Albert C. Broders' Paradigm Shifts Involving the Prognostication and Definition of Cancer

James R. Wright Jr, MD, PhD

• ***Context.***—**In the 19th and early 20th centuries, cancer was defined by the demonstration of invasion and metastases, based upon gross findings at surgery or autopsy. Although histopathologic examination of tumors became possible with greater and greater resolution over time, the definition of cancer remained the same. Tumors with features suggesting the biological ''potential'' to invade and metastasize were not cancers until they had achieved their potential. Prognostication based upon histopathologic analyses of tumor biopsies and resection specimens was not possible, as the concepts of tumor grading and staging did not exist until the 1920s and 1930s, respectively.**

Objective.—**To examine the history of tumor grading and the concept of ''carcinoma in situ'' and to explore the role of Albert C. Broders, MD, and others in these discoveries.**

Design.—**To address these topics, standard historiographic methods were used to examine available primary and secondary historical sources.**

Results.—**Early in his career, Broders described tumor grading, showing for the first time that histopathologic findings could independently predict prognosis. This discovery quickly begat tumor staging and eventually the whole predictive biomarker field. Later in his career, Broders described carcinoma in situ, thereby changing the very definition of cancer.**

Conclusion.—**Historians recognize that science progresses through a series of paradigm shifts. Most clinician-scientists, even those at the very top of their fields, never make a discovery so dramatic that it changes their field forever. In the 1920s and 1930s, Albert C. Broders published 2 observations that forever changed cancer diagnosis, prognostication, and treatment.**

(*Arch Pathol Lab Med.* 2012;136:1437–1446; doi: 10.5858/arpa.2011-0567-HP)

Historian of science Thomas Kuhn, PhD,[1] in *The Structure of Scientific Revolutions*, maintains that scientific progress is characterized by series of paradigm changes. In this article, I will attempt to prove that Albert Compton Broders, MD, (Figure 1), a pioneering surgical pathologist who spent most of his career at the Mayo Clinic (Rochester, Minnesota), was responsible for 2 major paradigm changes related to cancer pathology. First of all, early in his career, Broders developed the concept of grading, thus providing the first definitive proof that histopathology could provide prognostic information; this work quickly led to tumor staging and eventually the cancer biomarker field. Tumor grading actually proved to be a relatively ''easy sell,'' as the concept was readily accepted by most pathologists and surgeons. In stark contrast, Broders, later in his career, introduced carcinoma in situ, both the term and the concept, which remained controversial for many years. To date, with the exception of a brief unpublished memoir,[2] discussion in the chapter by Lewis B. Woolner, MD, in the Armed Forces Institute of Pathology (AFIP) fascicle on the history of surgical pathology,[3] and several obituaries published near the time of his death in 1964, there has been no biographical review of Broder's life and accomplishments, nor has there been a detailed historical review of either tumor grading or carcinoma in situ.

Albert Compton Broders was born on August 8, 1885, in Alexandria, Virginia; details of his early life are beyond the scope of this article but can be found elsewhere.[4] He graduated from the Medical College of Virginia (MCV; Richmond, Virginia) on the evening of May 18, 1910, just as Halley's Comet was making its closest pass to earth. He planned to become a surgeon and completed a 1-year internship at Memorial Hospital in Richmond, Virginia. However, according to Broders, ''as an intern working in the operating rooms I found myself becoming much interested in the nature of the material removed at operation, and I spent hours, especially at night, in the laboratory studying this surgical material, both grossly and microscopically.''[2] Upon finishing his internship, Charles R. Robins, MD, professor of Gynecology at MCV, hired Broders as his assistant, which involved helping him in the operating room in the morning (including administering anesthesia), helping with his office patients in the

Accepted for publication January 31, 2012.

From the Department of Pathology & Laboratory Medicine, University of Calgary/Alberta Health Services, Diagnostic and Scientific Centre, Calgary, Alberta, Canada.

The author has no relevant financial interest in the products or companies described in this article.

This article will be presented in part as an invited lecture at the Canadian Humanities in Pathology Club at the Canadian Association of Pathologists meetings in Calgary, Alberta, Canada, July 23, 2012.

Reprints: James R. Wright Jr, MD, PhD, Department of Pathology & Laboratory Medicine, University of Calgary/Alberta Health Services, Diagnostic and Scientific Centre, 9, 3535 Research Rd NW, Calgary, AB T2L 2K8, Canada (e-mail: jim.wright@cls.ab.ca).

Figure 1. *Albert Compton Broders, MD. Reprinted with permission from the Mayo Historical Unit, Mayo Clinic, Rochester, Minnesota.*

afternoon, and pursuing his interests in surgical pathology at night. Robins arranged for Broders to spend the summer of 1911 at Johns Hopkins (Baltimore, Maryland), working in the laboratory of surgeon/surgical pathologist Joseph Colt Bloodgood, MD, where he learned to cut frozen sections. When he returned to Richmond, the surgical staff had a small frozen-section laboratory built for him near the operating room. In June 1912, Professor Robins arranged for him to spend 2 more months in the Bloodgood laboratory and then to spend 6 weeks at the Mayo Clinic. Broders found the surgical pathology and autopsy work at the Mayo laboratory gratifying and asked Dr Robins if he could extend his time there beyond 6 weeks. After 6 to 7 months at the Mayo Clinic, William C. MacCarty, MD, the head of surgical pathology, after consulting with Will Mayo, MD, offered Broders a staff position. Broders began discussions with Dr Robins, initially via mail but later in person, about staying in Rochester. Broders and Robins eventually negotiated an agreement that resulted in Broders' staying at the Mayo Clinic but training Charles Phillips, MD, to take his place at Richmond.[2] Dr Phillips, after fulfilling this obligation, later served as professor of pathology at Wake Forest Medical College (Winston-Salem, North Carolina), followed by MCV; in 1931, Dr Phillips became director of laboratories at Scott & White Clinic (Temple, Texas), a position that he held until he reached the retirement age of 65. Ironically, Broders worked at the Mayo Clinic until 65, and then took a postretirement position at Scott & White.

According to Broders in his unpublished memoir:

Whether I should remain in Rochester and become a member of the staff of the Mayo Clinic or return to Richmond with Dr. Robins was the most difficult problem that I have ever had to solve. I am proud to say, however, that the matter was settled in a straightforward manner. Dr. Robins was one of the finest men I have ever known – a man of the very highest integrity and a gentleman always. We remained the closest of friends until his death at the age of nearly 80 years. He alone was responsible for my entree at Dr. Bloodgood's laboratory in the Johns Hopkins Hospital and at the Mayo Clinic. I owed him a debt of gratitude that I could never repay. For many years, however, I endeavoured to do so, at least in part, by serving as sort of unofficial consultant for the department of pathology of the Stuart Circle Hospital, Richmond, Virginia, in the founding of which Dr. Robins had a leading role.[2]

