze*) hervor, dass diese Neubildung auf der Haut an und für sich selten vorkommt, und bisher mehr Object anatomischer als klinischer Aufmerksamkeit gewesen ist. Daselbst werden zwei Krankheitsfälle mitgetheilt, in deren erstem Hautsarkome in grosser Anzahl als metastatische Bildungen, wahrscheinlich von den Lymphdrüsen der Leistengegend her, entstanden waren, während im zweiten Falle die allgemeine Sarkomatosis von einem seit Kindheit bestandenen Naevus des linken Zeigefingers ausgegangen war, der primär in ein pigmentirtes Spindelzellensarkom sich umgewandelt hatte. Beide Fälle endigten innerhalb drei Jahren tödtlich. Die Section war in einem derselben gestattet worden.

Figure 5. First page of Moritz Kaposi's original article from 1872 on a new skin cancer that became known as Kaposi sarcoma is shown.

Kaposi (1837-1902), a Hungarian dermatologist, came upon the first cases of a new malignant disease of the skin, which he called "idiopathic multiple pigmented sarcoma,"[42] that since then has been known eponymically as Kaposi sarcoma. After the 1980s, Kaposi sarcoma became recognized as one of the marker diseases for the acquired immunodeficiency syndrome in human immunodeficiency virus-infected patients (Fig. 5).

Although it was recognized in the 19th century that children with cancer required special care, very little was done about this issue because pediatric cancers were regarded as fatal diseases. After the publication of a nosology of pediatric diseases,[43] it was realized that early diagnosis and radical surgical treatment can be potentially lifesaving.

From the mid-1800s onward, advances in anesthesia and antiseptic techniques permitted surgeons to perform more and more daring operative procedures that induced wide subspecialization in surgery during the last decades of the 19th century. The field of dentistry was broadened to encompass the oral cavity and the jaw. New operative procedures were introduced and a new field, oral surgery, was inaugurated as a speciality.[44] Theodor Billroth (1829-1894), an Austrian pathologist surgeon specializing in surgery of the gastrointestinal tract, gained early worldwide recognition for his comprehensive illustrated textbook *Die Allgemeine Chirurgische Pathologie und Therapie*.[45] Approximately 20% of the book is devoted to tumors. Billroth is regarded as the founder of both head and neck and abdominal surgery because of his pioneering skilful resection of the tongue,[45] larynx,[46] esophagus,[47] and stomach (Bilroth I and Bilroth II operations).[48,49] He is credited with first recognizing that carcinomas spread preferentially through the lymphatics and sarcomas metastasize via blood vessels. He observed that the lymphatic gland nearest to the carcinoma (sentinel lymph node) is the one that harbors metastatic cancer cells first.[45] Billroth introduced many new terms, including "malignant lymphoma,"[45] "noninfiltrating and infiltrating acinar carcinoma" (in situ and infiltrating lobular carcinoma), and "tubular carcinoma of the breast."[50] Austria celebrated the 100th anniversary of Billroth's birth by issuing a 2-shilling piece. To the best of my knowledge, this is the only instance in which a government has minted a coin bearing the likeness of a physician.

Johann von Mikulicz (1850-1905) was one of Billroth's assistants who also specialized in surgery of the head and neck as well as intestinal tumors. He was the first to use the electric esophagoscope,[51] which had been invented the year before by the Viennese instrument maker Joseph Leiter. Mikulicz was also the first to perform plastic

reconstruction of the esophagus after resection of the upper one-third for carcinoma.[52] In 1903, he reported operative exteriorization in 16 cases of cancer of the colon coupled with removal of the nearest segment of the mesentery (lymphadenectomy).[53] He reported a 12% operative mortality rate. Earlier, in 1892, in his collected writings, he presented for the first time the syndrome of involvement of the salivary and lacrimal glands in lymphogranuloma malignum,[54] which has since been remembered as Mikulicz disease.

Also in 1892, inguinal, lumbar, and transverse colostomies were introduced for patients with cancer and stricture with ulceration (Crohn disease and ulcerative colitis).[55] The gastric tube was designed for obtaining cells by lavage for microscopic examination.[56] The use of gastric curettage was then initiated for the early diagnosis of cancer of the stomach,[57] and permanent gastrostomy was used to facilitate feeding in patients with inoperable esophageal carcinoma.[58]

Although transfusion had been introduced and was used sporadically for postpartum hemorrhage from the early 1800s onward,[1,59] resection of parenchymal organs such as the liver was prohibitive because of cruentation and profuse bleeding. In 1888, the situation changed for the better when the first successful liver resections for tumor were performed using a new, relatively bloodless surgery.[60]

The concept of the origin of adenomas and carcinomas of the thyroid from multiple foci of embryonal epithelial nests in the cortex of the gland[61] resulted in radical changes in thyroid surgery through the introduction of hemithyroidectomy and total thyroidectomy,[62] both novel radical operations for which Emil Theodor Kocher (1841-1917), a Swiss surgeon, was awarded the Nobel Prize in 1909.

Twenty years after the endoscope was introduced in urology,[12] bladder tumors were removed for the first time using transurethral catheter and forceps in 1884.[63] Five years later, 8 cases of bladder tumor were diagnosed and treated using an electrically lighted cystoscope.[64] The experience with cystoscopic diagnosis and the treatment of bladder tumors and the excellent results noted with a new and daring operative procedure, suprapubic cystotomy, reported a mortality rate of $< 20\%$ in 88 cases.[65]

Two closely related but distinctly different fields, neurology and neurosurgery, had a slow beginning. The first practical clinical treatise on intracranial tumors was published in 1888 by Byrom Bramwell (1847-1931), an English surgeon who specialized in surgery for brain tumors.[66] He also reported excision of a paraspinal tumor from the anterior nerve root of the cervical portion of the spinal cord.[67] Accurate clinical localization followed by operative removal of brain tumors, including gliomas, was performed in 10 patients. All patients except one survived.[68] A total of 38 cases of brain tumors were reported from the Boston City Hospital with attention to anatomic site, size, symptomatology, and postmortem findings.[69]

From the time the term "orthopedy" was introduced in the 1700s,[70] orthopedic surgeons had immense difficulty with regard to the preoperative localization of intraskeletal tumors. Despite this, at a few selected medical centers, surgeons gradually accumulated substantial experience in the surgical management of primary bone tumors. Samuel W. Gross (1837-1889), an American surgeon, followed his illustrious father, Samuel D. Gross[1](1805-1884) at the Jefferson Medical College in Philadelphia, Pennsylvania. In 1879, he published the first comprehensive writing on bone sarcomas in 2 lengthy papers.[71] On the basis of 165 cases of patients with bone sarcomas that he and his father operated on and studied macroscopically and microscopically, he introduced a histogenetic classification of bone sarcomas that remained in use with only minor changes to the present time. Gross tabulated the clinical and anatomic presentations and microscopy of the most common primary malignant tumors of long bones. He indicated that amputation added an extra 1 or 2 years to survival, except in the case of round cell sarcoma (Ewing sarcoma).[71] In desperation as the last hope for cure, Gross and other surgeons resorted to some of the most mutilating operative procedures. Disarticulation at major joints and interscapulothoracic amputation became routine in the treatment of soft tissue and bone sarcomas using the technique advanced by Paul Berger (1845-1908), a French surgeon.[72]

Uterine cervical carcinomas were treated by excision and amputation of the cervix from the early 1800s onward.[1] After some surgeons began to limit their practice to gynecologic surgery, the field extended to tumors of the uterus and ovary. Thomas S. Wells (1818-1897), an English gynecologist, was a pioneer ovariotomist and pelvic surgeon. In his book, *Diseases of the Ovaries: Their Diagnosis and Treatment*, published in 1865, he presented a series of new operative techniques with the intention of decreasing surgical mortality.[73] For example, he introduced operating on patients in a recumbent position for abdominal and pelvic tumors, because he found that performing surgery on patient in the traditional sitting posture was inconvenient and dangerous for patients as well as the surgeon. He insisted that only properly trained surgeons should perform gynecologic surgery because experience made a difference in outcome.

