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Author(s): James R. Wright Jr.

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WILLIAM OSLER MEDAL ESSAY

THE DEVELOPMENT OF THE FROZEN SECTION TECHNIQUE, THE EVOLUTION OF SURGICAL BIOPSY, AND THE ORIGINS OF SURGICAL PATHOLOGY

*James R. Wright, Jr.**

During the late nineteenth and early twentieth centuries, clinicians had few tools other than the patient's history and physical examination to aid them in the diagnosis of cancer. Often, by the time a tumor could be diagnosed clinically, it was inoperable. As early diagnosis was the key to surgical cure, surgeons exposed and examined any potentially malignant tumor. Even when this was done, it was not always apparent from the gross appearance of a lesion whether it was benign or malignant, and the surgeon often had to proceed on the basis of his experience, knowing that the result of an incorrect diagnosis could be unnecessary disfigurement or death for the patient. Many surgeons preferred to err in favor of more radical procedures. As Joseph C. Bloodgood, associate professor of surgery at the Johns Hopkins Hospital, wrote in 1904, "In regard to tumors ... lynch law is by far the better procedure than 'due process.' "[1]

Since the turn of the century, however, marked changes have occurred in surgical diagnosis, particularly in the area of the histologic diagnosis of benign and malignant tumors. At present, a biopsy with a rapid frozen section diagnosis is a standard diagnostic tool for the surgeon who is uncertain of the nature or extent of a lesion he has exposed surgically. With this technique, the surgeon can often have a definitive histologic diagnosis within minutes, while the patient is still on the operating table.

How did this change in surgical diagnosis come about? None of the numerous general histories of surgery and pathology have examined the

* I wish to express my gratitude to my graduate advisor John C. Burnham for the tools that enabled me to write this essay.

[1] Joseph C. Bloodgood, "The relation of surgical pathology to surgical diagnosis," *Detroit Med. J.*, 1904, *3*: 337–52, esp. p. 338. General sources on the history of cancer include: Lelland J. Rather, *The Genesis of Cancer: A Study in the History of Ideas* (Baltimore: The Johns Hopkins University Press, 1978); Michael B. Shimkin, *Contrary to Nature: Being An Illustrated Commentary on Some Persons and Events of Historical Importance in the Development of Knowledge Concerning Cancer* (Washington, D.C.: United States Department of Health, Education, and Welfare, 1977); Sigismund Peller, *Cancer Research Since 1900: An Evaluation* (New York: Philosophical Library, 1979); Daniel De Moulin, *A Short History of Breast Cancer* (Dordrecht and Boston: Martinus Nijhoff Publishers, 1983).

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development of the quick frozen section technique.[2] This paper will discuss the coming into use and acceptance of the frozen section as a technique for rapid diagnosis during an operation. It will also show how the adoption of frozen section techniques resulted in the increased use of biopsies and examine the effect of the frozen section technique on the evolution of surgical pathology as a subspecialty.

Nineteenth-Century Developments. A combination of three developments in the middle and late nineteenth century made rapid tissue diagnosis during operations possible by the beginning of the twentieth century. First, the introduction of anesthesia and aseptic technique allowed surgeons to perform longer, more complicated procedures requiring improved diagnostic skills. Second, the resolution and magnification capabilities of the microscope were increased as a result of technical innovations such as the Abbé condenser and the achromatic lens. Third, techniques for the preparation of tissue specimens for microscopy were improved. The relationship between this third development and the frozen section technique requires that a few principles related to these advances in histologic technique be outlined.

A key to histologic and cytologic fidelity in microscopy is the preparation of thin and uniform tissue sections. As most tissues are soft, some method of hardening the tissue is needed. One of the earliest hardening techniques, dating from the early nineteenth century, was freezing the tissue in a saline solution.[3] This was a simple method but it resulted in cell shrinkage and poor retention of cellular detail; it was soon replaced by procedures in which the tissue was embedded in a matrix such as paraffin or celloidin before being sectioned. Earlier hardening of the tissue (fixation) and dehydration were required to ensure satisfactory results. Once the tissue was properly hardened, sections were cut and stained to elicit nuclear and cytoplasmic detail. Before the 1870s, sections were usually cut freehand with a razor, but in the late nineteenth century, mechanical aids called microtomes were developed, improving both the quality of sections and the speed at which they could be produced.[4]

Despite the replacement of frozen sections by various embedding techniques, the technology for producing frozen sections continued to improve

[2] Esmond R. Long, *A History of Pathology* (Baltimore: Williams & Wilkins, 1928); Edward B. Krumbhaar, *Pathology* (New York: Hoeber Clio Medica, 1937); Esmond R. Long, *A History of American Pathology* (Springfield, Ill.: Charles C Thomas, 1962); Harvey Graham, *The Story of Surgery,* 2nd ed. (New York: Doubleday, Doran, 1939); Richard A. Leonardo, *History of Surgery* (New York: Froben Press, 1943); Leo M. Zimmerman and Ilza Veith, *Great Ideas in the History of Surgery,* 2nd rev. ed. (New York: Dover Publications, 1967); Owen H. Wangensteen and Sarah D. Wangensteen, *The Rise of Surgery from Empiric Craft to Scientific Discipline* (Minneapolis: University of Minnesota Press, 1978).

[3] Long, *History of Pathology,* pp. 211–14; Clarence B. Farrar, "The growth of histologic technique during the nineteenth century," *Rev. Neurol. Psychiat. (Edinb.),* 1905, *3:* 501–13.

[4] George Clark and Frederick H. Kasten, *History of Staining,* 3rd ed. (Baltimore: Williams and Wilkins, 1983). Brian Bracegirdle, *A History of Microtechnique* (Ithaca, New York: Cornell University Press, 1978) is the best source on the development of microscopic technique, but he does not include the clinical or pathological applications for the innovations.

throughout the later nineteenth century. Specimens were no longer frozen in brine and ice solutions prior to being placed on the microtome; instead, they were placed on the microtome and then frozen with compressed carbon dioxide, ether spray, or other gases.[5] A sampling of late nineteenth-century textbooks on the methods and techniques of microscopy and pathology demonstrates that the frozen section still had its uses.[6] Most authors described one or more methods of making frozen sections, although most qualified their descriptions with statements that the technique produced results that were not always satisfactory. Writing in 1901, W. M. Late Coplin, professor of pathology at Jefferson Medical College in Philadelphia, observed:

> After using the freezing method to a very large extent for about ten years, the author is thoroughly convinced that it is not to be relied upon. The ice crystals that form in freshly frozen tissue break up the cells and give results that may mislead the most experienced investigator . . . and . . . have led me to give them up entirely for laboratory work; only the crudest kind of pathologic work can be performed by the freezing and congelation methods at present at our disposal, and the results are always open to criticism.[7]

Although described in textbooks of microscopy by 1890, the use of frozen sections for the diagnosis of tissue during operations required further refinement of the techniques. The need for improved surgical diagnosis and the increasing commercial availability of freezing microtomes was to lead to widespread experimentation by surgeons and pathologists.

Thomas S. Cullen at the Johns Hopkins Pathology Laboratory. During the early 1890s, pathologists experimenting at the Johns Hopkins and other laboratories were attempting to develop a quick and practical method for hardening tissue that would not distort cell morphology and would permit tissue diagnosis during operations. In Baltimore in 1891, William H. Welch made a frozen section of a breast tumor while William S. Halsted operated, but it took Welch so long that the operation was completed before the microscopic diagnosis was finished.[8] Later that year, Thomas S. Cullen, a recent medical graduate of the University of Toronto, came to Welch's laboratory to study

[5] Bracegirdle, *History of Microtechnique,* pp. 135–209.

[6] Charles H. Stowell and Louisa R. Stowell, *Microscopical Diagnosis* (Detroit: George S. Davis, 1882), pp. 17–18; Carl Friedlaender, *A Manual of Microscopic Technology for Use in the Investigations of Medicine and Pathological Anatomy,* trans. Steven Y. Howell (New York: G. P. Putnam's Sons, 1885), p. 22; Francis Delafield and T. Mitchell Prudden, *A Handbook of Pathological Anatomy and Histology with an Introductory Section on Postmortem Examination and the Methods of Preserving and Examining Diseased Tissues* (New York: William Wood, 1885), p. 40; Frank L. James, *Elementary Microscopical Technology: A Manual for Students of Microscopy: Part I. The Technical History of a Slide from the Crude Materials to the Finished Mount* (St. Louis: St. Louis Medical & Surgical Journal, 1887), pp. 18–19; Heneage Gibbes, *Practical Pathology and Morbid Histology* (Philadelphia: Lea Brothers, 1891), pp. 37–40; Frank J. Wethered, *Medical Microscopy: A Guide to the Use of the Microscope in Medical Practice* (Philadelphia: P. Blakiston's Son, 1892), pp. 31–35, 55–56.

[7] W. M. Late Coplin, *Manual of Pathology Including Bacteriology, the Technic of Postmortems, and Methods of Pathologic Research* (Philadelphia: P. Blakiston's Son, 1901), pp. 62–63.

[8] Joseph C. Bloodgood, "Biopsy in diagnosis of malignancy," *Southern Med. J.,* 1927, *20:* 18–28, esp. p. 23.

pathology for several months before starting an internship in gynecology. After completing his internship and a European tour, Cullen returned to Welch's laboratory. He supervised gynecological pathology for three years while he waited for a vacancy in the Hopkins gynecology residency program. Like Welch, he experimented with frozen sections for rapid diagnosis. Frozen sections had been used at least occasionally by William T. Councilman during autopsies at Hopkins, and it is likely that Cullen learned the technique from him.[9]

Cullen studied pathology in Germany for five months in the laboratory of Johannes Orth during his European trip in 1893, the year that the fixative properties of formaldehyde were first reported. Orth advocated the use of formalin and developed a formalin-based fixative, "Orth's fluid." As a result, Cullen was familiar with and impressed by the properties of formalin, as one of his memos reveals:

> Formalin, formaldehyde, and formol are looked upon as synonymous terms. Formalin was first used by Blum of Frankfurt a.[m] M.[ain] in 1893 as a preservative for goldfish, frogs, mice, etc. The animals were not only well preserved but the colors were retained. Since then Hermann, Hoyer, and others have used it for histological purposes. The tissues hardened in this fluid are little if at all contracted. Accordingly the cells are in no way distorted but stand out with great distinctiveness. While working with formalin specimens it occurred to me that it might be of use in the preparation of frozen sections.[10]

Cullen found that frozen sections, if fixed in formalin for three to five minutes, could be "treated as an ordinary celloidin section, being stained and mounted in the same way."[11] This procedure took only fifteen minutes and thus permitted Cullen to make diagnoses while operations were in progress. Welch was so impressed when shown the new technique that he told Cullen to write a report of his findings immediately, and it was published in the April *Bulletin of the Johns Hopkins Hospital*.[12] Although the *Bulletin* had already gone to press, it was feared that another pathological laboratory might publish similar findings in the month preceding the next issue, and it was for this reason that special arrangements were made to publish the report immediately.[13] At the same time, Cullen published a description of the technique in a German journal.[14]

When asked later about this discovery, Cullen replied:

[9] Judith Robinson, *Tom Cullen of Baltimore* (London: Oxford University Press, 1949), pp. 83–84.

[10] Notes on Cullen's Formalin Method, n.d., Item 103, Thomas S. Cullen Papers, The Alan Mason Chesney Medical Archives, The Johns Hopkins Medical Institutions, Baltimore, Maryland.

[11] Thomas S. Cullen, "A rapid method of making permanent specimens from frozen sections by the use of formalin," *Bull. Johns Hopkins Hosp.*, 1895, *6:* 67. The article was reprinted verbatim in *ibid.*, 1897, *8:* 108–9.

[12] Cullen, "Rapid method," p. 67.

[13] Robinson, *Tom Cullen of Baltimore,* pp. 120–22.

[14] Thomas S. Cullen, "Beschleunigtes Verfahren zur Färbung frischer Gewebe mittelst Formalins," *Zentralbl. Allg. Path. Anat.*, 1895, *6:* 448–50.