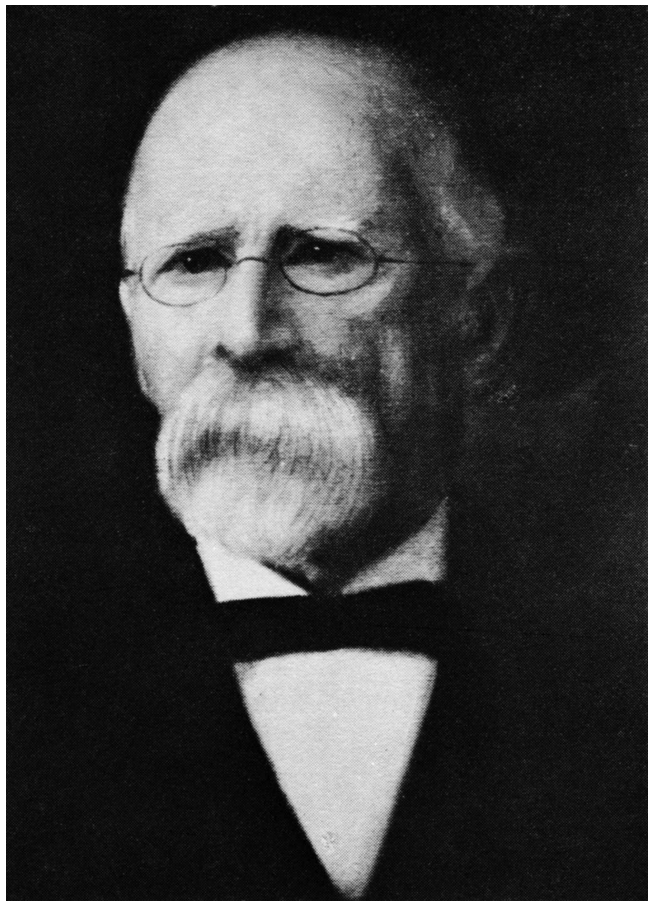

Figure 2. *William Henry Taylor, MD, ''the Sage of Richmond.'' Reprinted from ''The first 125 years of the Medical College of Virginia.''* Bull Med Coll Virginia. *1963;61(1):39. By permission of the Special Collections and Archives, Tompkins-McCaw Library, Virginia Commonwealth University.*

Albert C. Broder's unpublished memoir, which will be quoted and cited throughout this article, is notable, as much of it is not about him but rather others who influenced his life or with whom he interacted. Although a mere 73½ pages in length (double-spaced type with ample margins), 19 of the first 20 pages of the manuscript are about William H. Taylor, MD (Figure 2), who Broders called ''the most profound teacher and the wisest man on the faculty of the Medical College of Virginia'' and ''the Sage of Richmond''[2] (nb, in comparison, only 12 pages are dedicated to discussing the cancer pathology research for which Broders is remembered). Dr Taylor, a graduate of the MCV class of 1856, served as an assistant surgeon in the Confederate Army of Northern Virginia, served as a

professor of chemistry, toxicology, and medical jurisprudence at MCV, served as coroner for the City of Richmond, held the office of Virginia State Chemist, and wrote 2 books that influenced Broders' thinking. Broders was very proud of his Virginian heritage and admired Professor Taylor for being ''a born rebel and thorough individualist.'' According to Broders, ''we of the South have been regarded as pre-eminently rebels, and the term has been cast at us by our Northern countrymen as a reproach.''[2] Taylor wrote and lectured extensively about rebellion and frequently quoted Confederate General Robert E. Lee on the topic. According to Broders: ''In view of the fact that, even as a small boy, I was interested in scientific achievements and was myself, to a considerable extent, of a rebellious nature, one can understand my admiration for this great man, William H. Taylor, and his profound influence upon my thinking.''[2] Although Broders would have been considered politically incorrect in our times in relation to race issues (L. B. Woolner, oral communication, June 2, 2010), he was remarkably progressive in relation to religion, and like Taylor, strongly opposed to ''ecclesiastical fanaticism'' and was outspoken when ''the church'' opposed the advancement of science. Broders was raised in the South in the wake of the Civil War and this, reinforced by his interactions with the ''Sage of Richmond'' while in medical school, gave him the rebellious and independent nature required to upset not 1 but 2 cancer paradigms.

Broders' rebellious nature appears to have exerted itself even as a fellow and young staff pathologist at the Mayo Clinic. One of the Mayo Clinic's early claims to fame, in addition to providing outstanding surgical care, was its intraoperative ''fresh'' frozen section diagnostic method, which it promoted with great fanfare; although not the originators of either the concept of intraoperative frozen sections or even the actual fresh (ie, not formalin ''fixed'') frozen section technique,[5] Mayo doctors were incredible promoters of the Mayo method,[5] which was published in 1905 by founding Mayo pathologist Louis B. Wilson, MD.[6] Most surgeons or surgical trainees visiting the Mayo Clinic learned of this technique when they arrived at Mayo and then brought the technique back to their home institutions, thus propagating it around the world. Broders arrived at the Mayo Clinic already competent with frozen section methodology involving formalin fixation developed at Johns Hopkins and at Harvard (Cambridge, Massachusetts),[2] institutions that were competing nationally and internationally for methodologic supremacy.[5] Although Broders demonstrated his proficiency with the Mayo method to Wilson within 2½ hours of his arrival in Rochester, he used both the Mayo and Hopkins methods throughout his career at Mayo.[2] As the author of the standard reference on the history of frozen sections,[5] the author was unaware that any Mayo pathologist dared use any technique other than the Mayo method. Nevertheless, in 1931, Broders published the only major improvement to the Mayo method,[7] and he was proud of this accomplishment.[2]

Broders' first major discovery, while still a young man, was the introduction of prognostication by tumor grading. Before Broders, prognostication was limited to surgeons and pathologists knowing that some gross or histologic tumor types at a given anatomic site had a better prognosis than others at that same site.[8] For instance, it was known that, on average, mucinous rectal cancers behaved worse than other rectal cancers and that, among skin cancers, melanomas behaved worse than squamous cell carcinomas, which behaved worse than basal cell carcinomas. Surgeons could also rely on gross appearance to predict behavior. For instance, the Mayo brothers, Charles and Will, had been taught by their father, W. W. Mayo, MD, ''that a cancer that comes to you is less malignant than one that goes away from you.''[2] Clearly, cancer prognostication was an inexact science.

On March 6, 1920, Broders published his first article on numerical grading.[9] Broders, who began the work in 1914, examined 537 cases of squamous cell carcinoma of the lip and divided them into 4 histologic grades of malignancy, independent of any clinical history. Low-grade tumors were well differentiated and, thus, histologically most similar to the normal lip tissue from which they arose, while high-grade tumors were poorly differentiated and highly anaplastic (nb, not terminology Broders was aware of when he wrote his article). Grades were assigned on the basis of the percentage of differentiated epithelium. Tumors that were roughly 75% differentiated/25% undifferentiated were assigned grade I; those roughly 50%/50%, grade II; those roughly 25%/75%, grade III; and tumors with little tendency to differentiate, grade IV. Numbers of mitotic figures and cells with single, large, deeply stained nucleoli (''one-eyed cells'') also played special roles in determining the degree of differentiation. Broders found that greater than 90% of patients with grade I, 62% with grade II, 25% with grade III, and only 10% with grade IV carcinomas survived. True to his strong Virginian roots, he presented the paper at both the Richmond Academy of Medicine and Surgery on November 25, 1919, and the Roanoke Academy of Medicine on December 1, 1919, before its publication in the *Journal of the American Medical Association*.[9]

As noted by Broders in his memoir: ''This paper showed that it was possible by microscopic examination of tissue to determine with a high degree of accuracy the potentiality of cancer to metastasize and to indicate a prognosis, independent of the history. This paper was widely discussed in this country and abroad, and there was great demand for reprints of it.''[2]

This was quickly followed in succession by 3 more articles on numerical grading of cancers. The second involved grading of 256 squamous cell carcinomas of the skin, which was published in February 1921.[10] This article was also submitted to the Graduate Faculty at the University of Minnesota (Minneapolis) as his pathology master's thesis and Broders was awarded the degree (MSc) in June 1920. His third article applied numerical grading to 473 cases of carcinoma of the genitourinary organs; Broders presented this article to the section of pathology and physiology at the annual meeting of the American Medical Association in Boston on June 1921 and then published it in May 1922.[11] The fourth article described Broders' results in applying grading to head and neck carcinomas and was published in July 1925.[12] All 4 articles demonstrated the immense prognostic value of numerical grading of cancers.