Figure 6. A photograph of New York Women's Hospital is shown. It was renamed the New York Cancer Hospital in 1884 and is remembered as the first cancer hospital in the United States.

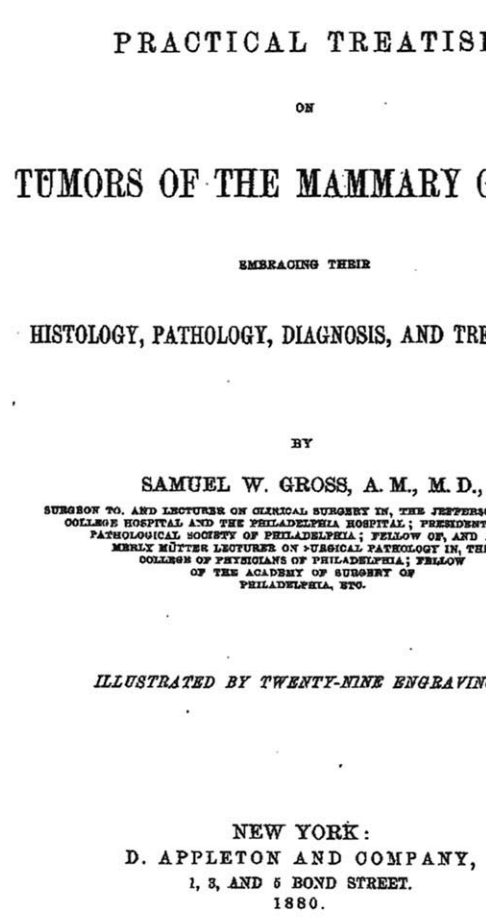
In New York, T. Gaillard Thomas (1832-1903), in his heavily illustrated book, *A Practical Treatise on the Diseases of Women* (published in 1876), presented hundreds of gynecologic tumor cases.[28] He introduced new instruments and operative techniques, including vaginal ovariectomy. Thomas recommended use of the microscope intraoperatively (intraoperative frozen section) to determine whether the tumor was benign or malignant. Also in New York, with the support of wealthy philanthropists and their socialite wives, the old New York Women's Hospital, established in 1854 under the direction of James M. Sims (1813-1883) (who is recognized for his innovative treatment of vesicovaginal fistula and treatment of cervical cancer by amputation of the cervix[74]), was renamed in 1884 as New York Cancer Hospital (Fig. 6). For over a decade it was the primary cancer hospital for women, and in 1899 became the Memorial Hospital for the Treatment of Cancer and Allied Diseases.

Cancer of the uterus was described as a fatal disease[75] and a warning was issued that when a woman enters the cancerous age (perimenopausal or postmenopausal age) and suffers from uterine bleeding, the possibility of cancer must be entertained. It was indicated that uterine hemorrhage was the first sign of cancer in 44% of diagnosed cases.[75] Cancer in women reached such a percentage in the mid-1800s that it was regarded as a public health problem. The result of the first survey of the geographic distribution and mortality of cancer in females in England and Wales showed a range of from 2 to 7 per 10,000 living women. The mortality was highest in cases of uterine cancer. It was found that cancer was most prevalent in industrial areas and along those rivers that flood their banks. The geographic distribution of the prevalence of cancer was depicted for the first time according to habitation and geographic regions by Alfred Haviland of London on his autogeneal 36 inch $\times$ 28 inch color map.[76] Haviland's groundbreaking discovery and statistical analysis provided the impetus in the late 19th century to search for airborne pollutants, waterborne contagion, insects, and parasites that might be a source of cancer.

Throughout history, breast cancer, the most common cancer in women, was the most feared destructive disease.[77] Seemingly all attempts at treatment failed until the late 18th century when early diagnosis and an aggressive surgical approach were introduced.[1] As surgeons gained experience, various forms of surgery were practiced. These ranged from en block resection of the tumor[78] to complete removal of the entire breast, axillary lymph nodes, and part of the pectoralis major muscle as well as extirpation of adjoining skin to prevent recurrence.[79] The end results of a large series of patients who underwent surgery in Vienna demonstrated that Billroth and his associates were able to achieve a 3-year survival rate of 5%.[80]

In 1880, the year after his text on bone tumors was printed,[71] Samuel W. Gross of Philadelphia published the first comprehensive surgical pathology book in English on tumors of the breast.[81] In *A Practical Treatise on Tumors of the Mammary Gland* (Fig. 7), Gross presented the clinical and pathologic findings by studying 712 carcinomatous cases and 138 benign cases. His most notable findings were the upper outer quadrant as the most common site of disease, multicentric presentation in 2% of cases, bilateral cancer in 4% of cases, retraction of the nipple in 52% of cases, axillary metastasis in 64% of cases, metastasis to lymph nodes in the neck in 22% of cases, and a hereditary predisposition in 11% of cases. In view of these findings, Gross recommended the removal of the whole breast and the axillary lymph nodes in every case of breast cancer. He concluded that by using the recommended operation, 9% of patients were cured for $>$ 3 years.[81] Ten years later, in a report from Copenhagen,[82] the 3-year survival rate after mastectomy and extirpation of palpable axillary lymph nodes was reported to be 20%.

For many decades, there were multiple attempts at standardizing the surgical treatment of breast cancer, but without success.[1,50,79-81] It was William S. Halsted (1852-1922), a Baltimore surgeon, who succeeded in gaining worldwide recognition for introducing his technique of radical mastectomy[83] in 1891. The wide skin excision, sharp dissection of the breast, removal of the



PRACTICAL TREATISE

ON

TUMORS OF THE MAMMARY GLAND:

EMBRACING THEIR

HISTOLOGY, PATHOLOGY, DIAGNOSIS, AND TREATMENT.

BY

SAMUEL W. GROSS, A. M., M. D.,

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ILLUSTRATED BY TWENTY-NINE ENGRAVINGS.

NEW YORK:
D. APPLETON AND COMPANY,
1, 3, AND 5 BOND STREET.
1880.

Figure 7. The title page of Samuel W. Gross's groundbreaking book on breast tumors is shown.

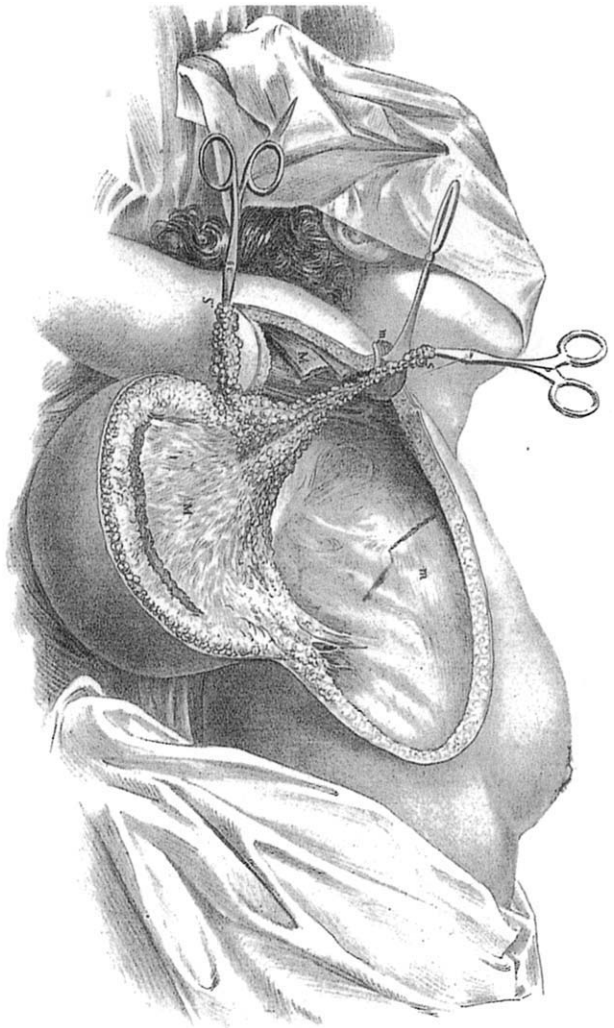


Figure 8. William S. Halsted's diagram illustrating his operative technique of radical mastectomy that he introduced in 1891 is shown.