> It was a great thing for a young fellow, to gain recognition by his work and to be first in a race where all started even, but beyond that was the chance that your discovery might help another man to his. My method of making permanent specimens, for instance; it was no time at all after I published before other men had improved on it; worked out methods of doing the same thing faster and more effectively and, just as I had used earlier findings in my work, they used mine in theirs.[15]

Although Cullen was the first to publish a description of a technique for producing rapid diagnostic frozen sections, it is unclear whether he was the first to use them.[16]

The Development of the Frozen Section in Germany. Henrique Plenge of the Pathological Anatomy Institute at Heidelberg and Ludwig Pick of the Landau Frauenklinik in Berlin both published accounts of similar techniques in 1896. Plenge insisted that he had discovered the technique, had used it since October of 1894, and had demonstrated it to some of his colleagues.[17] Pick asserted that his technique had been "used in the laboratory of the Landau Frauenklinik for some time," but credited Cullen with its development. He observed that, "Plenge employed it later, tested it thoroughly, and gave a description of the results obtained."[18]

All three men recognized the significance of their discoveries. Cullen published descriptions of his technique three times, twice in the United States (the second time because he had run out of reprints) and once in Germany; Plenge published descriptions twice in Germany; and Pick published descriptions twice in Germany, once in the United States, and once in Britain.[19]

[15] Robinson, *Tom Cullen of Baltimore,* pp. 121–22.

[16] John Collins Warren, "The early diagnosis of malignant growths," *Trans. Amer. Surg. Assoc.,* 1889, *7:* 9–24. Warren, a surgeon at the Massachusetts General Hospital, described a method for punch biopsies and mentioned that the specimens were sometimes examined immediately "with the freezing microtome," but did not describe his technique. Therefore, Warren's contribution to the development of the frozen section technique was minimal and he was never cited in the literature pertaining to frozen sections. Furthermore, neither the 1894 nor the 1900 edition of his textbook, *Surgical Pathology and Therapeutics,* described frozen section technique, although both include sections describing "scientific aids to surgical diagnosis." See John Collins Warren, *Surgical Pathology and Therapeutics* (Philadelphia: W. B. Saunders, 1894), pp. 807–8; *idem, Surgical Pathology and Therapeutics,* 2nd ed. (Philadelphia: W. B. Saunders, 1900), pp. 795–96. In 1895, Nicholas Senn, chairman of surgery at Rush Medical College in Chicago, suggested that "the freezing microtome ... should have a place in the operating room of every hospital." Nicholas Senn, *The Pathology and Surgical Treatment of Tumors* (Philadelphia: W. B. Saunders, 1895), p. 107. Senn, like Warren, made a vague suggestion rather than describing a technique. Although both Warren and Senn probably made use of frozen sections during operations, at least occasionally, before Cullen, Cullen was the first to publish practical step-by-step instructions for making such sections. His technique was recognized at a meeting of the New York Pathological Society on 28 January 1898 as the first successful frozen section technique: see Eugene Hodenpyl, "A modification of Cullen's method of preparing fresh frozen sections for microscopic work," *Med. Rec.,* 1898, *53:* 351.

[17] Henrique Plenge, "Zur Technik der Gefrierschnitte bei Härtung mit Formaldehydlösung," *Virchow's Arch.,* 1896, *144:* 409–31; *idem,* "Härtung mit Formaldehyd und Anfertigung von Gefrierschnitten, eine für die Schnelldiagnose äusserst brauchbare Methode," *Münch. med. Wochnschr.,* 1896, *43:* 71–72.

[18] Ludwig Pick, "A rapid method of staining and preparing tissue for microscopical diagnosis," *Amer. J. Obstet.,* 1896, *34:* 839–43. The quotation is on pp. 839–40.

[19] Ludwig Pick, "II. Eine weitere Abkürzung der Schnellanfertigung mikroskopischer Dauerpräparate (Anwendung formalinisirter Farbstofflösungen)," *Zentralbl. Gynäk.,* 1898, *22:* 227–31; Pick cites a second German reference within this paper; Ludwig Pick, "A rapid method of preparing permanent sections for microscopical diagnosis," *Brit. Med. J.,* 1897, *1:* 140–41.

Plenge's persistent attempts to claim credit for the discovery indicate his belief that it was important. Pick, who had never claimed priority, was offended when Cullen asserted that Pick had not arrived at his discovery independently, but had only adapted Cullen's method.[20] According to Cullen, the "slight modification ... recently suggested by L. Pick ... I cannot recommend. When first experimenting with formalin ... I tried staining the sections ... as Pick now suggests, [but] abandoned it and did not think it worthy of publication."[21] In light of this dispute, it is ironic that it is none of the principals but rather Louis B. Wilson of the Mayo Clinic who is generally remembered as the originator of the rapid diagnostic frozen section.[22]

The Development of the Frozen Section in Great Britain. There is evidence that two British pathologists may have made frozen section diagnoses during operations as early as 1897. Alfredo A. Kanthack, deputy professor of pathology at Cambridge University and pathologist at St. Bartholomew's Hospital, and T. Strangeways Pigg published an account of their technique in that year.[23] It consisted of first dropping the tissue specimen into boiling water for three to five minutes, then placing it on a freezing microtome, cutting frozen sections, staining, and mounting them as if they were paraffin sections. Preparation of a specimen generally took ten to fifteen minutes. The authors stated that they had "considerable experience" with the method and that it could be used "to make rapid diagnoses for the operating theatre and the post-mortem room."[24] This technique never reappeared in the literature and there is little evidence to suggest that it was used extensively for diagnosis in the course of operations.

The first well-documented use of frozen sections during operations in Great Britain was in early 1899. The pathologist Ernest H. Shaw and the surgeon Charles Barrett Lockwood developed their technique at the Great Northern Central Hospital in London.[25] Little is known about Shaw, but Lockwood was a four-time Hunterian professor at the Royal College of Surgeons; former president of the Anatomical Society, the Medical Society of London, and the Harveian Society of London; and consulting surgeon to St. Bartholomew's Hospital.[26] Lockwood had been routinely using frozen sections for

[20] Pick, "Weitere Abkürzung," esp. p. 228.

[21] Cullen, "Rapid method," footnote p. 109.

[22] Helen Clapesattle, *The Doctors Mayo* (Minneapolis: University of Minnesota Press, 1941), pp. 242–46; C. Alexander Hellwig, "Biopsy in tumors," *Arch. Path.*, 1932, *13:* 607–53, esp. p. 621; Waltman Walters, "Early interest in general surgery," *Proc. Mayo Clinic,* 1964, *39:* 656–61, esp. p. 657; Paul Starr, *The Social Transformation of American Medicine* (New York: Basic Books, 1982), p. 210; Joseph C. Bloodgood, "Biopsy in diagnosis of malignancy," pp. 18–28, esp. p. 23.

[23] Alfredo A. Kanthack and T. Strangeways Pigg, "Boiling water as a fixative and hardening agent—the revival of an old histological method for rapid diagnosis," *Trans. Path. Soc. London,* 1897, *48:* 279–82.

[24] *Ibid.*, p. 279.

[25] Ernest H. Shaw, "The immediate microscopic diagnosis of tumours at the time of operation," *Lancet,* 1910, *2:* 939–42; Charles B. Lockwood, *Cancer of the Breast: An Experience of a Series of Operations and Their Results* (London: Henry Frowde, Hodder & Stoughton, 1913), pp. 79–107.

[26] Eric C. O. Jewesbury, *The Royal Northern Hospital, 1856–1956: The Story of a Hundred Years' Work in North London* (London: H. K. Lewis, 1956); "Charles Barrett Lockwood, F.R.C.S. Eng.," *Lancet,* 1914, *2:* 1217–18.

diagnosis since 1899 but he did not publish a description of the technique until 1904 when his lecture, "Early microscopical diagnosis of tumours" was printed in the *British Medical Journal*.[27] It is possible that Lockwood was simply unconcerned about receiving credit for the discovery, but it is more likely that he knew that others had published their results before him, particularly since Pick had published his article in the *British Medical Journal* in January 1897. Lockwood never acknowledged a source for his idea of using frozen sections for diagnosis during operations, and it is possible that he developed it independently. Irrespective of this, Lockwood was probably the first general surgeon to employ diagnostic frozen sections routinely. Cullen, Plenge, and Pick used their techniques primarily for gynecological surgery.

The Shaw-Lockwood technique differed in that formalin was not used. Apparently Shaw had worked at a hospital in which all tissue specimens, both from operations and autopsies, were regularly prepared as frozen sections after they had been hardened in alcohol or Müller's fluid.[28] After years of experience, Shaw could produce good sections in as short a time as two minutes. It is interesting to note that the Shaw-Lockwood technique, as described in 1904, utilized methylene blue, the stain that Louis B. Wilson reported a year and half later to be the key to his method.[29]

The Mayo Frozen Section Story. According to Helen Clapesattle, the technique of frozen sections during operations was developed by Louis B. Wilson at the Mayo Clinic in 1905. Wilson had been hired in 1904, when the Mayos decided they needed a well-trained, full-time pathologist to organize and develop their pathology laboratory. By offering a larger salary, an unlimited laboratory budget, and academic freedom, the Mayos were able to attract to the position Louis B. Wilson, the assistant director of the bacteriological laboratory of the Minnesota State Board of Health. Wilson began his new duties on 1 January 1905. Later that month, William Mayo said to him, "I wish you pathologists would find a way to tell us surgeons whether a growth is cancer or not while the patient is still on the table."[30] Wilson realized that a quick method of hardening tissue specimens was needed for making rapid sections. He decided that the frozen section, distrusted by most tissue pathologists, might provide the solution, and he began to examine the literature and to experiment with the various published methods occasionally used in

[27] Charles B. Lockwood, "A clinical lecture upon the early microscopical diagnosis of tumours," *Brit. Med. J.*, 1904, *2*: 5–8.

[28] Ernest H. Shaw, "The immediate microscopic diagnosis of tumours at the time of operation," *Lancet*, 1923, *1*: 218–23.

[29] Michael F. Gavin, "The work in surgical pathology of the pathological and surgical departments," *Med. Surg. Rep. Boston City Hosp.*, 1900, *11*: 158–72. The surgical pathology laboratory at Boston City Hospital under Frank B. Mallory and William T. Councilman (who had recently left Hopkins) was also using frozen sections stained with methylene blue prior to Wilson's discovery. Gavin reported that frozen section diagnosis could be obtained in four minutes.

[30] Clapesattle, *Doctors Mayo*, p. 444.

autopsy pathology.[31] None, however, provided differential staining that was adequate for surgical diagnosis.

Wilson had been a high school biology teacher for eight years before entering medical school and had extensive experience with botanical techniques. He relied upon these skills in the development of his own method. He mounted tissue specimens in elder pith, placed them outside the window for a few minutes to freeze, cut sections freehand with a razor, stained them, and mounted them on glass slides with a glucose mixture used for botanical materials. He experimented with various stains until he settled upon methylene blue, a supravital (i.e., used on living cells) dye used in bacteriology and botany. Wilson was pleased by the cellular detail retained with this technique and attributed his success to the use of this stain. He purchased a freezing microtome to facilitate the preparation of his frozen sections. For several months, he practiced the technique and his diagnostic skills on normal and diseased fresh tissue. He compared his fresh tissue diagnoses with those obtained using ordinary methods. By the end of April, Wilson was diagnosing surgical specimens within five minutes of the time they were removed from the patient, and the Mayos were able to use these reports to guide them through difficult operations.[32]

On 2 December 1905, Wilson published an account of his work in the *Journal of the American Medical Association*.[33] In his article, he stated that he had been using his new technique routinely on surgical specimens for six months with about the same diagnostic accuracy as with fixed tissue. The advantage of the new method was that "the whole process can be gone through in one and a half minutes from the time the tissue is placed on the freezing plate of the microtome until the stained specimen is on the stage of the microscope. The resulting coloring is uniformly good with the tissue elements sharply contrasted in red, purple, and dark blue."[34] This paper is commonly regarded as marking the beginning of tissue diagnosis during operations in surgical pathology.[35] Although Wilson never claimed priority for his idea, he also did not cite the contributions of others in assisting the development of his technique. Wilson's method was not the first frozen section technique, but it soon became the most widely known.

Distrust of the Frozen Section Technique. Despite the efforts exerted in pathology laboratories in the United States to develop a rapid diagnostic tool, none of the methods described above had much immediate impact. Most of the authors of standard American textbooks of pathological techniques in

[31] *Ibid.*, p. 445.

[32] *Ibid.*, pp. 445–46. No archival records exist at the Mayo Foundation to document these events further.

[33] Louis B. Wilson, "A method for the rapid preparation of fresh tissues for the microscope," *JAMA*, 1905, *45*: 1737.