Each of these 4 studies had something else in common: they were massive. The first included 537 cases; the second, 256; the third, 473; and the fourth, 362; this was a total of 1628 cases. This was typical of articles from the Mayo Clinic and was part of what made it legendary. The Mayo brothers recognized very early the need, put into

modern day parlance, ''to go big or go home.'' They created a publicity plan that had them well represented at important surgical and medical meetings throughout the country. At meeting after meeting, someone from elsewhere would present a case report or a small case series and then Charles or Will Mayo or one of their staff physicians would present the Mayo Clinic experience on the same topic, but with massive numbers and more impressive results. To facilitate publicizing the Mayo experience, Charles and Will Mayo worked as railroad surgeons, resulting in free transit to medical conventions.[13] This constant exposure increased the Mayo Clinic's reputation.

Numerical grading quickly became ''standard of care'' at the Mayo Clinic, because of its huge numbers of visiting surgical fellows wanting research projects and the massive stockpile of cancer specimens, Mayo Clinic rapidly became the center for tumor grading research. According to Broders:

> About the time that the first paper was published, routine numerical microscopic grading of squamous cell epithelioma of the lip was instituted at the Clinic. This was soon followed by routine numerical microscopic grading of epitheliomas in other situations. Shortly after the publication of my first paper, one of my colleagues, Dr. Arthur E. Mahle, used the numerical microscopic grading system in a study of adenocarcinoma of the body of the uterus. Soon afterward, we began to use routinely the numerical microscopic grading of adenocarcinoma in various anatomic situations. Moreover, a fairly large number of fellows in the Mayo Foundation used the grading system in their theses.[2]

Not only did Mayo fellows help generate and publish additional applications for numerical grading, they also helped spread knowledge of the technique and its value.[14–20] The importance of this means of dissemination cannot be underestimated, as doctors of medicine from all over the world flocked to the Mayo Clinic to train as fellows.[21] Broders noted that on multiple occasions, they had up to 28 fellows training with them simultaneously. According to one of Broders' sons, Charles William Broders, MD, in a document prepared for Broders' obituary: ''During his long career at the Mayo Clinic, he was the sponsor of more theses written by the resident physicians in fulfillment for their postgraduate degrees than any other member of the Mayo Clinic staff.''[22] Clearly, residents and fellows played a major role in the dissemination of tumor grading—just as they had been responsible for disseminating the Mayo frozen section technique around the world.[5]

Broders' original 4 articles covered the time period of November 1904 to July 22, 1915. Broders, considering this information to be critical for patient care, then ''transferred the grading system to the old pathologic reports in Mayo's files…and graded lesions forward to the point in the 1920s at which the grading of various squamous-cell epitheliomas had become routine.''[2]

Although Broders arrived at the concept of grading independently, he later commented upon its relationship to Dr David von Hansemann's theory of anaplasia:

> It has been the impression of some that I had read the work of von Hansemann before I began my investigations. This is not true. Shortly after I published the first article …, Dr. E.T. Bell, professor of pathology at the University of Minnesota, at a meeting in New York, asked Dr. James Ewing, professor of pathology at Cornell University, if he had read the paper and, if so, what he thought of it. Doctor Ewing replied, in effect: ''It is the practical application of the Hansemann principle.'' Prior to that time, I had never heard of the Hansemann principle, and I immediately began to search the literature for an account of Hansemann's work. I was unable to find a clear explanation in any publication in the English language. I finally found a series of Hansemann's publications in German. These began about 1890 and extended over a period of about 12 years. I had these articles translated by two persons who were so competent that they made Hansemann's work understandable. There is no doubt that what Dr Ewing said was true: that my work was the practical application of the Hansemann principle. In the third chapter of volume 1 of *Treatment of Cancer and Allied Diseases*, by George T. Pack and Edward M. Livingston, published in 1940, I gave the details of Hansemann's work under the title ''The Microscopic Grading of Cancer.''[2]

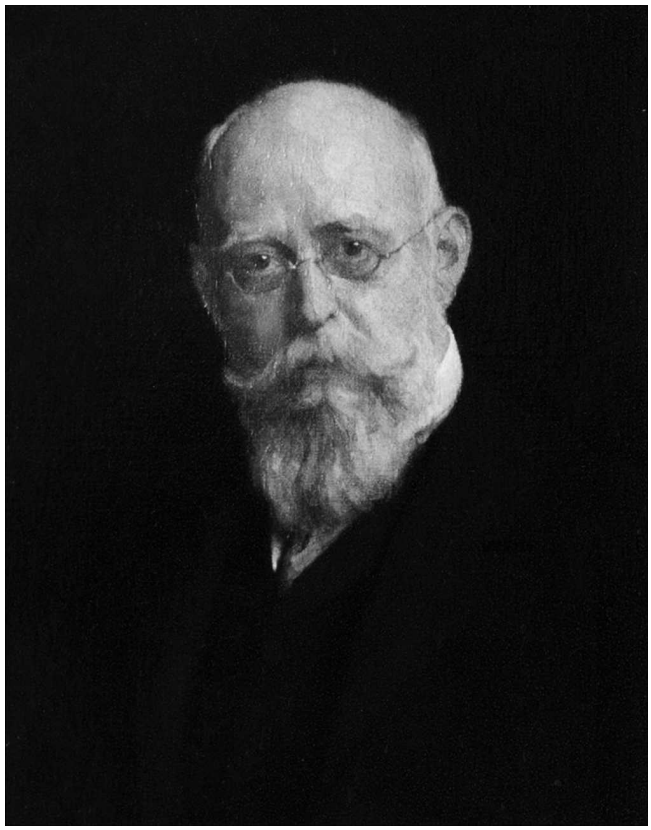

Figure 3. *David Paul von Hansemann, MD, PhD. Photograph of portrait provided by Leon Bignold. Permission to use the image was granted by Professor von Hansemann's grandson, Wolfgang von Hansemann.*

David Paul von Hansemann, MD, PhD, (Figure 3) studied medicine in Berlin, Kiel, and Leipzig, Germany. After defending his doctoral dissertation in 1886 under the direction of Julius Cohnheim, MD, Hansemann worked as an assistant to Rudolf Virchow, MD, and then held in succession the positions of lecturer, nominal professor, and honorary professor of pathologic anatomy at the University of Berlin.[23,24] In 1890, he described the concept of anaplasia, which postulated that the cancer cell's increased growth potential was accompanied by loss of differentiation and that asymmetrical mitoses were a characteristic of cancer, in an article entitled ''On the Asymmetrical Cell Division in Epithelial Cancers and its Biological Significance.''[25] Hansemann contrasted his theory of anaplasia (from the Greek, *ana* [backward] +

plassein [to form]) to the more popular theory of embryonalism because embryonal tissues had remained undifferentiated while anaplastic tissues had once been differentiated. These theories were further refined in his monograph, *Studies on the Specificity, Altruism, and Anaplasia of Cells*, published in 1893.[26] It is actually not surprising that Broders was unaware of Hansemann's work, as it was not well received in Germany,[24,27,28] had never been translated into English, and had been mostly forgotten.[24] Hansemann died in 1920, several months after Broders published his method of tumor grading, and it is highly doubtful that he was aware of Broders' new clinical application validating his theory of anaplasia. (Interestingly, even a 371-page scholarly biography of Hansemann published in 2007 does not make any connection between either Broders or cancer grading and Hansemann's work on anaplasia). Nevertheless, very recently, it has become clear that many of Hansemann's ideas about cancer that were maligned when he espoused them were right and that his contemporary critics were wrong.[24,29]