pectoralis major muscle and division of the pectoralis minor muscle, and the complete cleaning out of the axilla (and occasionally the infraclavicular and the supraclavicular region) were the characteristic features of his operation (Fig. 8). He also advised clinicians to remove all tissues in 1 piece, in continuity, without cutting across lymphatic channels. Halsted demonstrated[84] that his radical mastectomy improved surgical survival by reducing the local recurrence rate to 6%. Despite his excellent results with regard to local control, the majority of his first patients died with disseminated disease within 3 years because he operated on patients who already had metastatic carcinoma beyond the axilla. In 1907, Halsted reported his operative experience and end results in 210 cases,[85] claiming a 3-year disease-free survival in 89 patients (42%). There is little doubt that Halsted and his followers knew that radical surgery does not cure advanced cancer and that radical mastectomy may cause permanent lymphedema of the arm on the operative side.[86] Nonetheless, Halsted's technique of radical mastectomy remained the cromulent method of treatment of carcinoma of the breast, with minor modifications, for the next 100 years. Simultaneously, with the intent to find a cure for inoperable cancer of the breast, George T. Beatson (1848-1933), a Glasgow surgeon, introduced oophorectomy in 1896 on the theory that a lack of hormonal secretion of the ovary will produce atrophy of the breast tumor.[87]

During the decades of surgical specialization, chemistry and bacteriology made their entry into industrial and clinical practice. However, disappointingly, the search for cancer-causing chemicals and organisms in water, soil, and forests showed no results, with 1 exception. In 1879, autopsy findings revealed for the first time the occupational risk of lung cancer in miners in the Erz mountains in Europe.[88] The observers believed that the cancers and

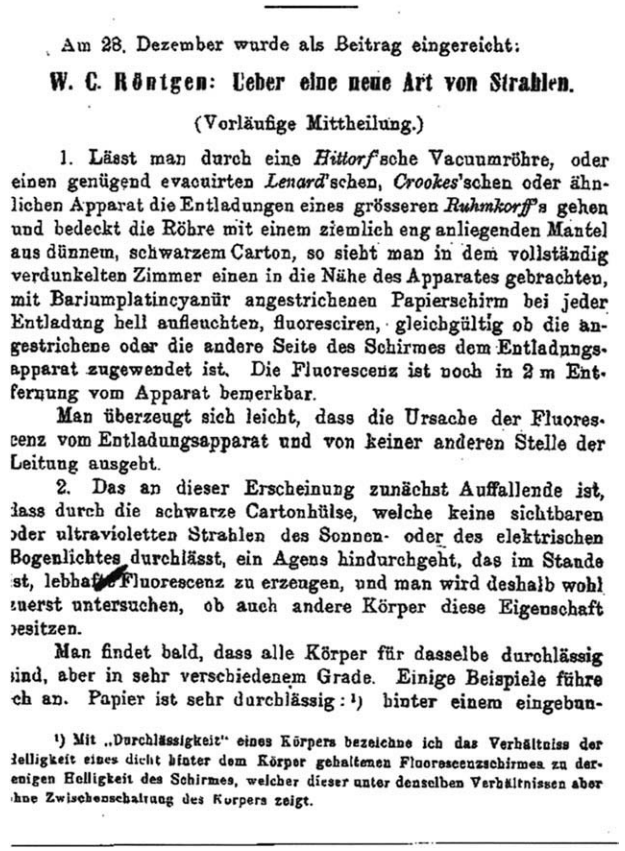
related pulmonary diseases were most likely due to inhalation of mine dust, which contained arsenic, bismuth, cobalt, nickel, and other chemicals. Decades later, it was shown that high levels of the radioactive substances radium and radon can be measured in mines in the Erz mountains and some other underground mines, and are the etiologic agents of lung cancer occurring in miners. Eventually, skin cancer was linked to the chronic use of industrial tar, coal tar, paraffin,[89] and arsenic.[90] Smoking was found to cause carcinoma of the tongue and lips.[91] Two cases of bladder papilloma and 1 carcinoma were found among 45 workers handling aniline and related chemicals in a rubber factory.[92] Skin cancers in farmers and sailors were linked to chronic exposure to sunlight.[93] Irritated nevi of the skin and the eye were named as potential sources of melanoma and it was discovered that melanomas have a preferential spread to regional lymph nodes.[86]

With the advent of microbiology, newly isolated organisms and parasites were claimed to be the cause of cancer without adequate proof. In 1889, Reginald Harrison (1838-1908), a British pathologist, reported the extraordinary frequency of bladder carcinoma among Egyptians infected with the parasite known as *Schistosoma haematobium*.[94] Bladder tumors remained the only human tumors documented to be associated with a parasite until the discovery of *Clonorchis sinensis* several decades later as a causative factor in cancer of the bile ducts in Asia.

In the preradiation therapy era, if a cancer could not be cured by surgery or cautery, the method of treatment was the internal or external use of a wide variety of home remedies and unproven medicinal preparations.[95]

In his desperation to treat inoperable cancer cases, William B. Coley (1862-1936), a New York surgeon, introduced a bacterial toxin treatment.[96] The toxin was injected into patients with advanced disease in hopes of assisting the body's immune system to arrest the growth of the cancer. Coley claimed good results, particularly in patients who had soft tissue or bone sarcomas. However, the treatment was discontinued gradually due to extreme toxicity. During the same period, with the intent of understanding oncogenesis, cancers were transplanted in animals. Mistislav A. Novinsky (1841-1914), a Russian veterinarian, successfully transplanted a malignant venereal tumor (condyloma) of dogs into unaffected dogs.[97] Spontaneous rat vulvar carcinoma was transplanted into the testes of male rats,[98] and the successful transplantation of mouse carcinoma was carried through 17 generations of mice.[99]

In 1895, 2 epoch-making events occurred. Alfred B. Nobel (1833-1896), a Swedish chemical engineer, inventor, and entrepreneur, established in his final will the



Am 28. Dezember wurde als Beitrag eingereicht:

W. C. Röntgen: Ueber eine neue Art von Strahlen.

(Vorläufige Mittheilung.)

1. Lässt man durch eine *Hittorf*'sche Vacuumröhre, oder einen genügend evacuirten *Lenard*'schen, *Crookes*'schen oder ähnlichen Apparat die Entladungen eines grösseren *Ruhmkorff*'s gehen und bedeckt die Röhre mit einem ziemlich eng anliegenden Mantel aus dünnem, schwarzem Carton, so sieht man in dem vollständig verdunkelten Zimmer einen in die Nähe des Apparates gebrachten, mit Bariumplatincyanür angestrichenen Papierschirm bei jeder Entladung hell aufleuchten, fluoresciren, gleichgültig ob die angestrichene oder die andere Seite des Schirmes dem Entladungsapparat zugewendet ist. Die Fluorescenz ist noch in 2 m Entfernung vom Apparat bemerkbar.

Man überzeugt sich leicht, dass die Ursache der Fluorescenz vom Entladungsapparat und von keiner anderen Stelle der Leitung ausgeht.

2. Das an dieser Erscheinung zunächst Auffallende ist, dass durch die schwarze Cartonhülse, welche keine sichtbaren oder ultravioletten Strahlen des Sonnen- oder des elektrischen Bogenlichtes durchlässt, ein Agens hindurchgeht, das im Stande ist, lebhafte Fluorescenz zu erzeugen, und man wird deshalb wohl zuerst untersuchen, ob auch andere Körper diese Eigenschaft besitzen.

Man findet bald, dass alle Körper für dasselbe durchlässig sind, aber in sehr verschiedenem Grade. Einige Beispiele führe ich an. Papier ist sehr durchlässig:[1]) hinter einem eingebun-

[1]) Mit „Durchlässigkeit" eines Körpers bezeichne ich das Verhältniss der Helligkeit eines dicht hinter dem Körper gehaltenen Fluorescenzschirmes zu derjenigen Helligkeit des Schirmes, welcher dieser unter denselben Verhältnissen aber ohne Zwischenschaltung des Körpers zeigt.

Figure 9. First page of Wilhelm Rontgen's 1895 article in which he announced his discovery of x-rays is shown.