[34] *Ibid.*

[35] Hellwig, "Biopsy in tumors," p. 621; Clapesattle, *Doctors Mayo*, pp. 442–46; Walters, "Early interest in general surgery," p. 657; Starr, *Social Transformation of American Medicine*, p. 210; William J. Mayo, "The story of the fresh frozen section," *Proc. Staff Meeting Mayo Clinic*, 1929, *4*: 274–75.

the early twentieth century mentioned that they existed, but minimized their significance. Francis Delafield and T. Mitchell Prudden's *A Handbook of Pathological Anatomy and Histology* included both Cullen's procedure and one of its modifications, but the authors concluded that the procedures took "a little more than an hour" and offered only "a fair chance for an early morphological diagnosis."[36] Aldred S. Warthin, in his *Practical Pathology for Students and Physicians* asserted that "stained sections may be had in a few minutes after removal of the tissue from the body" and that for "quick diagnostic work it has no equal. It may with advantage form part of the fittings of an operating room and the material examined on the spot." But he qualified these comments by stating, "Its application is chiefly for quick and rough diagnostic work, and even here it is subject to certain limitations."[37] By the time the second edition of his text was published in 1911, his opinion was even more negative:

> It must be emphasized here that the process of freezing is an active one, and alters the relation of cell structures. With many fresh tissues the changes resulting from the freezing are so great that no diagnosis can be made. It seems necessary here to warn against the routine employment of the rapid method of freezing and staining fresh tissues in the diagnosis of material obtained by surgical operation. It has become a fad with some surgeons to make a pathologic diagnosis by the freezing method while the patient is on the table. Consequently as the result of diagnoses made by the rapid freezing and staining method, many mistakes are made, even by supposed experts in this line.[38]

Other popular textbooks of pathological technique described one or more methods for making frozen sections but offered no insight into their usefulness for quick diagnosis. Wilson's fresh frozen section technique was conspicuously absent from these works; none of the standard pathology references even described it. Prior to 1925, few academic pathologists and none of the standard pathology textbook authors regarded the use of frozen sections during operations as an important technique.[39] In fact, perhaps the

[36] Francis Delafield and T. Mitchell Prudden, *A Handbook of Pathological Anatomy and Histology*, 6th ed. (New York: William Wood, 1901), pp. 51–52.

[37] Aldred S. Warthin, *Practical Pathology for Students and Physicians* (Ann Arbor, Mich.: George Wahr, 1897), p. 17.

[38] Aldred S. Warthin, *Practical Pathology for Students and Physicians*, 2nd ed. (Ann Arbor, Mich.: George Wahr, 1911), pp. 215–16.

[39] Frank B. Mallory and James H. Wright, *Pathologic Technique: A Practical Manual for Workers in Pathological Histology and Bacteriology Including Directions for the Performance of Autopsies and for Clinical Diagnosis by Laboratory Methods*, 7th ed. (Philadelphia: W. B. Saunders, 1918), pp. 20–22, 33–35; Francis C. Wood, Karl M. Vogel, and Lemuel W. Famulener, *Laboratory Technique* (New York: James T. Dougherty, 1922), p. 12; U.S. Surgeon-General's Office, *Laboratory Methods of the United States Army*, 2nd ed. (Philadelphia: Lea & Febiger, 1919), pp. 61–64. John A. Kolmer and Frederick Boerner, *Approved Laboratory Technic: Clinical Pathological, Bacteriological, Serological, Biochemical, Histological* (New York: D. Appleton-Century, 1931), esp. pp. 612–14, was the first pathology methods textbook to describe Wilson's method. This book was prepared under the auspices of the American Society of Clinical Pathologists (discussed later), an organization in which Mayo Clinic personnel were very active. The authors stated in the preface of their textbook that originally they had intended to omit histological methods but that "it is particularly gratifying to be able to include a chapter on Methods for the Microscopical Examination of Tissues by Dr. William C. MacCarty and Dr. W. L. A. Wellbrook."

only laboratory methods textbook strongly advocating quick diagnostic frozen sections was written specifically for general practitioners.[40]

Promotional Efforts by the Mayo Clinic Personnel. From about 1925 to 1935, a debate over the merits of the new frozen section technique was conducted in medical and surgical journals. Wilson set the stage for this battle. In an attempt to gain recognition for his technique, he published a series of papers on frozen section diagnosis. His papers appeared in many regional, as well as various specialty, journals. Wilson also presented or discussed his technique at many meetings of regional medical and surgical societies.[41]

Nor was Wilson the only physician describing his technique. Other pathologists and surgeons at the Mayo Clinic published articles endorsing the validity and importance of Wilson's procedure. For example, William C. MacCarty, head of the section on surgical pathology at Mayo after 1909, published more than a dozen articles relating to the topic. Another surgical pathologist at the Clinic, Albert C. Broders, also published a series of articles advocating this diagnostic tool. He developed a system for grading the severity of tumors from the frozen sections made, further enhancing the value of the technique by offering some insight into the patients' prognoses.[42] Even the renowned William J. Mayo added to this promotional effort by writing several favorable editorials.[43]

The early success of the Mayo Clinic has often been attributed to the ability of the Mayos to generate publicity. It is unlikely that many national or regional meetings at which surgical diagnosis or surgical pathology were discussed took place without a surgeon or surgical pathologist representing the Mayo Clinic. As late as 1953, a physician from the Division of Surgical Pathology at the Mayo Clinic was still publishing descriptions of its frozen section technique.[44] Moreover, thousands of domestic and foreign physicians

[40] Byron G. R. Williams and Edwin G. C. Williams, *Laboratory Methods With Special Reference to the Needs of the General Practitioner,* 3rd ed. (St. Louis: C. V. Mosby, 1917), pp. 78–82. Byron Williams was a general practitioner in Illinois and Edwin Williams was a former pathologist at the Northern Michigan Hospital for the Insane in Traverse City, Michigan.

[41] Louis B. Wilson, "The hospital laboratory with special reference to diagnosis in surgical cases," *St. Paul Med. J., 1910, 12:* 233–38; *idem,* "The microscopic examination of fresh tissues for the diagnosis of early cancer," *St. Paul Med. J.,* 1913, *15:* 274–78; *idem,* "Laboratory efficiency," *Indianapolis Med. J.,* 1913, *16:* 512–17; *idem,* "On staining fresh tissues for diagnostic purposes," *Internat. Assoc. Med. Museums Bull.,* 1915, *5:* 105; *idem,* "Staining sections of living tissue, unfixed," *J. Lab. Clin. Med.,* 1915, *1:* 40–45; *idem,* "Microscopic examination of fresh tissue, and necropsy service in relation to surgery," *Trans. South. Surg. Assoc.,* 1924, *37:* 241–48; and *idem,* "Microscopic examination of fresh tissue, and necropsy service in relation to surgery," *Ann. Surg.,* 1925, *81:* 863–68.

[42] Mayo Clinic, Rochester, Minn., *Physicians of the Mayo Clinic and the Mayo Foundation* (Minneapolis: University of Minnesota Press, 1937). See, for example, William C. MacCarty, "The diagnostic reliability of frozen sections," *Amer. J. Path.,* 1929, *5:* 377–80; Albert C. Broders, "The grading of cancer and its practical application," *Arch. Path. Lab. Med.,* 1926, *2:* 376–81.

[43] William J. Mayo, "The diagnostic value of microscopic examination of fresh frozen tissue," *Surg. Gynecol. Obstet.,* 1929, *49:* 859–60 and Mayo, "Story of the fresh frozen section," pp. 274–75.

[44] Malcolm B. Dockerty, "Rapid frozen sections: technique of their preparation and staining," *Surg. Gynecol. Obstet.,* 1953, *97:* 113–20.

who trained at the Mayo Clinic during the first third of the twentieth century carried away with them knowledge of Wilson's technique. Many Mayo alumni published articles or editorials supporting rapid frozen section diagnosis of biopsies.[45] In addition, laboratory diagnosis was a common topic of discussion at weekly staff meetings, the proceedings of which were published for alumni. Therefore, the staff of the Mayo Clinic played a major role in the promotion of the frozen section technique.

Bloodgood Promotes the Frozen Section. According to his peers, Joseph Colt Bloodgood at Johns Hopkins was the individual most responsible for promoting the routine use of rapid frozen sections during operations,[46] and the timing of his journal discussions of the topic confirms this impression. Early in his career, Bloodgood advocated the "naked-eye" recognition of tumors in situ, was opposed to biopsies with frozen section diagnosis, and was ambivalent about frozen sections.[47]

In 1925, Bloodgood began a public reversal of his opinion concerning the necessity of biopsy with frozen section diagnosis.[48] In his address as chairman of the section on surgery of the Southern Medical Association in November 1926, he noted that in the past five years he had become increasingly dependent on the use of frozen sections in the operating room.[49] By early 1927, Bloodgood had begun an aggressive campaign to promote frozen section diagnosis as a routine procedure and a mandatory standard to which the surgical profession should adhere. He wrote editorials, letters to colleagues, and manuscripts; he made platform presentations, and personal demonstrations of the technique.

His campaign began with an editorial in *Surgery, Gynecology and Obstetrics* asking that any "pathologists and surgeons interested in the immediate examination of tissue by frozen section in the operating room" contact him. Identical editorials appeared in the *Atlantic Medical Journal,* the *Virginia Medical Monthly,* and *California and Western Medicine.* It was also submitted

[45] Byrd Charles Willis, "The importance of a positive diagnosis in surgery by means of frozen sections," *Trans. Med. Soc. Virginia,* 1911, *42:* 114–16; Byrd Charles Willis, "The importance of frozen section in surgery," *Southern Med. Surg.,* 1929, *91:* 459–60; Pietro Frugoni, "In tema di cancro," *Archivio Ital. Chir.,* 1936, *44:* 577–88; Sidney J. S. Peirce, "On the technique of producing frozen sections for rapid diagnosis," *Internat. Assoc. Med. Museums Bull.,* 1915, *5:* 106–8; William L. A. Wellbrook, "The value of biopsy," *J. South Carolina Med. Assoc.,* 1932, *28:* 79–80; Harold D. Caylor, "The advantage of early examination of diseased tissue," *J. Lab. Clin. Med.,* 1928, *13:* 708; Harold D. Caylor and Truman E. Caylor, "An apparatus to facilitate the preparation of fresh frozen sections," *J. Lab. Clin. Med.,* 1930, *16:* 312–13; Harold D. Caylor and Allen A. C. Nickel, "Technical considerations of fresh and fixed frozen sections," *Med. J. Rec.,* 1932, *136:* 339–40.

[46] Hellwig, "Biopsy in tumors," pp. 621–22; Walter M. Simpson, "The frozen section fetish," *Amer. J. Clin. Path.,* 1937, 7: 96–102, esp. p. 102.

[47] Bloodgood, "Relation of surgical pathology to surgical diagnosis," pp. 337–52; *idem,* "Diagnosis and treatment of borderline pathological lesions," *Trans. Amer. Surg. Assoc. (Phila.),* 1913, *31:* 356–92; *idem,* "Diagnosis of cancer," *Boston Med. Surg. J.,* 1917, *176:* 317–18.

[48] Joseph C. Bloodgood, "Prevention, diagnosis and treatment of cancer in its earliest stages," *Southern Med. J.,* 1926, *19:* 287–92.

[49] Bloodgood, "Biopsy in diagnosis of malignancy," p. 23.

to the *American Journal of Pathology* but was rejected on the grounds that the journal did not print editorials.[50]

In another editorial in *Surgery, Gynecology and Obstetrics,* Bloodgood attacked small hospitals that did not have pathologists and hospitals without facilities for frozen sections:

> It is time now for the [American] College [of Surgeons] and the surgeons to take up this problem. In every operating room in this country either these operations requiring frozen-section diagnosis should not be done and referred elsewhere, or that hospital or that group of hospitals in one locality should prepare for this frozen-section diagnosis. Incomplete operation and delayed pathological diagnosis are dangers to the American public, and they are no longer necessary evils. This equipment should be part of the minimum requirements of every hospital in which operations of this character are performed.[51]

Also in 1927, Bloodgood offered a blanket invitation to all of the readers of the *Journal of the American Medical Association* who were interested in learning about "tissue diagnosis in the operating room" to come to the Surgical Pathological Laboratory of the Johns Hopkins Hospital for a demonstration on the Saturday following the annual American Medical Association meeting in Washington.[52] Although no records of attendance exist, the demonstration must have been successful because he repeated the offer again in 1930, but this time for a three-day period, and by form letter invitation and reservation only. Attendance was limited to forty persons per day, and participants were required to bring their own microscopes.[53] Thereafter, the demonstrations were offered several times yearly "through the generous financial aid of Francis P. Garvin, president of the Chemical Foundation."[54]

Bloodgood also published various papers dealing with the topic in both surgery and pathology journals. In an article in the *Southern Medical Journal* in 1928, Bloodgood asserted:

> To increase accuracy and diminish the element of error, the diagnosis of tissue in the operating room by any rapid method of cutting and staining must depend upon its routine employment, whether this is essential for diagnosis or not. The method must not be used only as an emergency when diagnosis is essential. . . . When tissue diagnosis in the operating room is a routine instead of an emergency occurrence, then the element of error in the interpretation of a section

[50] Joseph C. Bloodgood, "Tissue diagnosis in the operating room and immediate cover-slip examination of all fluids and pus," *Surg. Gynecol. Obstet.,* 1927, *44:* 838; and also *Atlantic Med. J.,* 1927, *30:* 386–87; *Virginia Med. Month.,* 1927, 805–6; *Calif. West. Med.,* 1927, *26:* 347. Frank B. Mallory to Joseph C. Bloodgood, 19 February 1927, Bloodgood to Mallory, 22 February 1927, Joseph C. Bloodgood Papers, The Alan Mason Chesney Medical Archives, The Johns Hopkins Medical Institutions, Baltimore, Maryland.