Grading quickly caught on worldwide and many publications confirmed the prognostic value of numerical grading.[30–36] Grading was not without some problems; these included subjectivity, interpathologist reproducibility, variability from field to field within some tissue sections, discussions on whether 1 or multiple pathologists should assign grades, discussions on whether the number of mitoses per se or whether only the numbers of abnormal mitoses were important, discussions on the validity of grading metastases, and others.[33,37] In some types of cancers, such as carcinoma of the esophagus, most lesions were of a high grade at the time of diagnosis and, thus, essentially all patients had a poor prognosis.[17] However, the Broders' method was generally considered by most pathologists to be accurate and easy to apply and the results correlated with prognosis. James Ewing, MD, of Memorial Hospital (New York City, New York), speaking of Broders' grading method, noted: ''in spite of its limitations it is a fact that an experienced pathologist can determine the age, rate of growth, danger of metastases, and probable outcome of many tumors with considerable accuracy, and this is of great help to surgeon and radiologist.'' [36] Nevertheless, Broders did make slight modifications to his grading system in response to some of these issues in an article he entitled ''Cancer's Self-control.'' [37] In the revised system, mitotic figures and cells with prominent nucleoli were given reduced significance and were simply considered to be undifferentiated cells. Grade I lesions were ones in which differentiation or ''selfcontrol'' ranged from 75% to almost 100%; grade II lesions had selfcontrol ranging from 50% to 75%; grade III lesions had a range from 25% to 50%; and grade IV lesions had a range from practically no selfcontrol to 25%.

Broders' numerical grading begat staging. Cuthbert Esquire Dukes, MD, OBE (Figure 4), a pathologist at St Mark's Hospital in London, United Kingdom, decided to replicate Broders' study.[8,38–40] He followed up more than 200 patients for more than 5 years and another 300 patients for more than 3 years after resection and demonstrated that patients with low-grade rectal adenocarcinomas fared much better after resection than patients with high-grade rectal adenocarcinomas. Death rates for grades I, II, III, and IV lesions were 20%, 36%, 48%, and 66%, respectively, at 3 years and 40%, 56%, 76%, and 100%, respectively, at 5 years. However, Dukes also saw an alternative interpretation for his results:

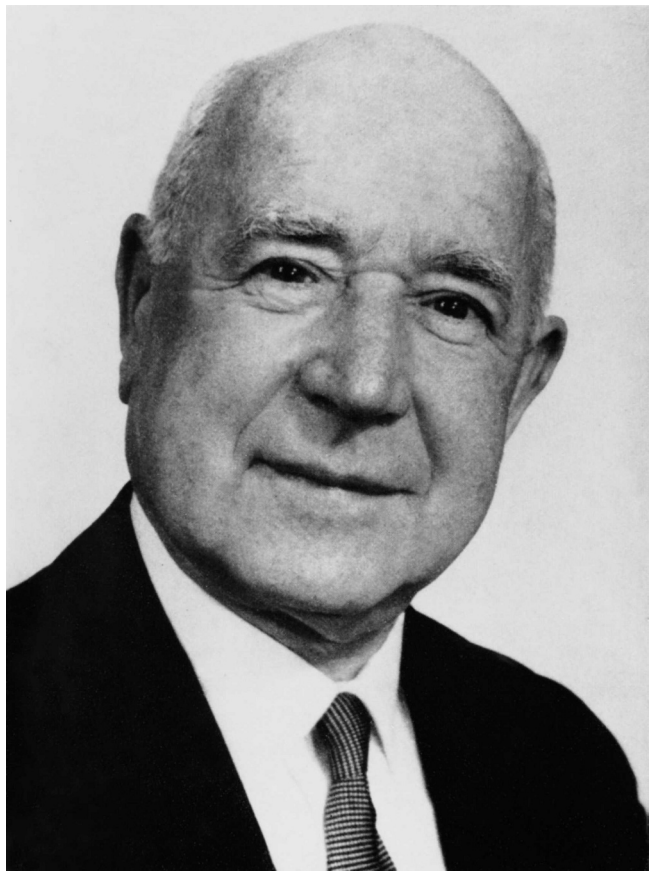

Figure 4. *Dr Cuthbert Dukes, MD, OBE. Reprinted from* A Short History of Clinical Pathology. *Edinburgh and London: W. D. Foster, E. & S. Livingstone Ltd; 1961. With permission from the publisher.*

> At first sight these figures would seem to show that the less differentiated types of malignant growths, such as Grades 3 and 4, grow more rapidly and kill the patient more quickly than the better differentiated tumours of Grades 1 and 2, but before accepting this seemingly obvious conclusion, allowance must be made for the extent of spread at the time of operation. We are not watching the natural uninterrupted march of malignant disease. These patients all underwent the operation of excision of the rectum for cancer and in some cases the disease was at an early stage and in others was actually beyond the scope of surgery at the time of operation. Looked at from this point of view, it might be argued that the survivors in each grade simply represent the proportion of cases which were at a curable stage at the time of operation. In other words, these striking differences in the numbers of deaths in each grade may not be a reflection of the rate of growth of the tumours but simply a measure of the proportion of patients in each grade who could be cured by the treatment they received. [40]

Dukes ''staged'' each patient's resected rectum specimen for depth of invasion and extent of spread. Dukes called tumors in which the growth was limited to the wall of the rectum, stage A; those extending into extrarectal tissues without metastases to regional lymph nodes, stage B; and those with invasion into extrarectal tissue and regional lymph node metastases, stage C. His 5-year survival rates were 93%, 65%, and 23% for stages A, B, and C, respectively. Dukes concluded that the difference in prognosis between high- and low-grade cancers was ''chiefly due to the fact

that the more anaplastic tumours are likely to have spread further than better differentiated growths at the time when they receive surgical treatment.''[40]

Histopathologic grading and staging are now standard prognostication tools provided by pathologists and routinely used by medical, radiation, and surgical oncologists. Broders was responsible for the concept of grading, which begat staging. Incidentally, Broders, working with a surgical fellow, responded to Dukes' study by publishing another study in which they found that staging and grading combined provide better prognostication than either technique alone, and this article is now considered to be a classic article in colonic and rectal surgery.[19,38]