Nobel prizes. As of today, among the nearly 900 Nobel laureates, there are over 50 scientists and physicians who have been recognized for their contribution to oncology.[100] The other event that took place is centered around Wilhelm C. Rontgen (1845-1923), a German physicist, for his accidental discovery of the rays he named x-rays (Fig. 9).[101] Rontgen's discovery created, seemingly overnight, a new field in medicine: diagnostic radiology. The first diagnostic radiology units were installed in hospitals in Europe and the United States in 1896. The same year, the first illustrated technical manual of radiology and diagnostic text was published.[102]

The dangers of x-ray exposure in the form of dermatitis and burns on hands were known shortly after news broke of Rontgen's discovery in 1895. However, a causal relation between x-rays and cancer was not realized until 1902, when the first radiation-induced carcinoma was reported on the hand of an x-ray technician.[103] The patient died 4 years later of metastatic squamous carcinoma. The first report was followed by voluminous literature on x-ray cancers. The majority of the reported cases

occurred in radiologists and were predominantly carcinoma, with occasional cases of leukemia and sarcoma.

The tumor-destructive effects of x-rays were discovered simultaneously with their carcinogenic potential, and Rontgen's discovery led to the birth of another new field, radiation therapy. In 1897, x-ray radiation was introduced for the treatment of inoperable breast cancer.[104] The first successful use of roentgen rays in the treatment of a microscopically proven carcinoma was reported in 1899.[105] The carcinoma was an advanced lesion of the cheek that healed rapidly after treatment. Without doubt, few discoveries have made such a tremendous impact on the field of medicine as Rontgen's discovery. Rontgen was awarded the first Nobel Prize for Physics in 1901.

Within a year of Rontgen's discovery, 2 closely linked groups of scientists in France, Antoine H. Becquerel (1852-1908) and Pierre Curie (1859-1906) and his Polish-born wife, Marie Sklodowska Curie (1867-1934)–while working with pitchblende, discovered the radioactivity of uranium[106] and isolated a highly potent radioactive substance they named radium.[107] The Nobel Prize was awarded jointly to Becquerel and the Curies for their discoveries in 1903. Marie Curie is also recognized for introducing the term "radioactivity." Without delay, the treatment of skin cancers with radium was introduced.[108] Two cases of basal cell carcinoma of the face were treated, with good results. A year later, Robert Abbe (1851-1928), a New York surgeon, reported the successful treatment of a series of 30 cases of superficial epithelioma (squamous carcinoma) and rodent ulcers (basal cell carcinoma) with radium he purchased from the Curie Laboratory.[109] It was also discovered that incidental radiation by alpha and beta rays can be filtered out without decreasing the deeply penetrating tumor-destructive effects of gamma rays of radium.[110]

During the closing years of the 19th century, the first cancer periodical, *Revue des Maladies Cancereuses*, of the French National Anti-Cancer League was inaugurated in Paris and in Buffalo, New York, Roswell Park (1852-1914), a cancer surgeon, published his book, *A Treatise on Surgery*, in 2 volumes.[111] Park advocated that cancer patients should be treated at specialized institutions dedicated to cancer care. He was a founder in 1911 of the New York State Institute for the Study of Malignant Diseases at Buffalo, New York, which was later renamed Roswell Park Cancer Institute. Benign and malignant mesothelial cells of the pleura were described and illustrated.[112] It would be remiss not to mention that during the same period the intraoperative rapid preparation of fresh tissue for microscopic examination (frozen section) was introduced[113]; the first case of synovial sarcoma was reported[114]; abdominoperineal surgery combined with removal of regional lymph nodes was initiated for the treatment of high rectal cancer[115]; and the first clear description of an embryonal tumor of the kidney, eponymously known as Wilms tumor, was published with a review of the literature.[116] In addition, the thought was advanced that at the time of the excision of primary melanoma, the neighboring lymph glands should also be removed (regional lymph node dissection).[117]

By the dawn of the 20th century, most pathologists and physicians interested in oncology were familiar with the names, clinical signs and symptoms, and microscopic composition of the most common solid tumors. Nevertheless, further advancement called for increased attention to the optimal application of clinical and radiologic detection, newly introduced surgical procedures, discoveries in cell biology and chemistry, and irradiation with Rontgen rays or radium as a new and promising treatment.

To facilitate nontraumatic biopsy, an exploratory aspiration syringe with a cutting needle was introduced to obtain cells and tissue samples for microscopic diagnosis from tumors and various organs, including the bone marrow.[118] The diagnosis of leukemia was regarded as a challenging undertaking. The first clear description of the microscopy and natural history of lymphocytic and myeloid leukemia was presented with color illustrations in the first hematology textbook published in the English language in 1901 by James Ewing (1866-1943), a New York pathologist.[119] Ewing traced the genesis of leukemia to the bone marrow and, using stained smears of bone marrow and peripheral blood, demonstrated that the leukemic cells were identical (Fig. 10). He recognized 2 distinctly different leukemias: myelogenous and lymphoid. By studying blood smears, Ewing was able to distinguish acute and chronic forms of myeloid and lymphoid leukemia through his attention to the morphology of the leukemic cells. Furthermore, he noted that chronic leukemias progressed slowly over years, whereas acute leukemias ended in death within months. He pointed out that excessive bleeding, profound anemia, and depletion of fibrin were contributory factors to death. In autopsied cases, Ewing found the liver and spleen to be enlarged due to massive infiltration by leukemic cells and tumor emboli. He warned that the diagnosis of leukemia should be made with caution because an increase of white blood cells can also be found in infections and pseudoleukemia (lymphoma).[119] Reviewing the literature on leukemia, Ewing indicated that despite leukemia having been known for several decades as a deadly disease,[1] no treatment was available (incidentally, the first successful treatment of leukemia with x-ray radiation was reported in

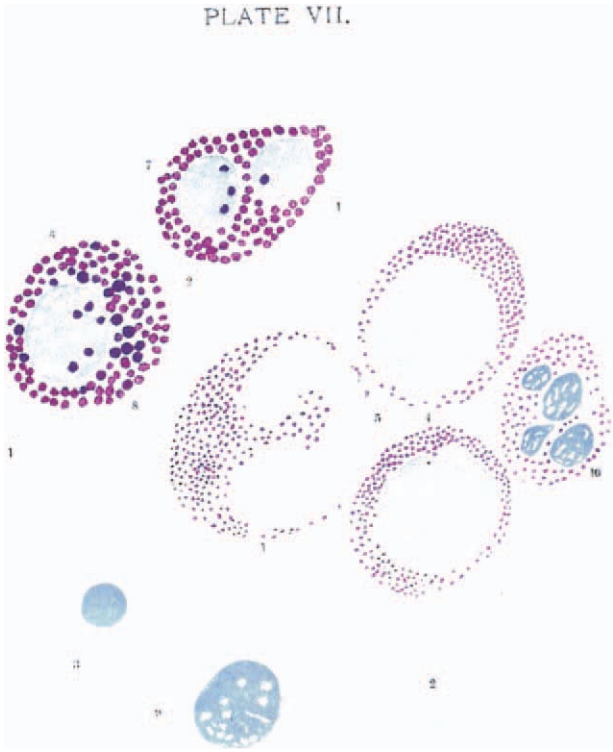


Figure 10. James Ewing's 1901 illustration of red blood cells (1-3), normal white blood cells (9-10), cells of myelogenous leukemia (4-6), eosinophile (7), and blood plates (8) are shown.

1903[120]). Ewing also described the hematologic changes in cancer patients with advanced disease. He wrote that cancer patients were usually cachectic and anemic, bled easily, and had a tendency to form thrombi in vessels (deep venous thrombosis).