[51] Joseph C. Bloodgood, "The danger of incomplete removal of small and apparently innocent lesions," *Surg. Gynecol. Obstet.,* 1927, *44:* 413–14.

[52] Joseph C. Bloodgood, "When cancer becomes a microscopic disease, there must be tissue diagnosis in the operating room," *JAMA,* 1927, *88:* 1022–23.

[53] Joseph C. Bloodgood to Colleagues, 15 May 1930, Bloodgood Papers.

[54] Joseph C. Bloodgood, "Biopsy in the treatment of malignancy," *J. Lab. Clin. Med.,* 1931, *16:* 692–703, esp. p. 701.

> obtained in five or ten minutes is no greater than one obtained from a section carefully prepared with an interval of one or more days' delay. . . . Tissue diagnosis in the operating room will have a very great educational value, if it is properly done. All the surgeons in the operating room will have an opportunity to compare, in a very short time, clinical, gross and microscopic pictures.[55]

Although Bloodgood felt very strongly that tissue diagnosis in the course of operations was necessary, he offered no firm opinion concerning which method was best. He stated that for many years he had used the method of boiling the tissue in formalin prior to cutting frozen sections, but, for the past several years, he had used the fresh frozen section stained with polychrome methylene blue. He also cited advantages of the methods of Terry, Shaw, and Dudgeon (discussed below). Finally, he suggested that, regardless of the method used, the operating room section should be checked later against a paraffin section.[56]

Bloodgood introduced the idea of placing the freezing microtome, slides, coverslips, fixatives, stains, and a two-headed microscope on a cart that could be rolled from one operating room to another. He suggested that this apparatus would save time, because the tissue specimen would not have to be carried to the laboratory. The portable apparatus, he pointed out, would also permit the surgeon to view the section "without impairing surgical cleanliness." This arrangement became known as "the Bloodgood portable frozen section table."[57]

In an editorial published in 1929, Bloodgood attributed his change in attitude concerning frozen section diagnosis to an enlightened public attitude toward cancer and a willingness to seek the surgeon's help earlier:

> Before 1915 it was rarely necessary for a surgeon well trained in gross pathology to need a frozen section to help him in diagnosis at the operating table. Since 1915, and especially since 1922, the public has become so enlightened that malignant disease formerly easily recognized either clinically or in the gross, now appears in our operating rooms devoid of its easily recognized clinical and gross appearance and can be properly discovered only by an immediate frozen section.

He stated that the records at the Johns Hopkins Hospital indicated that prior to 1900 more than 50 percent of cancers were inoperable when diagnosed, whereas after 1920, this percentage had decreased to less than five.[58]

[55] Joseph C. Bloodgood, "Tissue diagnosis in the operating room," *Southern Med. J.*, 1928, *21*: 179–84, esp. pp. 179, 182.

[56] *Ibid.*

[57] *Ibid.*, George S. Foster, "The Bloodgood portable frozen section table," *Med. Times Long Island Med. J.*, 1931, *59*: 111–12; Harold D. Caylor and Truman E. Caylor, "An apparatus to facilitate the preparation of fresh frozen sections," *J. Lab. Clin. Med.*, 1930, *16*: 312–13; Arthur S. Brumbaugh, "Technical difficulties in biopsy diagnosis," *Int. J. Med. Surg.*, 1933, *46*: 484–85.

[58] Bloodgood, "Tissue diagnosis in the operating room and examinations of fluids and pus," p. 838. This statement, although certainly not true by today's standards, is typical of the optimism of many members of the surgical profession in the early twentieth century.

Another factor affected Bloodgood's slow acceptance of the validity and importance of the frozen section technique. Bloodgood never recognized the fact that Thomas Cullen had developed the first technique for frozen section diagnosis during operations, though they were longtime friends. They had studied pathology together at Hopkins during the early 1890s and in Germany in 1893. Bloodgood and Cullen became directors of surgical pathology and gynecological pathology, respectively, at Hopkins. They were actively involved in educating the American public concerning cancer diagnosis and treatment through their activities in the American Society for the Control of Cancer. Yet Bloodgood credited Louis B. Wilson with developing the first useful frozen section technique. In one of his papers, Bloodgood described the early history of the technique and noted that he had experimented with it himself after returning from Germany in 1893. In his account, Bloodgood fails to mention Cullen's 1895 paper and continued his brief history by describing this case:

> In 1896, at the invitation of Dr. Weir, of New York, then Professor of Surgery at Columbia, I was present at a private operation, at which he explored and removed an encapsulated tumor of the breast. One of the best New York pathologists was present and made a frozen section. It was Dr. Weir's opinion that the tumor was a benign encapsulated adenoma. The pathologist was as firmly convinced that it was adenocarcinoma. Weir acted on his own diagnosis. This case is recorded in my laboratory. The patient whose breast was saved is living today.[59]

It is likely that the technique used in the operation was that of Cullen and that the pathologist's failure to make the correct diagnosis amused Bloodgood and prompted him to save the slide.[60]

It is apparent that Bloodgood and Cullen were competing to perfect a rapid frozen section technique and that Cullen won. Bloodgood, a surgeon, would not recognize this achievement of Cullen, a gynecologist, and minimized the significance of the frozen section for more than thirty years, maintaining that it was no better than naked eye diagnosis. Only in 1927 did Bloodgood finally admit its value and begin to promote the frozen section. The following letter from Cullen to Bloodgood, shortly after Bloodgood published his first two editorials promoting the frozen section technique, demonstrates Cullen's rebuttal of Bloodgood's selective memory:

> March 18, 1927
>
> My dear Joe,
>
> I am just in receipt of your letter of March 14th together with your letter of Feb. 3rd on Tissue Diagnosis in the Operating Room. I think it presents the subject very well. There is only one thing that an objection might be raised to

[59] Bloodgood, "Biopsy in diagnosis of malignancy," p. 23.

[60] Cullen's technique was well known to New York pathologists; see Hodenpyl, "Modification of Cullen's method," p. 351. Since Bloodgood was able to retain a permanent slide, the tissue was probably fixed in formalin (i.e., Cullen's technique).

and that is the beginning of paragraph three where you say "Before 1915 it was rarely necessary for a surgeon well trained in gross pathology to need a frozen section to help him in diagnosis at the operating table." If you do not include gynecologists as surgeons then no objection could be raised, but if you do include them as surgeons frozen sections of scrapings have been carried out and have been deemed essential in our Department at least at Hopkins since 1896.

With best regards and looking forward with pleasure to our trip on Monday,

Ever yours,
Thomas S. Cullen[61]

Improvements in the Frozen Section Technique. Since medical personnel generally believed that the cytologic fidelity of frozen sections was inferior to that of paraffin sections, many dozens of technical improvements were reported in the literature. Although few of these modifications greatly affected the utility of the technique, their numbers show that considerable interest existed in improving diagnostic accuracy.

Cullen's formalin technique was soon replaced by a method first introduced by James Homer Wright of the Massachusetts General Hospital. Wright quickly fixed the fresh tissue by boiling it in formalin for several minutes before freezing it and cutting sections, a modification that greatly improved morphological definition.[62] Karl Walz introduced a similar technique, which he called the "Kochmethode," in 1919. Walz, a prosector at Katharinen Hospital in Stuttgart, Germany, stated that he had developed the method because of shortages of gas, electricity, and paraffin during World War I.[63] Many others recognized the importance of the quick fixation in hot formalin and adopted the procedure.[64] According to Leopold Reiner, a pathologist at Beth Israel Hospital in Boston, the prefixation in boiling formalin was, to his knowledge, "the most widely used rapid section technic among pathologists" in the United States.[65] Walz's "Kochmethode" was, on the other hand, the most popular technique in Europe.[66]

[61] Thomas S. Cullen to Joseph C. Bloodgood, 18 March 1927, Bloodgood Papers.

[62] James H. Wright, "Eine schnelle Methode zur dauernden Aufbewahrung gefrorener Schnitte," *Zentralbl. Allg. Path.*, 1901, *12:* 634–35. Cullen's method was quickly forgotten. It was cited only once in the frozen section literature after 1901. Priority for Wright's method is generally attributed incorrectly to Karl Walz; see Karl Walz, "Ueber pathologisch-histologische Momentdiagnose," *Zentralbl. Allg. Path.*, 1919, *30:* 442–43.

[63] Walz, "Ueber pathologisch-histologische Momentdiagnose." Walz's abstract does not state that his sections were cut on a freezing microtome. In fact, it asserts that frozen sections are unreliable. However, others using the "Kochmethode" call it a frozen section method.

[64] S. Hoffheinz, "Zur Technik der histologischen Schnelldiagnose," *Zentralbl. Chir.*, 1927, *54*(*2*): 2498–501; Alphonse A. Thibaudeau, "The preparation and staining of frozen sections," *J. Lab. Clin. Mea.*, 1933, *19:* 204–9; Rutherford B. H. Gradwohl and Aram A. Krajian, "The frozen section method of tissue diagnosis: the method of choice," *Gradwohl Lab. Digest,* 1941, *4:* 11–15; Eugene Hildebrand and Ester L. Cheatle, "Frozen sections," *Amer. J. Clin. Path. Techn. Sect.,* 1946, *10:* 69; Lester M. Friedland, "A note on frozen section technic," *Amer. J. Clin. Path.,* 1951, *21:* 797.

[65] Leopold Reiner, "Principles of rapid frozen sectioning with a method of prefixation using undiluted formalin at 60° C," *Lab. Invest.,* 1953, *2:* 336–48.

[66] Hellwig, "Biopsy in tumors," pp. 622–23; J. Escalona Zapata, "La biopsia intraoperatoria: analisis critico," *Acta Oncol.* (Madrid), 1968, *7:* 229–37.

Wilson's technique continued to be used at the Mayo Clinic and elsewhere essentially unchanged until 1931, when Albert C. Broders, director of the Mayo Clinic's surgical pathology section B after 1922, recommended modifying the mounting medium.[67] Wilson's method did have two major disadvantages. First, the staining characteristics of methylene blue were often unacceptable to those accustomed to examining hematoxylin and eosin stains in paraffin sections, because adjustment to an unfamiliar color scheme was required. Those willing to adapt suggested that comparing fixed frozen sections to those prepared by Wilson's method was like comparing raisins to grapes.[68] But the main problem with Wilson's technique was the impermanence of the rapid sections. Wilson used neither a fixative nor a permanent stain. As a result, the slides dried out in a few hours. James W. Kernohan, a pathologist at the Mayo Clinic, further modified Wilson's method by sealing the edges of the cover slips with a quick-drying lacquer to slow the evaporation process, but this prolonged the life of the slide by at most several weeks.[69] Other changes were few. David C. Dahlin, a surgical pathologist at the Mayo Clinic, reported in 1980 that the technique used at the Clinic was essentially unaltered from that of Wilson.[70]

The most significant technical advance in the preparation of frozen sections was suggested by Otto Schultz-Brauns of the Pathological Institute at the University of Bonn in 1931. Schultz-Brauns used compressed carbon dioxide not only to freeze the tissue, as many had done before, but also to cool the microtome knife to minus five degrees centigrade. As a result, sections were less likely to stick to the knife and could be attached to room temperature glass slides by merely touching the slides to the knife. This eliminated two difficult tasks: first, removing each section from the knife with a camel's hair brush or glass rod and moving it through a series of fixatives, alcohols, water baths, stains, and so on; and, second, gluing each section to the glass slide after it had been stained. With this technique, even those with little manual dexterity could make good frozen sections.[71] The obvious advantages of the Schultz-Brauns method led to its immediate widespread ac-

[67] Albert C. Broders, "Modification of Wilson's fresh frozen section technic," *J. Lab. Clin. Med.*, 1931, *16:* 734–38.

[68] C. Alexander Hellwig, "Tissue diagnosis during operation: reliability of Terry's supravital technique in 1030 biopsies," *Surg. Gynecol. Obstet.*, 1935, *61:* 494–98, esp. pp. 494, 496.

