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Invention and Early History of Telepathology (1985-2000)

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Abstract

This narrative-based paper provides a first-person account of the early history of telepathology (1985–2000) by the field’s inventor, Ronald S. Weinstein, M. D. During the 1980s, Dr. Weinstein, a Massachusetts General Hospital-trained pathologist, was director of the Central Pathology Laboratory (CPL) for the National Cancer Institute-funded National Bladder Cancer Project, located at Rush Medical College in Chicago, IL. The CPL did post therapy revalidations of surgical pathology and cytopathology diagnoses before outcomes of the completed clinical trials were published. The CPL reported that interobserver variability was invalidating inclusion of dozens of treated bladder cancer patients in published reports on treatment outcomes. This problem seemed ripe for a technology-assisted solution. In an effort to solve the interobserver variability problem, Dr. Weinstein devised a novel solution, dynamic-robotic telepathology, that would potentially enable CPL uropathologists to consult on distant uropathology cases in real-time before their assignment to urinary bladder cancer, tumor stage, and grade-specific clinical trials. During the same period, universities were ramping up their support for faculty entrepreneurship and creating in-house technology transfer organizations. Dr. Weinstein recognized telepathology as a potential growth industry. He and his sister, Beth Newburger, were a successful brother–sister entrepreneur team. Their PC-based education software business, OWLCAT™, had just been acquired by Digital Research Inc., a leading software company, located in California. With funding from the COMSAT Corporation, a publically traded satellite communications company, the Weinstein-Newburger team brought the earliest dynamic-robotic telepathology systems to market. Dynamic-robotic telepathology became a dominant telepathology technology in the late 1990s. Dr. Weinstein, a serial entrepreneur, continued to innovate and, with a team of optical scientists at The University of Arizona’s College of Optical Sciences, developed the first sub-1-min whole-slide imaging system, the DMetrix DX-40 scanner, in the early 2000s.

Keywords: Digital pathology, innovation, medical education, pathology, telepathology, The University of Arizona, virtual pathology

INTRODUCTION

Telepathology is the diagnosis of surgical pathology cases at a distance using real-time video imaging or store-and-forward digitized images.¹⁻¹¹ The American Telemedicine Association clinical guidelines for telepathology define telepathology as: “A form of communication between medical professionals that includes the transmission of pathology images and associated clinical information for the purpose of various clinical applications including, but not limited to, primary diagnoses, rapid cytology interpretation, intraoperative and second opinion consultations, ancillary study review, archiving, and quality activities.”¹⁰

In this review of the early history of telepathology, we identify and discuss interconnected factors that help explain how robotic-dynamic telepathology became the technology-of-choice for the first sustainable telepathology programs in the United States, Canada, and Europe. The initial driver for the invention was a crisis in a National Cancer Institute (NCI)-funded National Organ Site Cancer Program, the National Bladder Cancer Project (NBCP), with the National Bladder Cancer Group (NBCG) the clinical trial arm of NBCP.

Why invent dynamic-robotic telepathology? For logistical reasons, the NBCP collaboratives’ “analytical diagnoses,” the diagnoses used for data analysis at the end of a clinical trial, were generated by the NBCG’s own Central Pathology Laboratory (CPL) located in Chicago, IL. These bladder cancer diagnoses, including re-staging and re-grading of

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cancers, were generated retrospectively, often after the clinical trial protocol was completed. It turned out that interobserver variability, comparing the originating institution’s surgical pathology and cytopathology diagnoses and the CPL’s diagnoses, was a significant problem, especially for some contributing institutions.\(^\text{[12-15]}\) Not infrequently, microscopic field selection, or up-and-down focusing of the light microscope, were at issue. Theoretically, dynamic-robotic telepathology (not yet invented) could provide a remote up-and-down focusing solution. There was general agreement that the ideal solution would be to introduce prospective CPL re-reviews of surgical pathology and cytopathology cases before the initiation of therapy in individual cases. This was not practical for logistical reasons in the 1970s and early 1980s. There was no technology solution that could provide immediate access to CPL uropathologists within the narrow window of time between the harvesting of tissue at surgery and histopathology and cytopathology sign-outs by pathologists and cytopathologists, and there was no infrastructure and environment to provide immediate telepathology services. This was all in the future.

To put the expenditure of resources for the creation of robotic-dynamic telepathology in some perspective, both in terms of time and money, it is stressed that this effort to reduce the interobserver variability challenge in urinary bladder cancer evaluations was in reaction to a very challenging situation. Urinary bladder cancer staging and grading are unusually challenging for pathologists, although many pathologists are quite unaware of that fact.\(^\text{[16]}\) Of the multiple organ-site-specific cancer trial programs funded by the NCI in the 1970s and 1980s, the NBCP was the only National Organ Site Cancer Program that could justify having a full-time NCI-funded CPL of its own.\(^\text{[17]}\)

The NBCP’s leadership successfully argued that this reflected the unusual difficulty and complexity of rendering reproducible urinary bladder cancer diagnoses. Various efforts to improve the reproducibility of surgical pathology diagnoses for urinary bladder cancers were unsuccessful. Annually, the NBCP uropathologists from 8 collaborating institutions (e.g., MGH, Roswell Park, etc.) would meet in Sarasota, FL, sit at multiheaded light microscopes, and try to work out their differences in the diagnoses they had rendered on “difficult” cases. Anecdotal evidence suggests that there were perhaps beneficial outcomes from these group meetings, but a change in practice by the surgical pathologists was not sustainable (R. S. Weinstein, unpublished observations, 1984). Interestingly, it is noteworthy that recent data collected for a different reason, gaining approval of the United States Food and Drug Administration for rendering primary diagnosis with whole-slide imaging (WSI), verified the relative difficulty of classifying bladder cancer patients in comparison with rendering cancer diagnosis in other organs.\(^\text{[16]}\)

The NBCG completed 15 clinical trials between 1974 and 1990, when the NBCG’s federal funding ended. CPL pathologists had re-reviewed 15,000 surgical pathology cases and 17,000 cytopathology cases. The interobserver variability, comparing the pathology diagnoses of the originating institution with the CPL diagnosis, was unacceptably high for some collaborating institutions. This resulted in post therapy rejection of urinary bladder cancer cases from inclusion in the analysis of the outcomes of certain urinary bladder cancer clinical trials.