With the accumulation of knowledge concerning the microscopy of various cancers, David P. von Hansemann (1858-1920), a German pathologist, in continuation of his splendid microscopic observations[39] announced in 1902 his concept of the microscopic grading of carcinomas according to differentiation of the tumor cells as well-differentiated and poorly differentiated forms.[121] At approximately the same time, a Hungarian pathologist named Edmund Krompecher (1870-1926) introduced the term "basal cell carcinoma."[122] Krompecher stressed the importance of distinguishing basal cell carcinoma from other skin cancers because the progression of basal cell carcinomas was slow and they do not tend to metastasize. A year later the term "cytodiagnosis" was proposed by a Boston pathologist in connection with the microscopic examination of smear preparations from the sediment of body cavity effusions.[123] In Germany, Siegfried Oberndorfer (1876-1944) introduced the term "carcinoid," meaning carcinoma-like, by describing small cell tumors of the intestine resembling poorly differentiated small cell adenocarcinoma.[124] Simultaneously, the first comprehensive illustrated book on the surgery of brain tumors and other intracranial lesions was published in England.[125] The author devoted 200 pages to the discussion of benign and malignant brain tumors, and presented his surgical experience with 400 tumors by adding that most of the cases were awful and had a dismal outcome. Among the rare tumors, intracranial fibrosarcoma (meningeal sarcoma) and acoustic neuroma were listed.[125]

After decades of the dismally inadequate treatment of cancers of the cervix and the body of the uterus by curettage, amputation of the cervix, vaginal hysterectomy, and simple abdominal hysterectomy,[1,73,74,126] Ernst Wertheim (1864-1920), an Austrian gynecologist, after the initial introduction of his radical procedure for removal of the entire uterus by abdominal hysterectomy,[127] gradually perfected his technique by excising the uterus and cervix, uterine ligaments, pelvic lymph nodes, ovaries, and periureteral fibrous adhesions. Using this arduous technique, he reduced operative mortality to 15% and the rate of disease recurrence to $< 10\%$.[128] Wertheim's radical hysterectomy technique was received by gynecologists worldwide with enthusiasm as the most promising operation to reduce the mortality and recurrence rate of cervical and uterine cancers.[129] Subsequently, Thomas S. Cullen (1868-1953), an American gynecologist, and others modified Wertheim's operation[130] but radical hysterectomy has remained in practice to the present day (Fig. 11).

The search to discover the causation and treatment of cancer continued and extended for the first time to viral etiology[131] and metaplastic transformation of surface-lining cells.[132] In 1906, Jean Bergonie (1857-1925) and Louis Tribondeau (1872-1918), both French physicians, observed that immature tumor cells and cells in an active state of division are more vulnerable to radiation than tumor cells that are well differentiated and are not in the active phase of mitosis.[133] Their observation set the foundation for the preferential selection of patients for radiation with consideration of cellular differentiation and the histological grade of the tumor.

For completeness, it is perhaps appropriate to add that in 1907, the American Association for Cancer Research was formed to foster communication among cancer researchers and to further new techniques in diagnosis and treatment. It was followed in 1913 by the founding of the American Society for the Control of Cancer, which ultimately evolved in 1944 into the American Cancer Society.

Shortly after the infectious organisms anthrax and tubercle bacillus were discovered in the late 1800s, specific

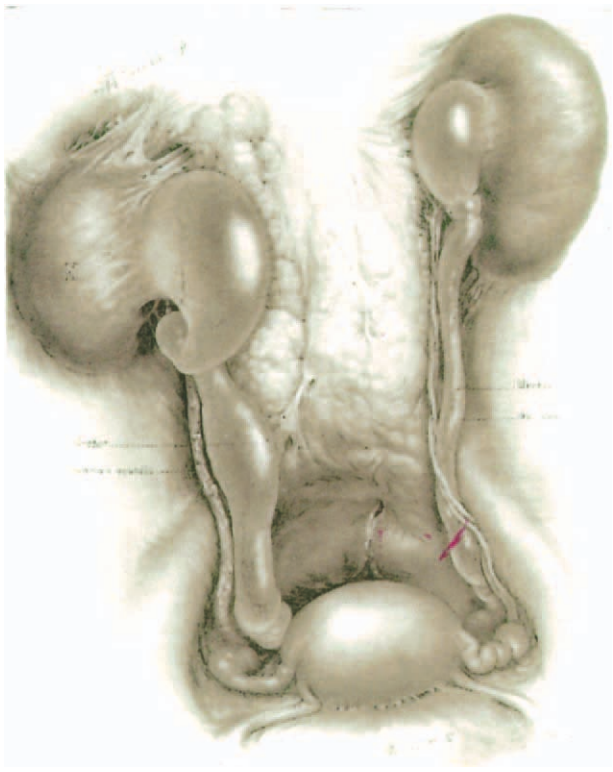


Figure 11. Thomas S. Cullen's photograph shows bilateral hydroureter and hydronephrosis due to obstructions caused by advanced metastatic cervical carcinoma.

chemical agents were introduced to kill specific germs. Paul Ehrlich (1854-1915), a German biochemist and immunologist, was the foremost advocate and user of chemical agents against microorganisms. His hyperprosexia on the biological and pathological processes that occur within cells resulted in numerous discoveries and led to Ehrlich sharing the Nobel Prize with Eli Metchnikoff (1845-1916), a Russian immunologist, in 1908. Years before Ehrlich was named as a Nobel laureate, he embarked on large-scale experiments in a new direction with the financial support of the newly emerging Hoechst Chemical Company. He injected rats and mice with pyocyanase and selenium in attempts to destroy cancer cells. On the basis of his laboratory work with chemicals, toxins (antigens), and antitoxins (antibodies), Ehrlich developed his theory on immunity by proposing that the link between antigen and antibody was specific and was determined by the internal chemical structure of each cell. He summarized his observations in a monograph, *Beitrage zur experimentellen Pathologie und Chemotherapie*, which was published in 1909 (Fig. 12).[134] He pointed out that malignant neoplasms are comprised of chemically sensitive cells and chemically resistant cells, and therefore one should not always expect a uniform response to treatment.

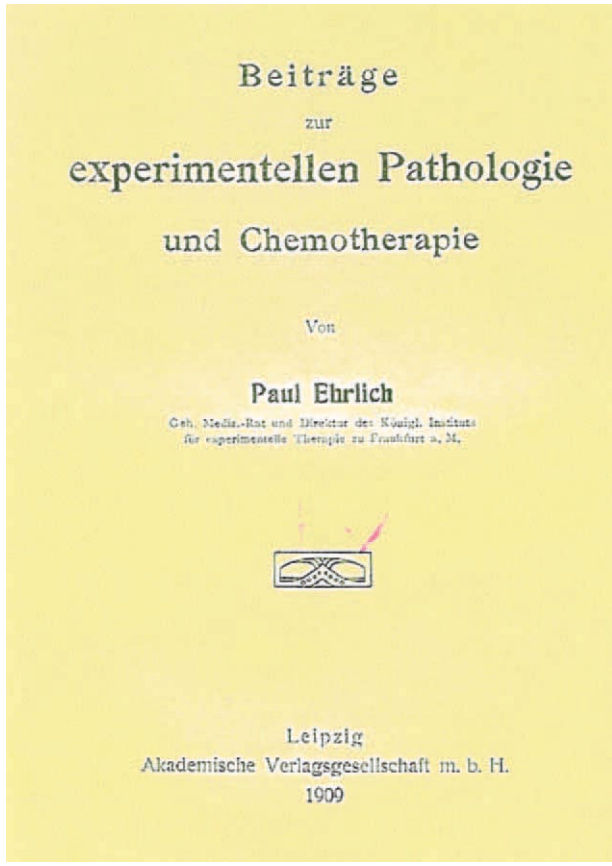


Figure 12. The cover of Paul Ehrlich's book on chemotherapy is shown.

Figure 13. Hen displaying Rous sarcoma induced by filterable virus, later known as Rous sarcoma virus, is shown.

Although his book is the first known text on chemotherapy, Ehrlich is also remembered for demonstrating for the first time the blood-brain barrier that prevents chemicals from passing through from capillaries into the substance of the brain.