[69] James W. Kernohan, "Method of temporarily preserving fresh frozen sections stained with polychrome methylene blue," *Amer. J. Clin. Path.*, 1936, *6:* 195.

[70] David C. Dahlin, "Seventy-five years' experience with frozen sections at the Mayo Clinic," *Mayo Clinic Proc.*, 1980, *55:* 721–23.

[71] Otto Schultz-Brauns, "Eine neue Methode des Gefrierschneidens für histologische Schnelluntersuchungen," *Klin. Wochnschr.*, 1931, *10:* 113–16; *idem,* "Verbesserungen und Erfahrungen bei Anwendung der Methode des Gefrierschneidens unfixierter Gewebe," *Zentralbl. Allg. Path.*, 1932, *54:* 225–34; *idem,* "Histotopochemische Untersuchungen an krankhaft veränderten Organen unter Anwendung der Schnittveraschung," *Virchow's Arch.*, 1929, *273:* 1–50; *idem,* "Die Methode der Schnittveraschung unfixierter tierischer Gewebe," *Z. Mikrosk.*, 1931, *48:* 161–91; *idem,* "Die Vorteile des Gefrierschneidens unfixierter Gewebe für die histologische Technik," *Zentralbl. Allg. Path.*, 1931, *50:* 273–77.

ceptance in Europe and at some American laboratories.[72] Surprisingly, when in 1947 Frank B. Adamstone and Aubrey B. Taylor introduced a conceptually similar, but very cumbersome technique, it was received by some Americans as if they were totally unfamiliar with the Schultz-Brauns cooled knife method.[73]

Techniques Competing with the Frozen Section Method. Recognition of the value of tissue diagnosis during operations is suggested by the number of competing methods of making sections that were developed at the same time as the frozen section.[74] Pathologists recognized the major shortcomings of frozen section diagnosis; some tried to improve the method, while others designed alternative methods for rapid tissue diagnosis.

The most important of the competing techniques was the razor section method of Benjamin T. Terry, professor of pathology at Vanderbilt University. Terry had seen MacCarty demonstrate Wilson's fresh frozen section technique while visiting the Mayo Clinic in 1919. He was particularly impressed by the supravital properties of Unna's polychrome methylene blue stain. He was told that the World War had made it difficult to obtain this high quality stain from Germany. Terry, who wished to use the stain in his laboratory work, was determined "to learn how to ripen" (i.e., polychrome) the generic methylene blue stain available in the United States. He found that heating improved its staining qualities and published a description of his method in 1920, after which it was adopted at the Mayo Clinic.[75] Thus began a long and mutually beneficial relationship between Terry and the surgical pathologists at the Mayo Clinic.

Terry continued to experiment with rapid diagnostic techniques and discovered that his polychrome methylene blue stain, when applied to a

[72] S. Zethraeus, "Modifikation der Schultz-Braunsschen Gefrierschnittmethode," *Ztschr. Wissensch. Mikr.*, 1937, *54:* 408–11; Escalona Zapata, "Biopsia intraoperatoria," pp. 229–37; S. Carl Werch, "The use of liquid air in cooling knives and of gelatin for mounting in frozen section technic," *J. Lab. Clin. Med.*, 1936, *21:* 1309; Wilhelm C. Hueper, "A simplification of the cooled knife method (Schultz-Brauns) for obtaining frozen sections," *Arch. Path.*, 1933, *16:* 670–71.

[73] Frank B. Adamstone and Aubrey B. Taylor, "A method for the rapid preparation of frozen tissue sections," *Anat. Rec.*, 1947, *99:* 639; Frank B. Adamstone and Aubrey B. Taylor, "The rapid preparation of frozen tissue sections," *Stain Technol.*, 1948, *23:* 109–16; Herbert Mescon, Herman Beerman, and Fred D. Weidman, "Adaption of the Adamstone-Taylor frozen section technic for rapid diagnosis of skin lesions," *J. Invest. Dermatol.*, 1951, *16:* 429–35; Edgar B. Taft, "An evaluation of the Adamstone-Taylor frozen section technic for use in routine surgical pathology," *Amer. J. Path.*, 1949, *25:* 824.

[74] William E. B. Hall, "Advances in rapid tissue section methods: an evaluation of more recently developed techniques," *Amer. J. Surg.*, 1938, *41:* 458–61; George T. Mowat, "Rapid histology in diagnosis," *Trans. Royal Med.-Chir. Soc. Glasgow*, 1930, *31:* 120–22; Escalona Zapata, "Biopsia intraoperatoria," pp. 229–37.

[75] Benjamin T. Terry, "Increasing the pathologist's usefulness and his rewards with directions for preparation and use of a polychrome methylene blue stain for frozen sections," *JAMA*, 1920, *74:* 1775–77; *idem*, "The rapid preparation of polychrome methylene blue stains for frozen sections of fresh and fixed tissue," *J. Lab. Clin. Med.*, 1922, *8:* 157–64; William C. MacCarty discussion of Benjamin T. Terry, "A new principle in the microscopic examination of fresh unfixed tissue," *Proc. Staff Meeting Mayo Clinic*, 1926, *1:* 209–11; Benjamin T. Terry, "A new and rapid method of examining tissue microscopically for malignancy," *J. Lab. Clin. Med.*, 1927, *13:* 550–65.

gross specimen, would allow him to see "a small area of malignancy contained in a larger mass of tissue that was not malignant."[76] Since very small tumors could not be seen with the naked eye, Terry developed and improved a technique for the microscopic examination of biopsy specimens stained with his methylene blue.[77] The success of the technique in its final form was based on three characteristics: 1) the supravital properties of polychrome methylene blue previously noted by Wilson; 2) the absence of artifacts caused by freezing, fixing, boiling, or dehydrating the tissue; 3) the histologic detail provided by relatively thick sections stained superficially on one side only and examined microscopically with bright transmitted light. C. Alexander Hellwig of Wichita described the third characteristic as follows: "Since only the upper cell layer is stained and the light is transmitted through the thick, unstained part of the tissue, one has the impression of seeing a perfectly thin microtome section."[78]

The razor section technique offered numerous advantages. First, it was easy to learn and required little manual dexterity. Second, it was extremely rapid. Many razor sections could be produced in the same period of time it would take to produce one frozen section, permitting greater diagnostic certainty. Third, it was easier to correlate gross and histological morphology because the greater thickness of the razor sections did not necessitate total destruction of the gross lesion. Fourth, it was possible to submit the same razor section specimen for later paraffin sections to confirm the rapid diagnosis. Fifth, the method was very inexpensive and easily transportable because it required only a razor blade, stain, glass slides with coverslips, and a microscope. It was ideal for the peripatetic pathologist.

The disadvantages of the technique were essentially the same as those of Wilson's fresh frozen section. The stain faded in minutes, and the sections, because they were not fixed, were not permanent. In addition, the technique did not work on darkly pigmented or extremely vascular tissues because they were opaque.[79]

Terry used his informal connection with the Mayo Clinic to obtain institutional endorsement of his work. On 14 June 1926, he left his wife and family in Nashville and moved to Rochester, Minnesota. For the next two

[76] Benjamin T. Terry, "Polychrome methylene blue used to help locate malignancy in tissues to be examined microscopically," *JAMA*, 1923, *80:* 1774; *idem*, "Rapid provisional microscopic diagnoses of malignancy without a microtome," *JAMA*, 1924, *83:* 1127–29, esp. p. 1127.

[77] Terry, "Rapid provisional diagnoses," pp. 1127–29; *idem*, "Eine verbesserte, schnelle und leichte Methode, fixierte Gewebe für mikroskopische Untersuchungen mit reflektiertem oder durchfallendem Lichte zu präparieren," *Münch. Med. Wochnschr.*, 1924, *71:* 1612–13; *idem*, "Provisorische mikroskopische Diagnose in Weniger als 60 Sekunden ohne Mikrotom," *Med. Klin.*, 1924, *34:* 1179–81; *idem*, "New and rapid method of examining tissue," pp. 550–65; *idem*, "Tissue prepared quickly for microscopic examination by staining razor sections with hematoxylin," *J. Techn. Method.*, 1929, *12:* 1267.

[78] C. Alexander Hellwig, "Rapid tissue diagnosis: comparison of microscopic diagnoses obtained from Terry's razor sections and from paraffin sections in 4,326 biopsies," *Arch. Surg.*, 1941, *42:* 788–94. The quote is on p. 789.

[79] Terry, "New and rapid method of examining tissue," pp. 550–65.

years, he worked in the Division of Surgical Pathology, apparently without pay, and tested his technique against the immense supply of surgical material available at the Mayo Clinic.[80] He concluded that his rapid diagnosis was correct 98 percent of the time.[81]

Terry adopted the promotional strategies of Wilson, MacCarty, Broders, and Bloodgood to publicize his work. From his hotel room at the Damon in Rochester, he corresponded extensively with pathologists who might be interested in his technique and with officials of professional organizations such as the American Medical Association and the American Society of Clinical Pathologists concerning the demonstration of his technique at their annual meetings. He attended numerous professional society meetings where he described his razor section technique during the discussion period following related presentations. Terry was always publicly supportive of Wilson's fresh frozen section technique, and the surgical pathologists of the Mayo Clinic were correspondingly publicly supportive of his method.[82]

Terry corresponded frequently and in friendly terms with Bloodgood concerning his progress in testing his technique at the Mayo Clinic and also concerning the possibility of demonstrating the razor section method "to you and your technicians on your own material and in competition with the methods you are now using."[83] Bloodgood's responses, though polite, were somewhat less cordial. Although he was unable to persuade Bloodgood, Terry had better luck with C. Alexander Hellwig, another influential proponent of the need for rapid diagnostic techniques during operations. Hellwig first observed Terry's technique in 1929, and after testing it thoroughly he substituted it for the frozen section method he had been using.[84] No record of Terry's overseas correspondence is available, but the Terry technique developed a following in Europe. The most prestigious advocate in Europe was Erwin Christeller of the Rudolf Virchow Krankenhaus in Berlin, who tested the reliability of the method and suggested that it opened a new era in the field of biopsy.[85]

[80] Terry is not listed in *Physicians of the Mayo Clinic and the Mayo Foundation*. Furthermore, the Mayo Foundation Historical Unit was unable to verify his employment at the Mayo Clinic.

[81] Benjamin T. Terry, "Improvement in technic and results made in examining microscopically by the razor section method: 2000 malignant tissues," *J. Lab. Clin. Med.*, 1928, *14:* 519–31.

[82] Terry, "New and rapid method of examining tissue," pp. 550–65, esp. p. 563; see also discussion by William C. MacCarty, p. 564; Terry, "New principle in the microscopic examination of fresh unfixed tissue," pp. 209–11; see also discussion, pp. 210–11; Harold D. Caylor, "A new method of examining fresh tissue," *J. Lab. Clin. Med.*, 1927, *12:* 1035.

[83] Benjamin T. Terry to Joseph C. Bloodgood, 9 March 1927, 12 March 1927, 20 March 1927, 3 January 1928. Quote from 12 March 1927. Bloodgood to Terry, 15 March 1927, Bloodgood Papers.

[84] Christian Alexander Hellwig was born in 1889 in Meissen, Germany, and received his M.D. in 1916 at Bonn. His post-graduate training was at Freiburg, Frankfurt-am-Main, and Augustana Hospital in Chicago. From 1924 to 1949, he was the Director of Laboratories and Pathology at St. Francis Hospital in Wichita, Kansas. Hellwig wrote several influential articles on biopsy and rapid diagnostic techniques. Joe J. Lin, director of laboratories, St. Francis Regional Medical Center, personal communication, 6 March 1984. Hellwig, "Tissue diagnosis during operation: Terry's technique," pp. 494–98; Hellwig, "Rapid tissue diagnosis: comparison of Terry's razor sections and paraffin sections," pp. 788–94.