Broders' first paradigm shift led to enhanced prognostication for cancer patients. The second paradigm shift actually was even more fundamental, changing the very definition of cancer. Before Broders, malignancy was defined by pathologists as the demonstration of a tumor's ability to invade and/or metastasize, a definition that was firmly entrenched in 19th century autopsy science. Throughout much of the 19th century, Americans wanting to learn pathology visited major Meccas in Germany and Austria, where the traditional European professors of pathology studied cancer only through autopsies. Autopsies on patients dying of advanced cancers generally showed macroscopically obvious invasion and metastases and, by the late 19th century, these could easily be confirmed by histology. However, this Central European approach didn't allow pathologists to observe the early features of cancers that could be seen in resected tumors or in biopsy specimens from tumors. This rigid definition, based upon many decades of German and Austrian autopsy science, began to butt heads with the newer, primarily American fields of biopsy and surgical pathology, beginning in the late 1880s and early 1890s.[5,8]

One of the earliest and most famous demonstrations of the inadequacy of the definition of cancer occurred in Germany in 1887–1888 and involved Rudolf Virchow, Germany's premier pathology professor, and his repeated inability to diagnose the malignancy that eventually killed German Crown Prince Frederick III. Because of the importance of the patient, the German government sought out the best otolaryngologist in the world to treat Frederick. The services of Sir Merril McKenzie, a British surgeon, were acquired over the objection of some in the German government, who thought it was a national embarrassment to use a foreign surgeon. McKenzie examined the patient and being uncertain—based on the clinical appearance of a small tumor on the Crown Prince's vocal cord—performed a series of biopsies, all of which were called benign by Virchow, who did not believe in the ''doctrine of the uniqueness of cancer cells''[27] and repeatedly noted that he could not see invasion into underlying tissue and hence the tumor was benign. Thus, a risky but possibly life-saving laryngectomy was never attempted. During the course of his illness, the Crown Prince's father died and Frederick III, a liberal pacifist married to the eldest daughter of Queen Victoria of Great Britain and a staunch opponent of conservative Chancellor Otto von Bismarck, became the new King of Prussia and Emperor of Germany; however, he died of metastatic laryngeal carcinoma 99 days later.[41–43] Virchow's rigid interpretation of malignancy, as being defined by invasion, had dire consequences that changed the course of 20th century world history,[44] as some historians believe that, had Frederick III lived, World War I and World War II could have been averted.

This whole story almost repeated itself in the United States in 1893, when President Grover Cleveland was found to have a grossly malignant-appearing lesion on the roof of his mouth.[45] A biopsy was performed and the specimen sent to the Army Medical Museum for diagnosis, without mention of the patient's name. The histology was reviewed by William H. Welch, MD, professor of pathology at Johns Hopkins, who concluded that it was an ''epithelioma.'' Although there were ''no positive proofs of malignancy,'' the surgical team decided to remove it anyway; the surgical procedure was performed secretly while floating down the Potomac River on a friend's private yacht. The president lived another 15 years after his secret cancer operations. The actual tumor, which resides in a bottle of fixative in the Mutter Medical Museum in Philadelphia, was examined by pathologists in the late 1970s and determined to be a verrucous carcinoma.[46]

Why could Virchow and Welch not diagnose cancer from biopsy specimens of these important world leaders? By histologic appearance alone, pathologists could only recognize as cancer those lesions that had invaded underlying tissues, as this was consistent with their macroscopic understanding of cancer based upon autopsy science. Pathologists could not recognize lesions that had either little tendency to invade (ie, verrucous carcinoma) or those with a strong tendency to invade but that had not yet invaded (ie, carcinoma in situ; Latin for ''in its place''), as these entities had not yet been described. Broders described carcinoma in situ in 1932[47] (see below), and Lauren V. Ackerman, MD, based at Barnes Hospital in St Louis, Missouri, described verrucous carcinoma in 1948.[48] Interestingly, Ackerman loved to recount the story of how he discovered verrucous carcinoma. Ackerman had received multiple biopsy specimens of an oral cavity lesion from a single patient over a period of time and had repeatedly diagnosed a benign ''papilloma.'' The frustrated surgeon eventually called him to the operating room to show him a tumor extending from the buccal mucosa to the skin of the cheek and reportedly said: ''Now, what do you think of THAT papilloma, doctor?'' to which Ackerman replied: ''Well, doctor, it still looks like a papilloma, but I must say it is the BAD kind of papilloma.''[49]

According to Broders' unpublished memoir:

> My next major research in cancer was on the earliest microscopic manifestation of carcinoma, a problem in which I had been interested for a number of years. I had been much impressed by what I had read in the literature, and I had observed at first hand and with much interest the outstanding cytological studies in the field of cancer by my colleague, Dr. W.C. MacCarty, of the Mayo Clinic, during the second and third decades of the century. From my own observations and those of others, I felt the urge to write a paper expressing a concept of the earliest microscopic manifestation of carcinoma and contrasting it with certain epithelial hyperplasias sometimes called ''carcinomatous'' but which in reality are benign. By the first of 1932 I was ready to prepare such a paper.[2]

Broders developed and clearly articulated the general concept of carcinoma in situ (CIS) and introduced the term in a seminal article published in the *Journal of the American Medical Association* in 1932.

Broders' article contained photomicrographs of several named pathologic entities that he considered to be

examples of CIS, including Bowen disease of the skin and Paget disease of the breast. He also identified, and illustrated with photomicrographs, CIS involving the uterine cervix, the larynx, the breast, and within an adenoma of the rectum.[47] Broders notes that CIS is often adjacent to invasive carcinoma, and in this instance, it can be missed without danger to the patient but that the real risk is when CIS occurs alone. Broders states, ''if carcinoma in situ appears alone, its recognition is necessary, for failure to recognize it may constitute an error of omission fraught with grave danger to the patient'' and he warned of the danger of undertreatment.[47]

Broders, as he noted above, built his concept of CIS upon the observations of others.[2,50] However, other than MacCarty, Broders does not clearly indicate upon whose work he relied. Therefore, some of the following analysis is highly speculative.

Roughly half of Broders' article deals with Paget disease; here he provides a detailed review of the literature, citing more than a dozen authors who had concluded that Paget disease is ''carcinomatous and not pre-carcinomatous.'' [47] The remainder of the article deals with the generic concept of CIS as well as other specific forms of CIS, for which his literature review is much weaker. The first figure in Broders' article illustrates cervical CIS, yet there is no review of this literature. Broders would have had to be familiar with the work of Thomas S. Cullen, MD. Cullen, the head of gynecologic pathology at Johns Hopkins, was a contemporary of Joseph Colt Bloodgood, the head of surgical pathology with whom Broders trained right after medical school. A decade earlier, Cullen and Bloodgood, while they were gynecology and surgery residents, respectively, had competed against each other to develop and publish the first intraoperative frozen section method and Cullen had won.[5] Although the Bloodgood laboratory in which Broders trained preferred the frozen section method developed in Boston a few years later by James Homer Wright, MD,[2] it is inconceivable that Broders did not meet Cullen and learn his frozen section method as well. Regardless, Cullen had a longstanding special interest in early carcinomas and had published observations noting a spatial relationship between noninvasive and invasive cervical carcinomas.[51–53] Friedell[53] notes that Cullen's work was preceded by that of Sir John Williams who presented his observations in his 1886 *Harveian Lecture*.