In 1910, the results of one of the most remarkable experiments in the history of cancer research were

Table 1. Chronology of Discoveries, First Descriptions, New Terms, and Other Salient Events

Year: Medical History	Year: World History
1860: Giant cell tumors of bone reported.	1860: Most of Italy united into 1 country.
1863: Rudolf Virchow's book on tumors published. The term "malignant lymphoma" introduced. Lymph node nearest to cancer is the site of earliest metastasis.	1863: Gettysburg address by Abraham Lincoln.
1864: Hyperplasia and metaplasia named as precursors of cancer.	1864: International Red Cross formed.
1865: Discovered that carcinomas are of epithelial origin. Smoking causes cancer of tongue and lips.	1865: Gregor Mendel's theory of inheritance published.
1867: Direct extension and tumor emboli are the sources of metastases.	1867: Johann Strauss composed "The Blue Danube."
1870: Myelogenous leukemia described.	1870: German states unified to form Germany.
1871: Primary squamous carcinoma of lung and primary malignant brain tumors reported. Nucleoprotein identified.	1871: British Columbia and Manitoba join Canada.
1872: Kaposi sarcoma and mesothelioma reported. Esophageal carcinoma resected.	1872: Brooklyn Bridge opened.
1874: Total laryngectomy performed.	1874: Winston Churchill born.
1875: Skin cancer linked to coal tar and hot paraffin.	1875: Leo Tolstoy's *Anna Karenina* published.
1876: Bronchioloalveolar carcinoma and metastatic choriocarcinoma reported.	1876: Alexander Graham Bell invents the telephone.
1877: Misplaced embryonal cells named the source of cancers.	1877: Thomas Edison invents the phonograph.
1879: Lung carcinoma described as an occupational disease of miners.	1879: Zulus defeat the British in southern Africa.
1880: First comprehensive book in English on breast tumors published.	1880: Auguste Rodin displays "The Thinker."
1882: von Reckninghausen disease reported.	1882: Igor Stravinsky born.
1884: Transurethral resection of bladder tumor. The first cancer hospital in the United States inaugurated.	1884: Oxford English Dictionary published.
1885: Theodor Billroth reported results of his type I and type II gastrectomies.	1885: European powers agree on partition of Africa.
1887: Disarticulation and interscapulothoracic amputation introduced.	1887: The first *Sherlock Holmes* story published.
1890: Ernest Wertheim's radical hysterectomy first performed.	1890: Vincent Van Gogh commits suicide.
1891: William S. Halsted's radical mastectomy and suprapubic cystotomy inaugurated.	1891: Jews forced into ghettos in Russia.
1892: Johann von Mikulicz describes the disease named after him. Emil Theodor Kocher performs total thyroidectomy.	1892: Ellis Island Immigration Center in New York City opens.
1893: Postradical mastectomy lymphedema reported. The term "lymphosarcoma" introduced. Permanent gastrostomy installed.	1893: Henry Ford builds his first car.
1894: Skin cancer linked to chronic exposure to sunlight.	1894: Thomas Edison introduces motion pictures.
1895: Wilhelm C. Rontgen discovers x-rays. Anilin named as a bladder cancer-causing chemical.	1895: Alfred Nobel establishes his prizes.
1896: Oophorectomy introduced for inoperable breast carcinomas. Krukenberg tumor described.	1896: Henri Becquerel discovers radioactivity of uranium.
1897: X-ray radiation used to treat breast carcinoma.	1897: J. J. Thomson discovers electron.
1898: Marie and Pierre Curie discover radium.	1898: United States declares war on Spain over Cuba.
1899: Skin carcinoma treated with x-ray radiation.	1899: War between Britain and the Boers of Africa.
1902: X-ray-induced skin carcinoma reported. Histologic grading of carcinomas introduced.	1902: Work begins on the Panama Canal.
1903: Treatment of carcinoma with radium. The term "basal cell carcinoma" introduced. Colectomy and resection of mesenteric lymph nodes performed.	1903: Airplane invented by the Wright brothers.
1904: Chronic inflammation and trauma named as causes of cancer.	1905: Albert Einstein formulates theory of special relativity.
1906: Radiosensitivity of cells defined.	1906: Alfred Dreyfus rehabilitated.
1907: The term "carcinoid" introduced. American Association for Cancer Research formed.	1907: Robert Baden-Powell founds the Boy Scout movement.
1909: Paul Ehrlich introduces chemotherapy.	1909: Plastic invented and produced in Belgium.
1910: Peyton Rous transmits sarcoma in hens by cell-free filtrate.	1910: China abolishes slavery.

published.[135] Peyton Rous (1879-1970), a research pathologist at the newly established Rockefeller Institute for Medical Research in New York City, demonstrated that sarcoma in hens could be transmitted to normal hens by the injection of cell-free filtrates of the original sarcoma (Fig. 13).

The filterable sarcoma-causing agent was identified later as a virus of the ribonucleic acid (RNA) group and was named the Rous sarcoma virus. Eventually, 5 decades later, in 1966, Rous was awarded the Nobel Prize for his discovery.

All things being considered and reflecting on this narrative, it seems that the progress made between 1860 and 1910 came about by specialization in cancer care and discoveries of immense importance. All these were made possible by the concerted efforts of many hardworking and foresighted physicians and scientists, chiefly in Europe and the United States (Table 1).