[85] Erwin Christeller, "Erfahrungen mit der verbesserten histologisch-diagnostischen Schnellmethode nach Terry," *Klin. Wochenschr.*, 1928, *7:* 448–50; Jean Sabrazes and Emile Magrou, "Diagnostic histologique quasi

In 1938 in a review of new techniques of rapid tissue diagnosis, William E. B. Hall of St. Louis stated that Terry's razor section method was superior to the others.[86] An essentially identical technique was described in the *New England Journal of Medicine* in 1944 by H. Edward MacMahon, a pathologist at Cambridge Hospital in Massachusetts, and his technician Shirley B. DelVecho. This method was introduced because of a shortage of carbon dioxide cylinders during World War II and was used very effectively by MacMahon at Tufts Medical School and the New England Medical Center until the late 1960s. The technique was still employed at least occasionally in the 1980s by some hospitals in New England and in eastern Canada.[87]

Terry's technique was apparently well received wherever it was tried. According to Terry, "The razor section method has now been tested by many physicians. When they have carried out the technique under my supervision and on favorable tissues, no one has failed. Most doctors make good sections at the first or second attempt."[88] It is unclear why this simple and reliable technique was displaced by the more costly and technically more difficult frozen section. One practical explanation for the demise of the method is that utilization of the technique did not result in a permanent slide for documentation of the diagnosis.[89]

Another competing method of the post-World War I period, Ultropak illumination, enjoyed a moderate popularity in Europe. The Leitz Ultropak Illuminator was an instrument that permitted microscopic examination of the surface of opaque objects. The cut surface of gross biopsy specimens could be stained and examined without further processing. The method offered several advantages. First, it was very rapid because no sections had to be cut. Second, it did not destroy the specimen, as did some other techniques. Therefore, the intact specimen could be submitted later to be processed for paraffin sections to confirm the rapid diagnosis. Third, it allowed

instantané par transillumination de segments, de tissus ou d'organes d'un millimètre environ d'épaisseur badigeonnés, sur la face regardant l'objectif, de bleu de toluidine phénique à 1%," *Ann. Anat. Path.,* 1928, *5:* 963–70. Henrique Parreira, "O método rápido de Benjamin Terry para exames microscópicos," *Lisboa Medica,* 1928, *5:* 345–46; Carlo A. Lang, "Le biopsie e gli accertamenti diagnostici rapidi: contributo al loro trattamento con metodo Terry," *Sperimentale,* 1929, *83:* 63–82; Escalona Zapata, "Biopsia intraoperatoria," pp. 229–37.

[86] Hall, "Advances in rapid tissue section methods," pp. 458–61.

[87] H. Edward MacMahon and Shirley B. DelVecho, "A simple technic for rapid sectioning," *New Eng. J. Med.,* 1944, *231:* 794; James S. Campbell, "An evaluation of a simple rapid-section technic for immediate histologic diagnosis," *New Eng. J. Med.,* 1952, *247:* 611–12. H. Edward MacMahon, formerly chairman of pathology at Tufts-New England Medical Center, personal communication, 18 March 1984; and James S. Campbell, Sir Frederick G. Banting Research Centre, Health and Welfare, Canada, and formerly resident at Tufts-New England Medical Center, personal communication, 28 March 1984 and 29 April 1984.

[88] Terry, "Improvement in technic and results," p. 530.

[89] According to George F. Gray, professor of pathology at Vanderbilt University, (personal communication, 5 March 1984) no one within his department has any personal recollection of either Terry or his method. Departmental records are sketchy prior to 1925 and little is known about Terry. He left Vanderbilt in 1925 and did not return after he left the Mayo Clinic ca. 1928. Gray doubts that Terry's method was used at Vanderbilt for long after Terry left and is certain that it was not used after the mid-1950s. Terry was apparently in private practice in Rochester, Minnesota, after leaving Mayo. In the early 1930s, Terry moved to Tacoma, Washington, and practiced pathology at Tacoma General Hospital.

the pathologist to examine any surface or multiple cut surfaces of the specimen in order to determine more precisely the extent of a malignancy. Although utilized at several major American hospitals by European-born pathologists such as Emmerich von Haam of Tulane University, the technique never became popular in the United States.[90]

Yet another technique for rapid diagnosis during operations was the "wet-film method" introduced in the 1920s by Leonard S. Dudgeon, professor of pathology at the University of London, and C. Vincent Patrick, a surgical resident at St. Thomas's Hospital in London. The method was actually a slight modification of a method of preparing wet-fixed films of protozoa. Dudgeon and Patrick scraped the cut surface of the biopsy specimen, made cytologic smears on glass slides, fixed the slides immediately in Schaudinn's fluid ("while still wet"), and stained them with hematoxylin and eosin. Experienced cytologists could make accurate diagnoses in less than ten minutes. Although the new method was introduced as a general alternative to Ernest H. Shaw's frozen section technique, it appears to have been most popular among gynecologists. Dudgeon's wet film method was a major advance in the field of cytology, but there is little evidence that the technique was used for rapid biopsy diagnosis outside of Great Britain.[91]

In 1929, Reinhold Dengler of the Allgemeinen Offentlichen Krankenhaus at Warnsdorf, Germany, described a technique using teasing, a very early method of tissue preparation that, like freezing, had been largely replaced by fixing, embedding, sectioning, and staining. The production of a teased preparation involved shredding a small tissue specimen as finely as possible with two small needles, placing the tissue on a glass slide in a drop of 1 percent acetic acid, putting a coverslip over the specimen, and examining it under the microscope. Dilute acetic acid was used to accentuate cellular detail and to increase the transparency of the connective tissue. This method, like that of Dudgeon and Patrick, utilized cytology rather than histology. It too was never widely used for rapid diagnosis in operations.[92]

[90] Mowat, "Rapid histology in diagnosis," pp. 120–22; Roger Leroux, "Technique nouvelle pour examens histologiques rapides," *Bull. Assoc. Franç. Étude Cancer,* 1931, *20:* 698–702; Roger Leroux, "L'examen histologique extemporane, technique de l'ultropak," *ibid,* 1938, *27:* 673–78; Georges Gander, "Histoire et cytodiagnostic des tumeurs malignes," *Arquivo Patol.* (Lisbon), 1949, *21:* 439–61; Emmerich von Haam, "The importance of biopsy in the diagnosis of cancer." *New Orleans Med. Surg. J.,* 1934, *87:* 153–58; John J. Clemmer, "Tumor clinic and pathologist," *Amer. J. Surg.,* 1936, *32:* 401–4, esp. p. 402; Escalona Zapata, "Biopsia intraoperatoria," pp. 229–37.

[91] Leonard S. Dudgeon and C. Vincent Patrick, "A new method for the rapid microscopical diagnosis of tumors: with an account of 200 cases so examined," *Brit. J. Surg.,* 1927, *15:* 250–61; *idem,* "A new method for the rapid microscopical diagnosis of tumors," *Internat. Clin.,* 1928, *1:* 220–23; Leonard S. Dudgeon and Norman R. Barrett, "The examination of fresh tissues by the wet-film method," *Brit. J. Surg.,* 1934, *22:* 4–22; Arthur J. Wrigley, "A method of rapid diagnosis of pathological specimens," *J. Obstet. Gynaec. Brit. Empire,* 1932, *39:* 527–38; Joseph Bamforth and Gladstone R. Osborn, "Diagnosis from cells," *J. Clin. Path.,* 1958, *11:* 473–82; Bernard Naylor, "The history of exfoliative cancer cytology," *Univ. Michigan Med. Bull.,* 1960, *26:* 289–96; Joseph Bamforth, "Pioneer work by Professor Dudgeon in cytological diagnosis," *J. Clin. Path.,* 1963, *16:* 395–98.

[92] Reinhold Dengler, "Zur histologischen Schnellerkennung bösartiger Geschwülste," *Zentralbl. Gynäk.,* 1929, *53:* 457–59.

The distrust of rapid frozen sections by several senior pathologists, primarily James Ewing of Memorial Hospital in New York and Aldred Warthin of the University of Michigan, led to much being done to develop rapid paraffin methods. Numerous paraffin techniques requiring fewer than twenty-four hours to complete, and some as little as one hour, were reported in the literature. Although none of these methods were really fast enough for diagnosis during operations, preparation of routine sections no longer required days or weeks. Paraffin section diagnosis within two days became standard. Many pathologists, particularly those who already opposed rapid diagnostic techniques, felt that the development of rapid paraffin methods reduced the need for frozen sections.[93]

The proliferation of techniques suggests the importance that surgeons placed on biopsies with immediate tissue diagnosis. Surgeons believed that biopsy represented the most certain form of diagnosis because tissue diagnosis was "anatomical" proof of the clinical diagnosis. Immediate diagnosis during an operation was perceived as the epitome of "scientific" surgery because the pathologist not only confirmed the diagnosis but could actually guide the surgeon's knife. The inferiority of frozen sections to paraffin sections for diagnosis led to the introduction of other techniques for immediate diagnosis, but all of these had drawbacks as well. Both the Terry razor section method and Ultropak illumination permitted rapid histologic diagnosis, but the preparations were not permanent. Wet films and teased preparations offered superior cytologic detail but did not allow the pathologist to evaluate the behavior of the cells as was possible with histological techniques. Rapid paraffin sections, although an improvement over older techniques, did not permit immediate diagnosis. None of the other techniques proved to be altogether superior to frozen sections. Furthermore, none, with the possible exception of the Terry method, was promoted as vigorously as the frozen section had been by Bloodgood and the staff of the Mayo Clinic.

Early Biopsy. Biopsy, which came to center so much on frozen sections, is not entirely a twentieth-century concept. An understanding of its history since the introduction of the frozen section in 1895 depends in part upon an understanding of earlier developments. In fact, as early as the 1840s, a handful

[93] Aldred S. Warthin, "Forty years as a clinical pathologist," *J. Lab. Clin. Med.,* 1931, *16:* 743–50; Ruth C. Wanstrom, "Rapid methods for preparing paraffin sections of tissues," *Amer. J. Clin. Path.,* 1937, *7:* 78–84; Simpson, "Frozen section fetish," pp. 96–102; E. G. Lane, "Rapid and routine preparation of tissue sections," *J. Lab. Clin. Med.,* 1927, *13:* 1143–45. As a practical matter, the indications for frozen section diagnosis became fewer with the advent of the rapid paraffin methods. However, surgeons have been slower to recognize this than pathologists; presently, many pathologists believe that the frozen section consultation is requested excessively by surgeons. See George W. Kindschi, "Frozen sections: their use and abuse," *JAMA,* 1984, *251:* 2559–60; Louis P. Dehner and Juan Rosai, "Frozen section examination in surgical pathology: a retrospective study of one year's experience, comprising 778 cases," *Minn. Med.,* 1977, *60:* 83–94, esp. pp. 91–93; Lauren V. Ackerman and Gustavo A. Ramirez, "The indications for and limitations of frozen section diagnoses: a review of 1269 consecutive frozen section diagnoses," *Brit. J. Surg.,* 1959, *46:* 336–50, esp. p. 336.

of clinicians and pathologists recognized the potential diagnostic value of microscopic examination of surgically removed lesions.[94]

Carl Ruge, a gynecologist at the Women's Hospital in Berlin, was the first to use the procedure of "Stuckchendiagnose," as he termed it, routinely. In 1879, Ruge reported the results of a study in which the clinical diagnosis of cancer could not be confirmed by histologic diagnosis in over half of the uterine cervices removed by a prominent gynecologist. Therefore, he suggested that the microscopic examination of biopsy material should be used to confirm the clinical diagnosis of cervical cancer. In 1881 Ruge reported that the diagnosis of uterine cancer could be made from curetted specimens. Prominent German pathologists ridiculed this idea, arguing that cancer could be diagnosed only by observing invasion of deeper structures and metastases at autopsy, not by examining curettings of epithelium from living patients. In 1888, for example, the eminent pathologist, Rudolf Virchow, who had misdiagnosed as benign a malignant biopsy specimen from the vocal cord of the German Emperor Frederick III one year previously, expressed his reservations concerning biopsy and echoed the belief that cancer was best studied through autopsy materials. Ruge responded that clinicians should bypass the pathology professors and do their own microscopic diagnosis of biopsy materials.[95]

Biopsies were also performed occasionally by dermatologists in the late nineteenth century. In fact, the term "biopsy" was actually coined by a French dermatologist, Ernest Besnier, shortly before the turn of the century. In Besnier's textbook, *La Pratique Dermatologique,* published in 1900, "biopsie" is defined as "une sorte d' 'autopsie' sur le vivant."[96]

In spite of the work of Ruge and Besnier, the use of biopsies, prior to the introduction of rapid histologic techniques between 1895 and 1905 was very rare. Occasional articles from the late nineteenth-century surgical literature recognized the importance of confirming the clinical diagnosis with histologic examination of the removed tissues, but this was not considered as different from examining tissue at autopsy. The goal in both cases was to confirm the diagnosis, not to assist in its formulation. Credit for the growing belief that histology might guide surgery has to be given to those who developed the techniques for rapid diagnosis during operations. J. Escalona Zapata of Madrid in 1969 credited the "dynamism of the Anglo-Saxon mentality" for the introduction of biopsy and stated further that American pathologists had found practical applications for pathology while Central

[94] Arthur B. McGraw and Frank W. Hartman, "Present status of the biopsy," *JAMA,* 1933, *101:* 1205–9; J. Marshall Neely, "The value of biopsy," *J. Lab. Clin. Med.,* 1936, *21:* 1124–30.