Several Austrian and German investigators had developed similar concepts, also based upon studies of the uterine cervix. For instance, W. Schauenstein, MD, a gynecologist at the women's hospital in Graz, Austria, described the continuity from precancerous to cancerous lesions of the cervix in 1908, outlining most of the essential elements of the CIS concept and calling it *oberflaechencarcinom* or surface carcinoma.[54,55] Schauenstein's theory was immediately supported by additional studies published by Karl Pronai of Vienna.[56] In 1912, Schottländer and Kermauner[57] provided further support for the concept and coined the term *Randbelag* to describe early surface carcinomas adjacent to invasive cervical carcinomas and published this work in a German textbook. However, it seems unlikely that Broders would have been aware of observations published in the German gynecology literature, since, as stated above, Broders did not have familiarity with the German literature on anaplasia. However, Schauenstein's work had been cited and supported with additional observations by Isidore C. Rubin, MD, a New York City gynecologist and former student of Schottländer,[55,58] and this was published in English in 1910.[59]

Regardless, it was Broders who described the concept of CIS in such clear manner that it was easily understandable by clinicians and pathologists alike and could be reproducibly diagnosed by pathologists. Therefore, primary credit for the discovery should go to him.

Nevertheless, Broders noted that it was a team effort in that he had working with him ''during the first quarter of 1932 a group of Fellows who had unusually keen, analytical, and critical minds'' and that he used them to critique both the concept and the paper as he developed both. These fellows ''were Drs. John L. Emmett, Emil D. Furrer, John S. Guthrie, Eleanor Fletcher (now Mrs. James W. Kernohan), Edith M. Parkhill, Roland G. Scherer, Harold C. Thornton and James R. Watson.'' [2] According to Broders:

> Much of the work on this paper I did at home, at night, and considerable discussion with my critics in the laboratory went on during the day. One of our difficult problems was a good title for the paper. After writing out various titles, submitting them to the critics, and discussing them at length, I finally decided that the most appropriate would be ''Carcinoma in Situ Contrasted with Benign Penetrating Epithelium.'' I then concentrated on a definition of ''carcinoma in situ.'' This was a major problem and one on which I worked for some time, submitting various definitions to my critics and requesting that they give me their frank opinions. This they did, noting the weak points in the several definitions submitted. We finally agreed upon the following definition: ''Carcinoma in situ is a condition in which malignant epithelial cells and their progeny are found in or near positions occupied by their ancestors before the ancestors underwent malignant transformation.'' This definition was elaborated upon in regard to the malignant epithelial cells as follows: ''At least they have not migrated beyond the juncture of the epithelium and connective tissue or the so-called basement membrane; such migration would be manifested by the cells entering the connective tissue interstices or any part of the blood or lymph vascular systems.[2]

Although Broders received immediate national and international accolades for his concept of numerical grading of cancer, documented by the review articles he was asked to write on the topic during more than 25 years,[60–67] the concept of CIS was not as widely accepted and remained controversial for many decades. Although Broders noted that he received many reprint requests for his article worldwide,[2] I can find no evidence that Broders was asked to write review articles on CIS. However, in 1956 he was asked to place his files and the original pathologic materials used to produce this article into a repository at the AFIP, documenting the importance of this work. According to one of his obituaries written by Mayo historian James Eckman, PhD, this article ''provoked much discussion in medical circles and is regarded as a classic contribution to the literature on pathology.'' [68] However, pathologists came around slowly, anatomic site by anatomic site, and the concept was ''rediscovered'' by a number of pathologists during the next 40 years. Much of the contentiousness preventing absolute across-the-board acceptance related to the level of ''proof'' required for cancer experts to say that CIS is truly malignant (ie, leads to invasive cancer) in each of the many anatomic sites that are afflicted by carcinomas. In general, there were 5 conditions that needed to be met to the satisfaction of most

cancer subspecialty experts. First, the involved epithelium must show all features of malignancy except invasion (ie, the epithelium is replaced full thickness by cytologically malignant-appearing cells lacking any maturation or differentiation). Second, the appearance of the involved epithelium must be identical to that often seen next to invasive carcinomas. Third, in situ changes must often be seen in earlier biopsy specimens from patients with invasive carcinoma. Fourth, exfoliated cells from the involved epithelium must be cytologically malignant. Fifth, retrospective studies of patients with untreated CIS must show that they often develop invasive carcinomas.[69] Because of the nature of these diverse conditions, they were not likely to be met in a single definitive publication for any given anatomic site. In some sites, such as skin or uterine cervix, these conditions were perhaps more easily and rapidly met than in others. For instance, for larynx and pharynx, the article considered to be ''definitive'' was published by Walter C. Bauer, MD, and Malcolm H. McGavran, MD, at Barnes Hospital in 1972, building upon work done by Altmann and coworkers in 1952.[49,70]

Broders, although brutally honest, was generous and gracious. Throughout the memoir, Broders praises many of his former Mayo colleagues as outstanding clinicians; however, in his discussion of Dr MacCarty, the sometimes controversial director of surgical pathology at Mayo, who had initially hired him, he praises his research skills but actually never mentions his diagnostic skills, which might seem odd as this is a pathologist's major function. To the average reader, this was so well hidden in the other praise that it would not even be noticeable except that I was already sensitized to look for this, as sources had indicated to me that MacCarty was not a strong diagnostician. Broders describes him as a ''surgical pathologist of world-wide renown,'' praises his excellent medical photography skills, notes he ''took beautiful photomicrographs,'' and states that ''no other man in the world did more to call our attention to the early microscopic diagnosis of cancer.'' [2] In fact, Broders even credits Dr MacCarty as an impetus for his groundbreaking work on CIS, as during the second and third decades of the 20th century, MacCarty had published a series of theoretic articles on the histogensis of cancer. MacCarty, now primarily remembered for having developed several confusing, complex cancer nomenclature schemes based upon nucleolar-nuclear ratios (including mathematical calculations of their relative volumes in μm^3) and for his ''showmanship'' ability, was known in some circles as ''one-cell MacCarty'' after his public argument with James Ewing in which MacCarty boldly claimed that ''a well-trained pathologist can make the diagnosis of cancer correctly from a single cell'' on a frozen section; when Ewing said that this was not possible, MacCarty quipped, ''what you mean is that you cannot ….'' [3] Although most of MaCarty's ideas gained little acceptance then and seem quite implausible now, clearly they were provocative and stimulated Broders.

Honesty, honor, and his Southern heritage were incredibly important to Broders, and this is why he thought so highly of the ''Sage of Richmond.'' According to his son Dr Charles W. Broders, his father ''was a man of simple tastes and scrupulous honesty and integrity. His colleagues and friends regarded him as the epitome of the 'Virginia gentleman.''' [22] The memoir further confirms this impression, as it contains a letter from Donald C. Balfour, MD, a leading senior Mayo surgeon and director of the Mayo Foundation, sent to ''Brodie'' at the time of his retirement. According to Balfour: ''I think what impressed me more than anything in your work through the years was your unswerving devotion to the truth. This was of enormous benefit to the Clinic through the years of its greatest development and it has set a standard which will last for all time.'' [2] Broders states that ''this letter meant so much to me that I am incorporating a copy of it in these memoirs.'' In fact, it is the only letter in the whole document.