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REFERENCES

1. Hajdu SI. A note from history: landmarks in history of cancer, part 3. *Cancer*. 2012;118:1155-1168.
2. Virchow R. Die krankhaften Geschwulste. Dreissing Vorlesungen gehalten wahrend des Wintersemesters 1862-1867 an der Universitat zu Berlin. Vol 1-3. Berlin, Germany: A. Hirschwald;1863-1865.
3. Hajdu SI. A note from history: Rudolph Virchow, pathologist, armed revolutionist, politician, and anthropologist. *Ann Clin Lab Sci*. 2005;35:203-205.
4. Thiersch C. Der Epithelialkrebs, namentlich der Haut. Eine anatomisch-klinische Untersuchung. Leipzig, Germany: Engelmann; 1865.
5. Waldeyer-Hartz HWG. Die Entwicklung der Carcinome. *Virchows Arch Pathol Anat*. 1867;41:470-523; 1872:55:67-159.
6. Ranvier LA, Cornil AV. Contribution a l'etude de developpement histologique des tumeurs epitheliales. *J Anat Physiol*. 1866;21:271-286.
7. Wyss O. Die heterologen Neubildungen der Vorsteherdruese. *Arch Pathol Anat Physiol Klin Med*. 1866;35:378-412.
8. Naunyn B. Ueber die Entwincklung der Leberkrebse. *Arch Pathol Anat Physiol Klin Med*. 1866;35:717-733.
9. Hajdu SI. Greco-Roman thought about cancer. *Cancer*. 2004;100: 2048-2051.
10. Beale LS. Examination of sputum from a case of cancer of the pharynx and adjacent parts. *Arch Med*. 1860;2:44-46.
11. Czermak JN. Der Kehlkopfspiegel und seine Verwerthung fur Physiologie und Medizin. Leipzig, Germany: Engelmann; 1860.
12. Desormeaux AJ. De l'Endoscope et de ses Applications au Diagnostic et au Traitement des Affections de l'Urethre et de la Vessie. Paris, France: J. B. Bailliere; 1865.
13. Dieulafay G. Aspiration of Morbid Fluids. Philadelphia, PA: J. B. Lippincott Company; 1873.
14. Woodward JJ. Toner Lecture. Washington, DC: Smithsonian Institute; 1873.
15. Cohnheim JF. Vorlesungen uber allgemeine Pathologie. 2 Vols. Berlin, Germany: A. Hirschwald; 1877.
16. Ribbert MWH. Geschwulstlehere fur Arzte und Studierende. Bonn, Germany: Cohen; 1904.
17. Nelaton E. De Tumeurs Benignes des Os, ou Tumeurs a Myeloplaxes. Paris, France: Rignaux; 1860.
18. Niemeyer F. A Text-Book of Practical Medicine. New York, NY: D. Appleton and Company; 1871.
19. Malassez L. Examen histologique d'un cas de cancer encephaloide du poumon (epithelioma). *Arch Physiol Norm Pathol*. 1876;3:353-372.
20. Eberth CJ. Myoma sarcomatodes renum. *Arch Pathol Anat Physiol Klin Med*. 1872;55:518-520.
21. Bright R. Clinical Memoirs on Abdominal Tumours and Intumescence. London, UK: The Sydenhan Society; 1860.
22. Krukenberg FE. Ueber das Fibrosarcoma ovarii mucocellulare (carcinomatodes). *Arch Gyanek*. 1896;50:287-321.
23. Bennett JR. Cancerous and Other Intra-Thoracic Growths. London, UK: J and A Churchill; 1872.
24. Neuman E. Ein Fall von Myoma striocellular am Hoden. *Virchows Arch Pathol Anat*. 1866;30:497-500.
25. Butlin HT. Recurrent ossifying spindle-celled sarcoma from the subcutaneous tissue of the thigh. *Tran Pathol Soc London*. 1873; 24:211-212.
26. Caen E. Chondroosteosarkom der weiblichen Brustdruse. *Deutsche Z Chir*. 1881;15:247-251.
27. Ribbert MWH. Ueber die Enchondrosis physalifora sphenooccipitalis. *Zentralbl Allg Path*. 1894;5:457-461.
28. Thomas TG. A Practical Treatise on the Diseases of Women. Philadelphia, PA: H. C. Lea; 1876.
29. Helmuth WT. A System of Surgery. 4th ed. New York, NY: Boericke and Tafel; 1879.
30. Pfannenstiel J. Das traubige Sarcom der Cervix uteri. *Virchows Arch Pathol Anat*. 1892;127:305-337.
31. Berard M. Tumeur embryonnaire du muscle striae. *Lyon Med*. 1894;77:52-54.
32. Adami JG. Pathological Notes. Montreal, Quebec, Canada: J. Lovell; 1898.
33. Kolaczek T. Ueber das Angio-Sarkom. *Dtsch Z Chir*. 1878;9: 889-890.
34. Sanger M. Ueber desmoide Geschwulste der Bauchwand und deren Operation mit Resection des Peritoneum parietale. *Arch f Gynälol*. 1884;24:1-9.
35. Borst M. Die Lehre von den Geschwulsten mit einem Mikroscopischen Atlas. Wiesbadden, Germany: J. F. Bergmann; 1902.
36. Neumann E. Ein Fall von Leukemie mit Erkrankung des Knochenmarkes. *Arch Heilk*. 1870;11:1-14.
37. Kundrat H. Ueber Lympho-Sarkomatosis. *Wien Klin Wochenschr*. 1893;6:211-213; 234-239.
38. Poll H. Die vergleichende Entwicklung der nebennieren-systeme. In: Hertwig WAO, ed. Lehrbuch der Entwicklungsgeschichte des Menschen und der Wirbelthiere. Jena, Germany: G. Fischer; 1886.
39. von Hansemann DP. Ueber asymmetrische zelltheilung in epithelkrebsen und deren bilogische Bedeutung. *Arch Pathol Anat Phys Klin Med*. 1890;119:299-326.
40. von Recklinghausen FD. Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen. Berlin, Germany: Hirschwald; 1882.
41. Miescher JF. Ueber die chemische Zusammensetzung der Eiterzellen. In: Hoppe-Seyler F, ed. Medicinisch-chemische Untersuchungen. Berlin, Germany: Hirschwald; 1871.
42. Kaposi M. Idiopathisches multiples Pigmentsarkom der Haut. *Arch Dermatol Syph*. 1872;4:265-273.
43. Keating JM. Cyclopaedia of the Diseases of Children. Philadelphia, PA: J. B. Lippincott Company.; 1890.
44. Garretson JE. A Treatise on the Diseases and Surgery of the Mouth, Jaws and Associate Parts. Philadelphia, PA: J. B. Lippincott Company; 1869.
45. Billroth T. Die allgemeine chirurgische Pathologie und Therapie. Berlin, Germany: Georg Reimer; 1863.
46. Billroth T. Ueber die erste am Menschen ausgefurhrte Kehlkopf-Extirpation. *Arch Klin Chir*. 1874;17:343-356.
47. Billroth T. Ueber die Resection des Oesophagus. *Arch Klin Chir*. 1872;13:65-69.
48. Billroth T. Offenes Schreiben an Herrn Dr. L. Wittelschofer. *Wien Med Wochenschr*. 1881;31:162-165.
49. Billroth T. Zur Casuistik und Statistik der Magenresektionen und Gastroenterostomieen. *Arch Klin Chir*. 1885;32:616.
50. Billroth T. Diseases of the female mammary glands. In: Grandin EH, ed. Cyclopaedia of Obstetrics and Gynecology. New York: W. Wood; 1887.
51. Mikulicz J. Ueber Gastroskopie und Oesophagoskopie. *Wiener Med Pres*. 1881;22:1405-1408.
52. Mikulicz J. Ein Fall von Resection des carcinomatosen Oesophagus mit plastischem Ersatz des excidierten Stuckes. *Prag Med Wchnschr*. 1886;11:93-94.
53. Mikulicz J. Chirurgische Erfahrungen uber das Dramcarcinoma. *Arch Klin Chir*. 1903;69:28-47.
54. Mikulicz J. Ueber eigenartige symmetrische Erkrankung der Thranen-und Mundspeicheldrusen. Stuttgart, Germany: F. Enke; 1892.
55. Allingham HW. Colotomy, Inguinal, Lumbar, and Transverse, for Cancer or Stricture with Ulceration of the Large Intestine. London: Bailliere and Tindall; 1892.
56. Ewald CA. Diseases of the Stomach. New York, NY: D. Appleton and Company; 1894.
57. Hemmeter JC. The early diagnosis of cancer of the stomach. *Med Record*. 1899;56:577-579.
58. Frank R. Ein new Methode der Gastrostomie bei Carcinoma oesophagie. *Wien Klin Wochenschr*. 1893;6:231-234.
59. Hajdu SI. Blood transfusion from antiquity to the discovery of the Rh factor. *Ann Clin Lab Sci*. 2003;33:471-473.
60. von Langenbuch C. Ein Fall von Resecktion eines linksseitigen Schnurlappens der Leber. *Berl Klin Wochenschr*. 1888;25:37-38.
61. Wolfler A. Ueber die Entwinckelung und den Bau des Kropfes. *Arch Klin Chir*. 1883;29:1-97.
62. Kocher T. Chirurgische Operationslehre. Jena, Germany: G. Fischer; 1892.
63. Thompson H. On Tumors of the Bladder, Their Nature, Symptoms, And Surgical Treatment. London, UK: J and A Churchill; 1884.