[95] Robert Meyer, "Carl Ruge," *Zentralbl. Gynäk.,* 1926, *50:* 1618; Volker Becker, "Carl Ruge, 100 Jahre Stuckchen-Diagnose," *Arch. Gynecol.,* 1979, *227:* 193–204; Hellwig, "Biopsy in tumors," pp. 609–610; Erwin H. Ackerknecht, *Rudolf Virchow: Doctor, Statesman, Anthropologist* (Madison: University of Wisconsin Press, 1953), p. 29.

[96] Arthur I. Spriggs, "An old neologism," *Lancet,* 1958, *2:* 851.

European academicians had rigidly studied autopsies.[97] Escalona Zapata was simply recognizing the obvious fact that although the process of biopsy had its roots in Europe, it became a largely American technique.

Early twentieth-century American physicians and surgeons were quick to adopt these new techniques because they were perceived to be "scientific." Claims to use scientific methods were a distinguishing characteristic of the allopath at the turn of the century, setting him apart from the irregular physicians, homeopaths, and quacks. By the second decade of the twentieth century, the idea of biopsy had a wide appeal, but few hospitals were capable of producing immediate frozen sections and even fewer pathologists were willing or able to make immediate diagnoses from them. Therefore, American physicians and surgeons performed biopsies without the aid of immediate frozen section diagnosis. Routine histologic preparations required days or weeks, thus raising a question about the safety of biopsy as a procedure. Many believed that cutting into a tumor to remove a diagnostic specimen, closing the incision, and upon diagnosis of malignancy, reopening to perform radical surgery, promoted metastases and diminished the patient's chance of a cure. By contrast, few held the belief that the use of frozen sections promoted metastases. When a malignancy was found by this technique, a curative operation could be performed while the patient was still under the same anesthesia. The fear of promoting metastasis served as an impetus to the application of frozen section diagnosis.[98]

Specialization During the Early Twentieth Century and the Emergence of the "Clinical" Pathologist. As the foregoing account has shown, numerous frozen section techniques were available by 1905, but the technique was not widely used until the 1920s and 1930s. Surgeons had quickly recognized the potential diagnostic value of information acquired through biopsy, but early twentieth-century pathologists were unenthusiastic about frozen section diagnosis or biopsies in general.

In the nineteenth century, pathology was not a clinical subject. Pathologists were academicians who taught courses on the theory of disease and performed autopsies for the advancement of science. The goal of pathology research was to describe and understand disease; clinically related research was not generally of great interest to the pathologist. This attitude, adopted from the German tradition under which the late nineteenth-century pathologists of the world had trained, is illustrated by the ridicule Ruge attracted in the 1880s by requesting German pathologists to study biopsy materials.

In nineteenth-century America, the few laboratory tests used by clinicians

[97] Escalona Zapata, "Biopsia intraoperatoria," esp. p. 231.

[98] James R. Wright, Jr., "The Origin and Development of the Rapid Frozen Section Technique" (M.A. thesis, Ohio State University, 1984); the danger of a second anesthesia was also a major impetus for the use of frozen section diagnosis. General sources on the history of the concept of metastasis are: Robert J. Wilder, "The historical development of the concept of metastases," *J. Mt. Sinai Hosp.*, 1956, *23*: 728–34; Wilson I. B. Onuigbo, "A history of the cell theory of cancer metastasis," *Gesnerus*, 1963, *20*: 90–95.

were generally done by clinicians. In the early twentieth century, a dramatic increase in the number of laboratory tests occurring at the same time as the development and multiplication of community hospitals created a new niche for a specialist, the "clinical" pathologist.[99] Frozen section diagnosis was soon available in many prominent institutions and university hospitals, because pathologists and facilities were already available. Routine use in community hospitals necessitated the establishment of a new specialist rather than teaching and research responsibilities.

The early decades of the twentieth century were characterized by increasing medical specialization in America and low incomes for physicians because of the oversupply of medical practitioners.[100] The better trained physicians protected their interests by banding together and establishing specialty organizations and later, specialty boards. Membership in a specialty group was granted after a certain level of competence was demonstrated. Specialists believed that consumers of medical or surgical services would naturally choose members of these elite guilds instead of other physicians so that the interests of both the specialists and the patients would be furthered.[101]

In 1921, clinical pathology was a specialty offering a relatively low income and low status, and there were only 450 clinical pathologists registered with the American Medical Association. Much of the clinician's ever increasing laboratory workload was being sent either to large commercial laboratories, which advertised low prices in medical journals, or to state public health laboratories, which often charged nothing at all, rather than to hospital laboratories under the clinical pathologist's supervision. In addition to the financial issue, clinical pathologists were treated as technicians rather than as peers and consultants by the rest of the medical profession. These issues prompted the formation, in 1922, of the American Society of Clinical Pathologists.[102]

[99] Aaron G. Signy, "Trends in clinical pathologists," *J. Clin. Path.*, 1970, *23*: 744–50; Warthin, "Forty years as a clinical pathologist," pp. 743–50; Arthur H. Sanford, "The development of clinical pathology as a specialty," *Minnesota Med.*, 1943, *26*: 52–57. References dealing with economic factors related to the origin of clinical pathology are William D. White, *Public Health and Private Gain: The Economics of Licensing Clinical Laboratory Personnel* (Chicago: Maaroufa Press, 1979) and William G. Rothstein, "Pathology: the evolution of a specialty in American medicine," *Medical Care*, 1979, *17*: 975–88. A recent article on clinical pathology in Philadelphia is Edward T. Morman, "Clinical pathology in America, 1865–1915: Philadelphia as a test case," *Bull. Hist. Med.*, 1984, *58*: 198–214.

[100] Lester S. King, *American Medicine Comes of Age, 1840–1920: Essays to Commemorate the Founding of the Journal of the American Medical Association, July 14, 1883* (Chicago: American Medical Association, 1984), pp. 96–107.

[101] James G. Burrow, *Organized Medicine in the Progressive Era: The Move Toward Monopoly* (Baltimore: The Johns Hopkins University Press, 1977); Rosemary Stevens, *American Medicine and the Public Interest* (New Haven: Yale University Press, 1971).

[102] "On to Philadelphia! History of the American Society of Clinical Pathologists," *J. Lab. Clin. Med.*, 1925, *10*: 678–90; Long, *History of American Pathology*, pp. 199–202. It is interesting to note that similar economic and status problems for clinical pathologists were occurring simultaneously in Great Britain. As a result, British pathologists formed the British Pathologists' Association in 1927. In 1930, the organization assumed its present name, the Association of Clinical Pathologists. See William D. Foster, *A Short History of Clinical Pathology* (Edinburgh: E. & S. Livingston, 1961), pp. 130–32. Pathologists in Central European countries were not affected by these factors because academic pathologists were subsidized by their hospitals.

One of the Society's first actions was to attack the policies of the Advertising Committee of the American Medical Association for allowing unprofessional advertisements that quoted fees for laboratory services in the *Journal.* The Society also initiated an editorial and lecture campaign to promote the notion that physicians should "consult" the clinical pathologists they knew rather than use commercial laboratories, because the latter were often businesses managed by laymen for profits that did not have adequate methods of standardization of tests and whose test results were not interpreted by clinical pathologists.[103]

The plight of the clinical pathologist also concerned surgeons. In 1913, the American College of Surgeons had been formed as an honorary society for the surgical elite. The College's goal was to elevate both surgical practice and hospital standards. According to William D. White, surgeons wanted to establish clinical pathologists and clinical laboratories in hospitals "to impose a minimum check on the quality of care being provided in hospitals" because "these checks ... provid[ed] a potential way to cut down on competition from nonspecialists, who presumably were practicing lower-quality surgery than specialists."[104]

In 1918, the College established a series of "minimum standards" for hospitals. Those hospitals meeting the criteria were "approved" by the College; all others were not. The 1918 standards pertaining to the practice of pathology required that hospitals provide "chemical, bacteriological, serological, and pathological services" and that these be "under competent medical supervision."[105] In 1926, the College's minimum standard was upgraded to specify "that the clinical laboratory shall be under the direction of a graduate in medicine, especially trained in clinical pathology."[106] The guidelines also stated, "All tissues removed at operations shall be examined in the laboratory and reports rendered thereon."[107] These revised guidelines were, in part, the result of lobbying by the American Society of Clinical Pathologists.[108]

Importance of Frozen Section Diagnosis to the Status of Clinical Pathologists. As has been noted, commercial laboratories were willing to perform laboratory tests inexpensively, but the American Society of Clinical Pathologists

[103] Robert A. Kilduffe, "The choice of a pathologist," *J. Lab. Clin. Med.,* 1926, *11:* 694–96; Bowman C. Crowell, "The mutual relations existing between the clinic and the laboratory," *J. Lab. Clin. Med.,* 1925, *11:* 37–43.

[104] White, *Public Health and Private Gain,* p. 55.

[105] American College of Surgeons, *American College of Surgeons: Thirteenth Year Book* (Chicago: American College of Surgeons, 1926), pp. 33–44, esp. p. 36; William M. German, *Doctors Anonymous: The Story of Laboratory Medicine* (New York: Duell, Sloan, & Pearce, 1941), pp. 50–51.

[106] American College of Surgeons, *American College of Surgeons: Fourteenth Year Book* (Chicago: American College of Surgeons, 1927), pp. 43–74, esp. pp. 64–65; *idem, American College of Surgeons: Fifteenth Year Book* (Chicago: American College of Surgeons, 1928), p. 30.

[107] *ACS: Fifteenth Year Book,* p. 30.

[108] White, *Public Health and Private Gain,* pp. 50–56, focuses on the role of the American College of Surgeons in establishing pathologists and clinical laboratories in hospitals and ignores the role of the American Society of Clinical Pathologists.

campaigned vigorously for giving its members the work, arguing that because the tests were clinically important, they should be performed and standardized by physicians with clinical training. The examination of surgical tissues became an important weapon in this campaign because it required considerable clinical experience and could not, therefore, be performed by nonphysician laboratory technicians.

During its early years, Society members placed much emphasis on frozen section diagnosis because it required the immediate availability of clinical pathologists in hospitals. Unlike other laboratory tests which could be sent out to commercial laboratories, frozen sections had to be done in the hospital at the time of surgery.

In addition to helping bolster their position in the community hospital, clinical pathologists viewed frozen section diagnosis as a way to increase their relatively meager incomes. Terry, speaking before the Section on Pathology and Physiology at the annual American Medical Association meeting in 1920, said, "It is hoped that many pathologists may be induced to try this method (frozen section), for increasing the pathologist's usefulness is one of the surest ways of increasing his rewards."[109]

Tissue pathology, though a small part of the daily activity of the pathologist, was glorified because it required the closest relationship with the clinician or surgeon and allowed the pathologist to demonstrate his clinical acumen. Dozens of papers and editorials concerning frozen section diagnosis were published by clinical pathologists in just a few years. Almost without exception, each stressed that fresh tissue diagnosis was consultation, that the clinical pathologist was not merely a histologist, but rather a physician with clinical expertise, and that it was important to include a summary of all relevant clinical information with the specimen. Some clinical pathologists even insisted upon gathering their own histories and doing their own physical examinations before patients were taken to surgery.[110]

Frozen section diagnosis in particular allowed pathologists to acquire a new sense of dignity as clinicians. During a heated discussion concerning the merits of the technique at the fifth annual convention of the American Society of Clinical Pathologists in 1926, one of the discussants, Herman Spitz of Baptist Hospital in Nashville, Tennessee, stated:

> It seems to me that we are missing the most important point in regard to frozen sections. You will recall that during the first year of our existence as a Society, our president, Dr. Hillkowitz, carried on quite a protracted discussion with the American Medical Association in regard to advertising. As a result of that discussion, the Advertising Committee of the American Medical Association classified us as "manipulators of test tubes and other inanimate objects." Now it seems

[109] Terry, "Increasing the pathologist's usefulness and his rewards," p. 1777.

[110] E. Ellice McDonald and William C. Hueper, "Cancer and the laboratory," *J. Lab. Clin. Med.*, 1931, *16:* 713–33; Alvin B. Foord, "The role of the pathologist in the cancer problem," *Amer. J. Clin. Path.*, 1934, *4:* 321–26; Violet H. Keiller, "Idle thoughts on tissue diagnosis," *Texas State J. Med.*, 1930, *26:* 525–27.