Broders' outside interests were vegetable gardening and, like many other early Mayo pathologists, duck and pheasant hunting. He was founding member of the Issac Walton League in Rochester, Minnesota, and did much to preserve the natural environment for game birds. Dr and Mrs Broders had 1 daughter, Mrs Elizabeth Beckstrand, and 2 sons, Dr Charles William Broders and Dr Albert Compton Broders Jr.[22]

Broders spent almost his whole career at the Mayo Clinic, arriving as a trainee on August 12, 1912, and retiring as the director of the Mayo Division of Surgical Pathology and professor of pathology in the Mayo Foundation, Graduate School, University of Minnesota on December 31, 1950. During this interval, he took 1 leave of absence, serving from August 1, 1935, to August 1, 1936, as professor of surgical pathology and director of cancer research at his alma mater, MCV. After his retirement date, Dr Broders, being a Southerner, returned to the South, and like many retired Mayo physicians, worked at Scott & White Clinic in Temple, Texas.[71] Broders worked for another 10 years at Scott & White, serving as a senior consultant in surgical pathology under James C. Stinson, MD, who was the department chair and a former Mayo resident trained by Broders. Broders fully retired at the age of 75 and died in Temple on March 26, 1964, following a stroke; Scott & White instituted the *Albert Compton Broders Memorial Lecture in Pathology*. Although Broders was the subject of multiple obituaries, to date, no one has published a historical article describing his major accomplishments and the 2 cancer paradigms he shifted.

Today, there are many hundreds of different grading and staging schemes for various types of cancer,[72–75] which are all sequentially derived from Broders' first discovery. The sequelae of Broders' first discovery crosses paths with his second, since in the TNM staging system, CIS is classified as TisN0M0 (stage 0). Broders' classic article listed about a dozen examples of CIS. Now, CIS is documented as occurring in many more anatomic sites, and new types of ''intraepithelial neoplasias'' have been postulated on a regular basis (nb, a PubMed search in January 2012 yielded >37 000 hits). We now know that CIS, in many instances, is a middle stage in a progression from mild cytologic atypia to invasive carcinoma. Both topics have become much more complicated than in the time of Broders. However, because of Broders' epic work, pathologists can now tell surgeons with a much higher degree of certainty not only which tumors are benign and which are malignant, but also which patients can be cured.

The following individuals and institutions are thanked for help with obtaining articles, historical materials, or historical insights: Lewis B. Woolner, MD; Dottie Hawthorne, Mayo Clinic Libraries; Renee E. Ziemer and Kristen Van Hoven, Mayo Historical Unit; Robert F. Peterson, MD, Chairman Emeritus, Department of Pathology, Scott & White Clinic; Sherry Mount;

Docs for Docs. The following individuals are thanked for reviewing drafts of this manuscript and for helpful suggestions: Leland Baskin, MD, and Lewis B. Woolner, MD.

