The 100-Year Anniversary of the Description of the Frozen Section Procedure

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In contemporary society, the pathologist is largely unknown or poorly understood. Accordingly, few lay persons, whether healthy or ill, have direct professional interaction with pathologists.1 If a poll of the lay public were undertaken, many would respond that the pathologist is “not a physician,” “the keeper of the dead,” or “the person who performs the autopsy.” Certainly, the portrayal of the pathologist in printed press, cinema, and television, notably in the popular Crime Scene Investigation (CSI) television series, is frequently a distortion of reality.2

While autopsies represent a small and ever-diminishing part of medical practice, most contemporary pathologists are actively and directly involved in rendering care to the living patient through the various facets of the modern clinical laboratory. One of the most crucial tasks of the pathologist is the performance and interpretation of the frozen section or intraoperative consultation for diagnosis, margin assessment, and procurement of tissue for research purposes. This procedure is critical for the performance of accurate surgery: its outcome may guide the surgeon to continue or abort the surgical procedure.

From a historical perspective, the advances in the late 19th century in surgical technique, anesthesia, hemostasis, and control of infection became the cornerstones of modern surgical practice.3 As a result, physicians in departments of surgery or gynecology applied their surgical craft and studied tissues from living patients. Most pathologists of that time, however, were more devoted to autopsies and research and were largely disinterested in practical clinical applications of pathology.4 Yet there were a few brave pathologists who abandoned the trail of the past and ventured into novel applications of microscopy and histotechnique during their colleagues’ surgical procedures.

In 1905, William Mayo told his new chief of pathology at the Mayo Clinic in Rochester, Minn, Louis B. Wilson, MD, “I wish you pathologists could tell us if a tissue is cancer or not while the patient is on the table.”4 A biology teacher familiar with the use of botanical stains, Wilson deduced a very simple technique using methylene blue to stain frozen tissue specimens during surgery.5 Wilson’s technique allowed for a diagnosis within minutes while the patient was still on the operating table. His technique, with modifications, is still in use at the Mayo Clinic.6,7

In the December 2, 1905, issue of JAMA, Wilson published his description of a reliable technique for the intraoperative frozen section (FIGURE).3 Although various frozen section techniques had been described by other authors for several decades, it is generally recognized that this landmark article in JAMA provided the first well-publicized, consistent method of rendering a dependable frozen section diagnosis that affected patient care during surgery.8,9 The impact of the frozen section on patient care since the beginning of the 20th century cannot be overemphasized. As noted in 1927 by Bloodgood,10 the rate of inoperable cancer at Johns Hopkins Hospital had decreased from 50% in 1900 to less than 5% by 1920 thanks to intraoperative frozen section. During the 20th century, intraoperative frozen section and preoperative biopsy led to vastly improved patient care and to the emergence of the surgical pathologist as a diagnostic consultant to surgeons and other clinicians.3,8,9,11

December 2005 marks the 100-year anniversary of Wilson’s seminal article. In celebration of this anniversary, the December issue of Archives of Pathology & Laboratory Medicine features a series of 12 articles by recognized experts reviewing current intraoperative consultation and frozen section diagnosis in multiple major organ systems; these 12 articles include more than 300 color images.

Even while celebrating Wilson’s historic article, it is important to remember that like many other discoveries and innovations in medicine and other fields, this advance had predecessors and competitors and subsequent modifications. The idea that tissues could be hardened for sectioning by freezing was not new when Wilson published his procedure in 1905. Several other reports of the use of a frozen tissue technique came intermittently from Europe and North America during the 19th century. At the Glasgow Western Infirmary in the early 1880s, frozen sections were used for examination of autopsy tissue, but the technique was not...

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A METHOD FOR THE RAPID PREPARATION OF FRESH TISSUES FOR THE MICROSCOPE.

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While engaged in general pathologic work I shared the common practice of frozen sections for microscopic diagnosis. On taking charge recently of the laboratory of the Drs. Mayo, surgeons, I carefully tested the various methods hitherto published and found they either too slow for results while the patient waits under the anesthetic or require the use of formalin. After considerable experimentation the following technique was discovered, and for the last six months it has given uniformly excellent preparations:

1. Bits of fresh tissue not more than 2x10x10 mm. are frozen in dry ice solution and cut in sections from 6 to 15 microns thick.
2. The sections are removed from the knife with the tip of the finger and allowed to thaw thereon.
3. The sections are unrolled with camel’s hair brushes in 1 per cent. NaCl solution.
4. The sections are stained from 10 to 20 seconds in neutral Unna’s polychrome methylene blue.
5. They are washed out in 1 per cent. NaCl solution.
6. They are mounted in Brun’s glucose medium.