> to me that here is a splendid opportunity to refute that classification. We are doctors, as much so as any other members of the American Medical Association. We are called into consultation by the surgeon when we are asked to do a frozen section. The surgeon waits with bated breath until we give him our report. If we tell him to cut wide, he does so. If we tell him he has done enough and that no further surgery is required, he is satisfied. Now, if this is dealing with "test tubes and inanimate substances" somebody should rewrite the dictionary. The method of doing a frozen section, the technic [*sic*] employed, the stains used, etc., are matters of personal preference. The real value in this paper is the fact that it tells the Advertising Committee of the American Medical Association that we are real doctors, dealing with life, just as all other physicians deal with life, and that we do something besides "manipulate test tubes and other inanimate substances."[111]

Clearly the fervor of this discussion grew out of the new importance of frozen section diagnosis for the clinical pathologist's status. Often the discussions of tangentially related topics became discussions of the frozen section technique.[112] For the clinical pathologist, doing frozen section diagnosis became a source of status, not only in the medical community, but also in the popular literature. The public was introduced to frozen section diagnosis through glorified and dramatic accounts of teamwork between surgeon and pathologist, who saved lives and spared patients from unnecessarily mutilating operations.[113] Ironically, at the time when surgeons and clinicians were striving to improve their practices by becoming more "scientific," pathologists, who had always been recognized as scientific, were striving for recognition as clinical diagnosticians.

Final Acceptance of the Validity of Frozen Section Diagnosis. No single date marks the final acceptance of the biopsy with rapid frozen section. As previously mentioned, there was never very much resistance from surgeons. Surgeons were more than willing to share the responsibility for operating room diagnosis with pathologists. In fact, the strongest support for routine frozen sections came from Bloodgood and other surgeons. Bloodgood, in one of his 1927 editorials, stated that the matter of hospitals without facilities for frozen section and diagnosis needed to be considered by the American College of Surgeons.[114]

On 17 October 1929, the Board of Regents of the College voted "to

[111] Herman Spitz, discussion of Louis A. Turley, "The difficulties and value of frozen section methods," [appended to end of Turley's article] *J. Lab. Clin. Med.*, 1927, *12:* 492–500. Quote is on p. 499. Spitz was a member of the Executive Committee of the American Society of Clinical Pathologists and its representative to the American College of Surgeons. See "Dr. Spitz's address before the Clinical Congress of Surgeons," *J. Lab. Clin. Med.*, 1925, *11:* 207.

[112] Discussion of Frederick H. Lamb, "Symposium on surgical diagnosis. Part III. Laboratory procedures," *J. Iowa State Med. Soc.*, 1921, *11:* 244–50, esp. pp. 248–49; discussion of Turley, "Difficulties and value of frozen section methods," pp. 498–500; discussion of Louis A. Turley, "The value and character of reports and records of tissue examination," *J. Lab. Clin. Med.*, 1926, *11:* 827–31, esp. pp. 830–31.

[113] Jennie Q. Adatto, "Cold facts," *Hygeia*, 1948, *26:* 340–41, 374; German, *Doctors Anonymous*, pp. 5–9.

[114] Bloodgood, "Danger of incomplete removal of small and apparently innocent lesions," p. 414.

undertake the promotion of better cancer service throughout the continent and entrusted to the Committee on the Treatment of Malignant Diseases the task of perfecting the details by which this can be accomplished." Three of the fourteen members of the Committee, including its chairman, had been actively promoting frozen section diagnosis in the literature while none had actively opposed the method. It is, therefore, not surprising that the Committee's guidelines, published in 1930, stated that cancer clinics in general hospitals should have "a pathologist skilled in tumor pathology" and a "pathological laboratory service, including frozen section diagnosis convenient to the operating room." The Committee also stated that the early diagnosis of cancer is "extremely difficult and may be impossible without an exploratory operation . . . (and) diagnosis . . . by means of a frozen section."[115] Although this Committee report did not have the clout of the Minimum Standards for Hospitals, it did set additional national standards towards which hospitals should work. Other groups of surgeons also followed with their own guidelines.[116]

While surgeons were willing to share the responsibility of operating room diagnosis with pathologists, some prominent pathologists opposed rapid frozen section diagnosis. At the fifth annual convention of the American Society of Clinical Pathologists in 1926, Louis A. Turley noted that "at every meeting of this Society in the last several years, the question as to the value of frozen sections in tissue diagnosis has come up and the society has been pretty much divided into two camps, those in favor and those opposed to frozen sections."[117]

Many of the pathologists opposed to frozen section diagnosis believed that the technique was occasionally valuable but that surgeons abused their privilege by asking for frozen section diagnosis even when the diagnosis was apparent from the gross appearance of the lesion. Foremost among these skeptics was James Ewing of Memorial Hospital in New York. Others questioned the claimed superiority of the technique to gross diagnosis.[118] However, several statistical studies involving large numbers of patients strongly supported the superior accuracy of histological diagnosis of biopsy material.[119]

Some pathologists were offended by the circus-like atmosphere sur-

[115] "Organization of service for the diagnosis and treatment of cancer," *Surg. Gynecol. Obstet.*, 1930, *51*: 570–74. The quotation is on pp. 572–73.

[116] See, for example, "Report of Breast Tumors Committee," *Calif. West. Med.*, 1932, *37*: 208–9.

[117] Turley, "Difficulties and value of frozen section methods," p. 492.

[118] Simpson, "Frozen section fetish," pp. 96–102; Miles J. Breuer, "Frozen-section biopsy at operation," *Amer. J. Clin. Path.*, 1938, *8*: 153–69; Michael G. Wohl, discussion of Turley, "Difficulties and the value of frozen section methods," p. 499; James Ewing, "The diagnosis of cancer," *JAMA*, 1925, *84*: 1–4, esp. pp. 1–2.

[119] William C. MacCarty, "Absolutely necessary microscopic diagnosis," *Minnesota Med.*, 1918, *1*: 178–81; *idem*, "Efficiency in the diagnosis of neoplasms," *Surg. Gynecol. Obstet.*, 1922, *35*: 209–15; Walther Fischer, "Über die Diagnose der Pathologen und Chirurgen," *Verhandl. deutsch. path. Gesellsch.*, 1927, *22*: 182–85; Hellwig, "Biopsy in tumors," p. 629; Elmer R. Jennings and James W. Landers, "The use of frozen section in cancer diagnosis," *Surg. Gynecol. Obstet.*, 1957, *104*: 60–62.

rounding frozen section diagnosis. For instance, Warthin considered frozen section diagnosis a "fad" and Simpson considered it a "fetish." Simpson described the frozen section "consultation" in this way:

> The buzzer rings. The pathologist leaps to his feet, hastily excuses himself from his consultation with a member of the medical staff, and runs to the operating room. Seated on the amphitheater benches are a dozen visiting physicians to whom the surgeon has just described the hard fixed nodule in the breast of the woman who is asleep on the operating table. Greeting the panting pathologist with a patronizing smile, he turns to the audience: "Here is our pathologist! He will have the diagnosis for us in three minutes!" Like a trained seal, the pathologist catches the small bit of tissue and rushes back to his laboratory. A few deft motions and the stained section is placed on the stage of the microscope. Realizing that the surgeon and his expectant audience await the diagnosis within three minutes, the pathologist hastily glances through the microscope and rushes back to the operating room. "Scirrhous carcinoma!" he gasps, and withdraws as the surgeon undertakes the radical operation.[120]

Separation of Surgical Pathology from Clinical Pathology. As outlined, clinical pathology became a viable subspecialty during the 1920s and early 1930s.[121] Before 1926, many clinical pathologists were general pathologists doing laboratory diagnostic tests, autopsy pathology, and surgical pathology. Since specimens removed at surgery were thrown into the waste can unless the surgeon requested a histopathologic diagnosis, the burden of surgical pathologic diagnosis was not great and could be handled by the clinical pathologist in his spare time. Nevertheless, frozen section diagnosis was inconvenient, as was pointed out by Miles J. Breuer, a clinical pathologist from Lincoln, Nebraska:

> To any other consultation, the consultant is asked as to an appointment between peers and his convenience is considered. To one of the occasions, the pathologist is summoned arbitrarily through subordinates; his sensations are those of being subpoenaed. A general attitude prevails about the hospital that any surgical operation is an emergency and is entitled to ride rough-shod over every other consideration in the institution. Though considered less so than the clinician, the pathologist is nevertheless somewhat human. To be unceremoniously called, in disregard of previous appointments and other important duties, will, in spite

[120] Simpson, "Frozen section fetish," p. 96.

[121] Essentially, the American College of Surgeons' minimum standards established clinical pathology as a viable subspecialty and clinical pathologists as consultants. In 1982, the clinical pathologist's status as a consultant again became precarious. Following passage of enabling legislation by the Congress, the Health Care Financing Administration issued regulations setting maximum rates that will be paid by the federal government for certain medical services (Diagnosis Related Groups). These rate limitations affect primarily physicians not involved in direct patient care, such as clinical pathologists. Personal communication, Donald A. Senhauser, chairman of the department of pathology, Ohio State University, 31 January 1984; see also Jean Shaw, "Proposed regulations on reimbursement attacked," *Amer. Med. News*, 3 December 1982, 1, 10–11. Ironically, surgical pathology, an off-shoot of clinical pathology, is not as adversely affected by these regulations.

> of his own conscientious efforts to be obliging and cooperative, prove distracting to his diagnostic reasoning.[122]

This matter of the inconvenience of frozen section diagnosis was partially responsible for the separation of surgical pathology and clinical pathology.

The primary reason for the eventual separation of surgical pathology from clinical pathology was the 1926 modification of the American College of Surgeons' minimum standard. The upgraded standard required that all surgical specimens be examined by a pathologist and that a report be made upon each specimen. This standard essentially brought about the existence of a surgical pathology laboratory in every hospital whose authorities wanted College approval. After 1926, the burden of examining all tissue removed at surgery became so great in most hospitals that tissue diagnosis could no longer be done by the clinical pathologist in his spare time. Over the next decade, this development gave birth to a new specialty, surgical pathology. Examining surgical specimens became a full-time profession.

Surgical pathology and clinical pathology required different types of specialized knowledge and skills. The dissimilarity between tissue pathology and the remainder of clinical pathology was, therefore, a major factor in the eventual separation of clinical and surgical pathology. This separation was officially sanctioned in 1936 when the American Board of Pathology was established by the joint action of the American Society of Clinical Pathologists and the American Medical Association's Section on Pathology and Physiology. The American Board of Pathology approved three types of certification: 1) anatomical pathology, 2) clinical pathology, and 3) anatomical pathology and clinical pathology. Surgical pathology, because it involved the study of tissue, was included in the first category, anatomical pathology, and was distinguished from clinical pathology.[123]

In the late nineteenth century, the term "surgical pathology" referred to the surgeon's knowledge of gross pathology, and his ability to recognize lesions in situ with the naked eye. Authorities in the field were surgeons with an unusual interest in pathology (e.g., Sir James Paget and Theodor Billroth), not pathologists who worked with surgical specimens. Although well-trained surgeons realized that pathology was the foundation of surgery, the idea that a pathologist might guide the surgeon's knife did not appear until the early twentieth century.[124] John Stewart, in his address to the Canadian Medical Association in 1902, made the analogy, "What navigation was

[122] Breuer, "Frozen-section biopsy at operation," p. 163.

[123] Frederick H. Lamb, "Certification of clinical pathologists," *Amer. J. Clin. Path.*, 1935, *5:* 261–65; Foster M. Johns, "Establishing certification and regulation of the practice of pathology," *Amer. J. Clin. Path.*, 1936, *6:* 323–29; "The American Board of Pathology," *Amer. J. Clin. Path.*, 1936, *6:* 514–15.

[124] Henry T. Butlin, "The Cavendish lecture on the application of pathology to surgery," *Brit. Med. J.*, 1900, *1:* 1577–82; also *Lancet*, 1900, *1:* 1856–59; *St. Louis Med. Rev.*, 1900, *63:* 104; John Stewart, "The contribution of pathology to surgery," *Montreal Med. J.*, 1902, *31:* 700–709; also *Canada Pract. Rev.* (Toronto), 1902, *27:* 569–78; *Canada Lancet* (Toronto), 1902, *36:* 86–94.

to seamanship, pathology is to surgery."[125] At this time, the navigator was still the surgeon, guided by his knowledge of pathology. Within a few years, navigation became, in part, the responsibility of the pathologist. In a symposium on cancer in New York in 1934, Steven Curtis, a pathologist, modified the analogy, "the relation of the pathologist to the cancer problem is somewhat like that of the navigator aboard ship. The navigator with his nautical instruments plots his course, thus assisting the pilot in guiding his ship."[126] This new allocation of responsibility (and credit) was, in part, the result of the expanding use of the rapid frozen section.

[125] Stewart, "Contribution of pathology to surgery," p. 571.

[126] Steven H. Curtis, "The relation of the pathologist to the cancer problem." *N.Y. State J. Med.*, 1934, *34*: 598–99, esp. p. 598.