References

1. Kuhn TS. *The Structure of Scientific Revolutions*. Chicago, IL: University of Chicago Press; 1962.
2. Broders AC. *Milestones in a Medical Career* [unpublished memoir]. c 1960; 74 p. Available at: History of Medicine Library, Mayo Foundation, Rochester, MN (MHU No. 0670). (NB, a second, 46-page long version of this document is available through Scott & White Clinic Archives and is obviously an earlier draft. The memoir was written by Broders while working post retirement at Scott & White and then sent to the Mayo Editorial Department to finalize and retype. The final version has larger margins and added polish but is otherwise almost identical. Page numbers given throughout my article are from the longer Mayo version). Quotes are from pages 19–20, 20–21, 33, 36, 38, 43–44, 46, 47–48, 67, 68–69, and 71.
3. Woolner LB. Surgical pathology at the Mayo Clinic. In: Rosai, ed. *Guiding the Surgeon's Hand: The History of American Surgical Pathology*. Washington, DC: Armed Forces Institute of Pathology; 1997:145–179.
4. Albert Compton Broders, MD, Burnquist, JA. In: *Minnesota and Its People*. Vol. IV. Chicago, IL: S.J. Clarke Publishing Co; 1924:164–165.
5. Wright JR Jr. The development of the frozen section technique, the evolution of surgical biopsy, and the origins of surgical pathology (William Osler Medal Essay). *Bull Hist Med*. 1985;59(3):295–326.
6. Wilson LB. A method for the rapid preparation of fresh tissues for the microscope. *JAMA*. 1905;45:1737.
7. Broders AC. Modification of Wilson's fresh frozen section technic. *J Lab Clin Med*. 1931;16:734–738.
8. Wright JR Jr. Relationship of surgical oncology and pathology in early 20th century America. In: Kawakita Y, Sakai S, Otsuka Y, eds. *History of Ideas in Surgery: Proceedings of the 17th International Symposium on the Comparative History of Medicine— East and West*. Tokyo, Japan: Ishiyaku EuroAmerica Publishers; 1997:241–266.
9. Broders AC. Squamous cell cancer of the lip: a study of five hundred and thirty-seven cases. *JAMA*. 1920;74:656–664.
10. Broders AC. Squamous cell epithelioma of the skin: a study of 256 cases. *Ann Surg*. 1921;73:1141–1160.
11. Broders AC. Epithelioma of the genitor-urinary organs. *Ann Surg*. 1922;75: 574–604.
12. Broders AC. Epithelioma of the cavities and internal organs of the head and neck. *Arch Surg*. 1925;11:43–73.
13. Clapesattle HB. *The Doctors Mayo*. Minneapolis, MN: University of Minnesota Press; 1941.
14. Mahle AE. The morphological histology of adenocarcinoma of the body of the uterus in relation to longevity: a study of 186 cases. *Surg Gynec Obstet*. 1923; 36:385–395.
15. Bueermann WH. *A Clinical and Pathological Study of the Carcinomatous Gastric Ulcer With Particular Reference to Grading of Malignancy* [PhD thesis]. Graduate School of the University of Minnesota; June 1927. (Also published monthly in a piecemeal fashion between November 1930 and December 1931 in *Western Journal of Surgery, Obstetrics and Gynecology*).
16. Rankin FW, Broders AC. Factors influencing prognosis in carcinoma of the rectum. *Surg Gynec Obstet*. 1928;46:660–667.
17. Broders AC, Vinson PP. The degree of malignancy of carcinoma of the esophagus. *Arch Otolaryngol*. 1928;8:79–80.
18. Ochsenhirt NC. The significance of mucous-forming cells in carcinoma of the large intestine and rectum. *Surg Gynec Obstet*. 1928;47:32–35.
19. Broders AC, Buie LA, Laird DR. Prognosis in carcinoma of the rectum: a comparison of the Broders and Dukes methods of classification. *JAMA*. 1940; 115:1066–1071. (republished in the ''Classic Articles in Colonic and Rectal Surgery'' series in Dis Colon Rectum. 1985;28(9):687–694).
20. Broders AC, Hargrave R, Meyerding HW. Pathological features of soft tissue fibrosarcoma with special reference to the grading of its malignancy. *Surg Gynec Obstet*. 1939;69:267–280.
21. Division of Publications, Mayo Clinic. *Physicians of the Mayo Clinic and the Mayo Foundation*. Minneapolis, MN: University of Minnesota Press; 1937.
22. Broders CW. Albert Compton Broders, MD [unpublished text to be used for obituaries]. Temple, TX: Directory of Scott & White Doctors, bio-file, Scott & White Archives. 3p. Quote from p 2.
23. Sturzbecher M, von Hansemann DP. Pathologischer Anatom, 5.9.1858 Eupen b. Aachen—28.8.1920 Berlin. *Sonderdruck aus Neue Deutsche Biographie 7*. Berlin, Germany: Bavarian Academy of Science; 1966:629–630.
24. Bignold LP, Coghlan BLD, Jersmann HPA, von Hansemann DP. *Contributions to Oncology: Context, Comments and Translations*. Germany: Birkhauser Verlag; 2007.
25. Hansemann D. Ueber asymmetrische Zelltheilung in Epithelkrebsen und deren biologische Bedeutung. *Arch Pathol Anat etc Berl (Virchow's Arch)*. 1890; 119:299–326.
26. Hansemann D. *Studien uber die spezificitat den Altuismus und die Anaplasie der Zellen*. Berlin, Germany: Verlag von August Hirschwald; 1893.
27. Rather LJ. *The Genesis of Cancer: A Study in the History of Ideas*. Baltimore, MD: The Johns Hopkins Press; 1978.
28. Wolff J. The *Science of Cancerous Disease from the Earliest Times to the Present*. Cambridge: Science History Publications; 1989 (originally published in German in 1907).
29. Bignold LP, Coghlan BLD, Jersmann HPA. Hansemann, Boveri, chromosomes and the gametogenesis-related theories of tumours. *Cell Biol Int*. 2006; 30(7):640–644.
30. Greenhough RB. Varying degrees of malignancy in cancers of the breast. *J Cancer Res*. 1925;9:425–463.
31. Harrington SW. Unilateral and bilateral carcinoma of the breast (including Paget's disease): results three, five, ten, fifteen and twenty years after operation. *Minnesota Med*. 1938;21:1–8.
32. Edmonson WF. Microscopic grading of cancer and its practical implications. *Arch Derm Syphilol*. 1948;57:141–150.
33. Lindberg L. Fundamental principles in the grading of malignancy of tumors. *Southwestern Med*. 1935;19:413–421.
34. Stein JJ. The clinico-pathologic significance of the grading of cancer. *J Med (Cincinnati)*. 1935;16:352–358.
35. Peery TM. The pathological grading of malignant tumors. *J S Carolina Med Assoc*. 1937;33:47–49.
36. Ewing J. Some results of modern clinical cancer research. *J Med (Cincinnati)*. 1935;16:15–20. Quote from p 17.
37. Broders AC. Cancer's selfcontrol. *Med J Rec*. 1925;121:133–135.
38. Shampo MA. Dukes and Broders: pathologic classifications of cancer of the rectum. *J Pelvic Surg*. 2001;7:5–7.
39. Dukes CE. The classification of cancer of the rectum. *J Pathol*. 1932;35: 323–332.
40. Dukes C. Histological grading of rectal cancer. *Proc Royal Soc Med*. 1937; 30:371–376.
41. Ober WB. The case of the Kaiser's cancer. *Pathol Annu*. 1970;5:207–216.
42. Lin JI. *Death of a Kaiser: A Medical Historical Narrative*. Dayton, OH: Landfall Press; 1985.
43. Lin JI. Virchow's pathological reports on Frederick III's cancer. *NEJM*. 1984;311(19):1261–1264.
44. Frederick III, German Emperor. Wikipedia Web site. http://en.wikipedia.org/wiki/Frederick_III,_German_Emperor. Accessed August 1, 2011.
45. Keen WW. *The Surgical Operations on President Cleveland in 1893*. Philadelphia, PA: George W. Jacobs & Co; 1917.
46. Brooks JJ, Enterline HT, Aponte GE. The final diagnosis of President Cleveland's lesion. *Trans Stud Coll Physicians Phila*. 1980;2(1):1–25.
47. Broders AC. Carcinoma in situ contrasted with benign penetrating epithelium. *JAMA*. 1932;99:1670–1674. Quote from p 1673.
48. Ackerman LV. Verrucous carcinoma of the oral cavity. *Surgery*. 1948;23: 670–678.
49. Fechner RE. A brief history of head and neck pathology. *Mod Pathol*. 2002; 15(3):221–228. Quote on p 223.
50. Fechner RE. One century of Mammary carcinoma in situ: what have we learned? *Am J Clin Pathol*. 1993;100(6):654–661.
51. Cullen TS. *Cancer of the Uterus*. New York, NY: D. Appleton & Co; 1900.
52. Cullen TS. Early squamous-cell carcinoma in the cervix, accidentally discovered when the body of the uterus was being curetted for hemorrhage caused by hyperplasia of the endometrium and by a small submucous myoma. *Surg Gynecol Obstet*. 1921;33:137–144.
53. Friedell GH. Carcinoma, carcinoma in situ, and ''early lesions'' of the uterine cervix and the urinary bladder: introduction and definitions. *Cancer Res*. 1976;36:2482–2484.
54. Schauenstein W. Histologische Utersuchungen uber atypisches Plattenepithel an der Portio und an der innenflache der Cervix Uteri. *Arch F Gynakol*. 1908;85:576–616.
55. Koss LG. Schauenstein's contributions [letter]. *Int J Gynecol Pathol*. 2002; 21(4):424.
56. Pronai K. Zur Lehre von der Histogenese und dem Wachsthum des Uteruscarcinoms. *Arch F Gynakol*. 1909;89(3):596–607.
57. Schottländer I, Kermauner F. *Zur Kenntnis des Uteruskarzinoms: monographische Studie uber Morphologie: Entwicklung, Wachstum nebst Beitragen zur klinik der Erkrankung*. Berlin, Germany: S. Karger; 1912.
58. Gray LA, Barnes ML, Lee JJ. Carcinoma-in-situ and dysplasia of the cervix. *Ann Surg*. 1960;151(6):951–960.
59. Rubin IC. The pathological diagnosis of incipient carcinoma of the uterus. *Am J Obstet Gynecol*. 1910;62:668–676.
60. Broders AC. The grading of carcinoma. *Minnesota Med*. 1925;8:726–730.
61. Broders AC. Carcinoma grading and practical applications. *Arch Pathol Lab Med*. 1926;2:376–381.
62. Broders AC. Practical points on the microscopic grading of carcinoma. *New York State J Med*. 1932;32:667–671 and *J Am Soc Control Cancer*. 1932;14:1–3.
63. Broders AC. The grading of cancer: its relationship to metastases and prognosis. *Texas State J Med*. 1933;29:520–525.
64. Broders AC. The grading of cancer; its practical value [editorial]. *Am J Clin Pathol*. 1935;5:254–256.
65. Broders AC. The microscopic grading of cancer. In: Pack GT, Livingstone EM, eds. *The Treatment of Cancer and Allied Diseases*. Vol 1. New York, NY: Paul B. Hoeber Inc; 1940:55–61.
66. Broders AC. The microscopic grading of cancer. *Surg Clin N Am*. 1941;21: 947–962.
67. Goyanna R, Torres ET, Broders AC. [Histological grading of malignant tumors: Broders' method]. *Hospital (Rio J)*. 1951;39:791–818.

68. Eckman J. In memoriam: Albert Compton Broders, MD, 1885-1964. *Am J Clin Pathol*. 1964;42:300–301.
69. Rosai J, Ackerman LV. The pathology of tumors, part III: grading, staging & classification. *Ca Cancer J Clin*. 1979;29(2):66–77.
70. Bauer WC, McGavran MH. Carcinoma in situ and evaluation of epithelial changes in larnygopharyngeal biopsies. *JAMA*. 1972;221:72–75.
71. Kelley D. *With Scalpel and Scope: A History of Scott and White*. Waco, TX: Texian Press; 1970.
72. Damjanov I, Fan F. *Cancer Grading Manual*. New York, NY: Springer; 2007.
73. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.
74. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. *AJCC Cancer Staging Handbook: From the AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.
75. Sobin LH. *TNM Classification of Malignant Tumours (UICC)*. 7th ed. London, United Kingdom: John Wiley & Sons; 2009.