64. Nitze M. Lehrbuch der Kystoskope. Wiesbaden, Germany: Bergmann; 1889.
65. Albarran J. Les Tumeurs de la Vessie. Paris, France: Steinheil; 1891.
66. Bramwell B. Intracranial Tumours. Philadelphia, PA: J. B. Lippincott Company; 1888.
67. Bramwell B. Diseases of the Spinal Cord. New York, NY: W. Wood; 1882.
68. Horsley VAH. Remarks on ten consecutive cases of operations upon the brain and cranial cavity to illustrate the details and safety of the method employed. *BMJ*. 1887;1:863-865.
69. Knapp PC. The Pathology, Diagnosis and Treatment of Intracranial Growths. Boston, MA: Rockwell and Churchill; 1891.
70. Hajdu SI. A note from history: landmarks in history of cancer, part 2. *Cancer*. 2011;117:2811-2820.
71. Gross SW. Sarcoma of the long bones. *Am J Med Sci*. 1879;78: 17-57; 338-377.
72. Berger P. L'Amputation du Membre Superior Dans la Contiguite du Tronc (Amputation Interscapulo-thoracique). Paris, France: Masson; 1887.
73. Wells TS. Diseases of the Ovaries: Their Diagnosis and Treatment. London: Churchill; 1865.
74. Sims JM. Amputation of the cervix uteri. *Trans New York Med Soc*. 1861;367-371.
75. Hewitt G. The Pathology, Diagnosis, and Treatment of the Diseases of Women. New York: E. B. Treat; 1891.
76. Haviland A. Geographic Distribution of Cancer in England and Wales. London, UK: W and A Johnson; 1875.
77. Hajdu SI. A note from history: landmarks in history of cancer, part 1. *Cancer*. 2011;117:1097-1102.
78. Pancoast J. A Treatise on Operative Surgery. Philadelphia, PA: Carey and Hart; 1852.
79. Moore CH. On the influence of inadequate operations on the theory of cancer. *Medico-Chirurg Trans*. 1867;50:245-280.
80. Winiwarter A. Beitrage zur Statistik der Carcinoma. Stuttgart, Germany: F. Enke; 1878.
81. Gross SW. A Practical Treatise on Tumors of the Mammary Gland. New York: D. Appleton and Company; 1880.
82. Poulsen KLJ. Die Geschwulste der Mamma. *Arch Klin Chir*. 1891;42:593-644.
83. Halsted WS. The treatment of wounds with especial reference to the value of the blood clot in the management of dead spaces. Operations for carcinoma of the breast. *Johns Hopkins Hosp Rep*. 1890-1891;2:255-314.
84. Halsted WS. The results of operation for cure of the breast performed at the Johns Hopkins Hospital from 1889 to 1894. *Ann Surg*. 1894;20:497-550.
85. Halsted WS. The results of radical operations for the cure of cancer of the breast. *Tr Am Surg Assoc*. 1907;25:61-79.
86. Sutton JB. Tumours, Innocent and Malignant. Philadelphia, PA: Lea Brothers; 1893.
87. Beatson GT. On the treatment of inoperable cancer of the mamma. *Lancet*. 1896;2:104-107; 162-165.
88. Harting FH, Hesse W. Der Lungenkrebs die Bergkrankheit in den Schneeberger Gruben. *Viertel Gerichtl Med Oeff Sanitaetswes*. 1879;31:102-132.
89. Volkman R. Beitrage zur Chirurgie, anschlissenend an einen Bericht uber die Thatigkeit der chirurgischen Universitats-Klinik. Leipzig, Germany: Breitkopf and Hartel; 1875.
90. Hutchinson J. On some examples of arsenic-keratosis of the skin and of arsenic cancer. *Trans Path Soc London*. 1888;39:352-363.
91. Cooke TW. On Cancer: Its Allies and Counterfeits. London, UK: Longmans and Green; 1865.
92. Rehn L. Ueber Blasentumorem bei Fuchsinarbeitem. *Arch Klin Chir*. 1895;50:588-600.
93. Unna PG. Die Histopathologie der Hautkrankheiten. Berlin, Germany: Hirschwald; 1894.
94. Harrison R. Specimens of Bilharzia affecting the urinary organs. *Lancet*. 1889;2:163.
95. Hajdu SI. 2000 years of chemotherapy of tumors. *Cancer*. 2005; 103:1097-1102.
96. Coley WB. Treatment of inoperable malignant tumors with the toxins of erysipelas and the bacillus prodigious. *Am J Med Sci*. 1894;108:50-66.
97. Novinsky MA. On the Question of Inoculation of Malignant Neoplasms. St. Petersburg, Russia: P. Y. Trey; 1877.
98. Hanau AN. Experimentelle Uebertragung von Carcinom von Ratte auf Ratte. *Arch Klin Chir*. 1889;39:678-679.
99. Morau H. Inoculation en serie d'une tumeur epitheliale de la souris blanche. *C R Soc Biol*. 1891;3:289-290.
100. Hajdu SI. Nobel laureate pathologists. *Ann Clin Lab Sci*. 2009;39: 196-198.
101. Rontgen WC. Ueber eine neue Art von Strahlen. *Sitzber Phys Med Ges Wurzburg*. 1895;132-141.
102. Morton WJ, Hammer EW. The X-Ray: Or Photography of the Invisible and Its Value in Surgery. New York: American Technical Book Company; 1896.
103. Frieben EAFA. Cancroids des rechten handruckens, das sich nach langdauernder einwirkung von Roentgenstrahlen entwickelt hatte. *Fortsch Geb Roentgenstr*. 1902;6:106.
104. Gocht H. Therapeutische Verwendungen der Rontgenstrahlen. *Fortschr Geb Rontg-Strahl*. 1897-1898;1:14-22.
105. Sjogren TAU. Fall af Epitheliom Behandladt Roentgenstralar. Stockholm, Sweden: Forhand Svenska Lakare-Sallsk Sam-mank; 1899:208.
106. Becquerel AH. Sur les radiations emises phosphorescence. *C R H Acad Sci*. 1896;122:420-421.
107. Curie P, Curie MS. Sur une substance nouvelle radio-active, contenue dans la pechblende. *Acad Sci*. 1898;127:175-178; 1215-1217.
108. Goldberg SW, London ES. Zur Frage der Beziehungen zwischen Bequerelstrahlen und Hautaffectionen. *Dermatol Zeitschrift*. 1903; 10:457-462.
109. Abbe R. Radium and radio-activity. *Yale Medical News*. 1904; 10:433.
110. Dominici H. De l'utilisation du rayonnement gamma du radium en therapeutique. *Cong Franc D Med*. 1908;429-431.
111. Park R. A Treatise on Surgery. Philadelphia, PA: Lea Brothers; 1896.
112. Warthin AS. The Diagnosis of Primary Sarcoma of the Pleura. Philadelphia, PA: Lea Brothers; 1897.
113. Pick L. A rapid method of preparing permanent sections for microscopical diagnosis. *BMJ*. 1897;1:140-141.
114. Marsh H. Primary sarcoma of the synovial membrane of kneejoint. *Lancet*. 1898;2:1330.
115. Quenu EAVA. Chirurgie du Rectum. Paris, France: G. Steinheil; 1899.
116. Wilms M. Die Mischgeschwulste. Leipzig, Germany: Georgi; 1899.
117. Allbutt TC. A System of Medicine. London, UK: The Macmillan Company; 1900.
118. Senn N. The Pathology and Surgical Treatment of Tumors. Philadelphia, PA: W. B. Saunders; 1900.
119. Ewing J. Clinical Pathology of the Blood. Philadelphia, PA: Lea Brothers; 1901.
120. Senn N. Case of splenomedullary leukaemia successfully treated by the use of the Rontgen ray. *Med Rep*. 1903;64:281-282.
121. von Hansemann DP. Die mikroskopischen Diagnose der bosartigen Geschwulste. Berlin, Germany: A. Hirschwald; 1902.
122. Krompecher E. Der Basalzellenkrebs. Jena, Germany: G. Fischer; 1903.
123. Mallory FB. Pathological Technique. Philadelphia: W. B. Saunders Company; 1904.
124. Oberndorfer S. Karzinoide tumoren des dunndarms. *Frankf Z Pathol*. 1907;1:426-432.
125. Ballance C. Some Points in the Surgery of the Brain and its Membranes. London, UK: The Macmillan Company; 1907.
126. Arnaud H. De la Colpo-Hysterectomie Abdomino-Vaginale dans Le Cancer de l'Uterus. Montpellier, France: Cooperative Ouvriere; 1909.
127. Wertheim E. Zur Frage der Radicaloperation beim Uteruskrebs. *Arch Gynäkol*. 1900;61:627-668.

128. Wertheim E. The radical abdominal operation in carcinoma of cervix uteri. *Surg Gynecol Obstet*. 1907;4:1-10.
129. Anderson LG, Platt K. Malignant diseases of the uterus. *J Obstet Gynaecol Br Empire*. 1908;14:381-392.
130. Cullen TS. Cancer of the Uterus. Its Pathology, Symptomatology, Diagnosis and Treatment. Philadelphia: W. B. Saunders and Company; 1909.
131. Borrel A. Le problem du cancer. *Bull Inst Pasteur*. 1907;5: 497-512.
132. Menetrier P. Des etats morbides precancereux et de la formation du cancer a leurs depens. *Bull Assoc Franc l'Etude Cancer*. 1908; 1:29-57.
133. Bergonie J, Tribondeau L. Interpretation de quelques resultats de la radiotherapie. *C R Acad Sci*. 1906;143:983-985.
134. Ehrlich P. Betrage zur Pathologie und Chemotherapie. Leipzig, Germany: Acad Verlagsgesel; 1909.
135. Rous P. Transmission of avian neoplasm (sarcoma of the common fowl). *J Exp Med*. 1910;12:696-705.