The microtome which I use is the Spengler automatic in which the tissue is substituted for brass in the wall of the freezing chamber, thus insuring the freezing plate. Thawing the section on the finger prevents to a great extent the formation of bubbles. The well-made camel’s hair brushes used by artists are much more useful for handling tissues than those usually furnished by laboratory supply houses. A heavy, shallow watch glass over a black surface is the best receptacle in which to unroll sections. Sections are best handled in the stain folded over a lifter made of a small glass rod drawn out and bent at convenient angle. The section is kept constantly moving while it is in the stain. The stain is contained in a minute cup to facilitate the rapid recovery of the section should it slip from the lifter. Washing out is done in several ounces of salt solution in a white porcelain dish and is continued only while the stain comes away freely. Brun’s glucose medium (which is made by mixing distilled water 160 c.c., glucose 40 c.c., and glycerin 10 c.c., then adding ammonated spirit 10 c.c. and filtering), is held in an oval dish of porcelain (an “uncorked” dish safe) of such a size that a three-inch slide will rest in a slanting position, with one end in the bottom of the dish and the other on its edge. The section is spread out on the slide while it is in this position. The slide is then carefully withdrawn from the dish, the excess fluid removed, a cover-slip dropped over the section and the specimen is ready for the microscope.

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.

A diagnosis may be made from such preparations in a large percentage of surgical cases in which a diagnosis is possible by a study of sections of the same thickness cut from fixed tissues and stained with hematoxylin and cosin.

Figure. The Landmark Article by Louis B. Wilson, MD, Describing a Reliable Intraoperative Frozen Section Procedure

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Technology Licensing
Lessons From the US Experience

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In recent years, there has been substantial focus on patenting scientific discoveries from public and private research institutions. The push for increased patenting has been driven most strongly in the United States, but has also extended to other countries. Although the multiple roles for technology development and transfer can yield important social benefits, some are potentially detrimental. One reason for the attention on patenting is the belief that licensing patented technologies could generate income that in turn could finance additional research and socially valuable programs. This belief has surfaced in discussions of public policy, most notably in developing countries. The assumption that technology licensing is a principal answer to unlocking a revenue goldmine is faulty and can lead to undesirable consequences. In this article, we analyze the US licensing experience longitudinally, discuss policy implications, address emerging trends specifically among developing nations, and suggest that royalty revenue-driven technology licensing in developing countries is the wrong public policy to adopt.

The US Technology Licensing Environment

Enactment of the Patent and Trademark Law Amendments Act (the Bayh-Dole Act [35 USC §200-212]) in 1980 encouraged research institutions in the United States to patent technology developed with federal funding. This act allowed such institutions to license patented technologies in exchange for royalty payments. Along with a favorable economic landscape in the 1970s and key court cases such as Diamond v Chakrabarty (447 US 303 [1980]), the Bayh-Dole Act enabled substantial growth in patenting and has given rise to technology transfer offices at most US research institutions.

Since 1980, the average number of patents granted by the US Patent and Trademark Office to US research institutions each year has increased by more than 480%. What have the effects of the Bayh-Dole boom in licensing been on US research institutions?

A sample of US institutions reveals a nuanced picture of licensing. The Association of University Technology Managers reports that for a general sample, average gross licensing income per institution increased steadily from approximately $2 million in 1996 to approximately $3 million in 2001. When we consider a more specific sample of 84 major US universities, hospitals, and research institutes that has the benefit of reporting data consistently from 1996-2001, nearly $100 billion worth of research sponsored by government, industry, and the institution was conducted. Simultaneously, these 84 institutions earned a combined gross income of $3.6 billion in licensing fees. However, during the same time period, the median net licensing income per institution—a measure that is more realistic than those usually described because it subtracts legal expenditures and payments to other institutions from gross licensing income—was only $1.13 million per year. Notably, the net income was not divided evenly among the institutions. Only 13% of the institutions earned more than $10 million per year in net income, and the 6 highest earners (top 7%) obtained nearly 60% of all income. This distribution represents a classic “winner-take-all” phenomenon with a few earning most of the income. Resources allocated for operating technology transfer offices might be better spent elsewhere, as costs may exceed revenues over time.

In general, institutions with a greater amount of sponsored research were more likely to realize appreciable licensing income. Generally, average annual net licensing income and average annual amount of sponsored research are correlated. Only 3 institutions with less than $200 million

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