Figure 1 and Table 1 show unpublished interobserver variability data for the 8 institutions contributing urinary bladder cancer cases to the NBCG’s consortium studies during the 1983–1984 academic year. It can be said that this data set triggered the invention of dynamic-robotic telepathology (R. S. Weinstein, unpublished data, 1984). In the 1983–1984 time frame, major discrepancies were defined, by the CPL, as a one level or more difference in tumor stage or two levels of variance in tumor grade (R. S. Weinstein, unpublished data, 1984).

The bar graph in Figure 1 shows the major and minor discrepancies in the staging and grading of urinary bladder cancer cases at the 8 academic medical centers participating in NCI-sponsored clinical trials for the 1983–1984 academic year. The data supporting the bar graph in Figure 1 are shown in Table 1 (R. S. Weinstein, unpublished data, 1984). There was a statistically significant difference between institutions for major discrepancies ($\chi^2 = 47.13$, $P < 0.0001$), minor discrepancies ($\chi^2 = 14.24$, $P = 0.0472$), and total number of cases ($\chi^2 = 17.83$, $P = 0.0128$).

### Table 1: Concordance Rates at the National Bladder Cancer Groups’ Central Pathology Laboratory^\text{*}\(^\text{a}\)

<table>
<thead>
<tr>
<th>Institution number</th>
<th>Total number of cases</th>
<th>Major discrepancies</th>
<th>Minor discrepancies</th>
<th>Total number of discordant cases</th>
<th>Total discordances</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>number of cases</td>
<td>% of cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>186</td>
<td>9</td>
<td>4.84</td>
<td>17</td>
<td>9.14</td>
</tr>
<tr>
<td>2</td>
<td>118</td>
<td>4</td>
<td>3.39</td>
<td>17</td>
<td>14.40</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>14</td>
<td>18.67</td>
<td>19</td>
<td>23.33</td>
</tr>
<tr>
<td>4</td>
<td>154</td>
<td>18</td>
<td>11.69</td>
<td>12</td>
<td>7.79</td>
</tr>
<tr>
<td>5</td>
<td>185</td>
<td>38</td>
<td>20.54</td>
<td>7</td>
<td>3.78</td>
</tr>
<tr>
<td>6</td>
<td>58</td>
<td>12</td>
<td>20.68</td>
<td>15</td>
<td>25.86</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>13</td>
<td>18.57</td>
<td>10</td>
<td>14.29</td>
</tr>
<tr>
<td>8</td>
<td>70</td>
<td>13</td>
<td>18.57</td>
<td>5</td>
<td>7.14</td>
</tr>
<tr>
<td>Total</td>
<td>916</td>
<td>121</td>
<td>102</td>
<td>223</td>
<td></td>
</tr>
</tbody>
</table>

^\text{*}\(\text{a}\)R.S. Weinstein, previously unpublished data, 1984
CPL case re-review diagnoses served as the standard for comparison. In Figure 1, each column represents one of the 8 individual participating institutions. Major discrepancies (orange) ranged from 4% (Institution #1) to 23% (Institution #6). Major discrepancies resulted in disqualifying a patient’s data from inclusion in the analysis of the outcomes of clinical trials. Minor discrepancies (yellow) most often represented one level of difference in tumor grading and did not affect the data analysis for a clinical trial. Numbers at the top of each column represent the total number of cases accessioned into clinical protocol analysis in the 1983–1984 academic year.

Based on concerns over the variability of the performances of pathologists, as compared to CPL retrospective diagnosis, especially at institutions 3, 6, and 8, telepathology was conceived of as a possible solution to this interobserver variability challenge in these bladder cancer clinical trials (R. S. Weinstein, unpublished data, 1984). The idea was that by centralizing the diagnoses of the urinary bladder cancers at the CPL, with immediate readouts by telepathology, and then utilizing these CPL initial surgical pathology diagnoses for assigning bladder cancer patients to disease-specific therapeutic trial protocols, the interobserver variability in diagnoses might be minimized.

**Invention of Dynamic-Robotic Telepathology**

Dr. Weinstein was encouraged by NBCP leaders to create the means for CPL uropathologists to analyze the NBCG’s patients’ urinary bladder cancers before their entry into clinical trials.[15,16] In 1985, he co-founded Corabi International Telemetrics, Inc., the first company to bring dynamic-robotic microscopy to market. He invented and patented the first dynamic robotic telepathology system while he was Director of the NBCP’s CPL, located at Rush-Presbyterian St. Luke’s Medical Center (1982–1990).[18‑27] The first customer for a Corabi International Telemetrics system was Grady Memorial Hospital, in Atlanta, Georgia. It was linked to Emory University Medical Center 4 miles away using a bi-directional microwave telecommunications system. The system became operational in 1989. Tragically, the entire National Organ Site Cancer Program, which supported the NBCP and other individual Organ Site Cancer Programs, was defunded by the NCI the same year, for reasons unrelated to the NBCP and its CPL. Ironically, the primary reason for inventing dynamic-robotic telepathology, to provide a means for the rapid re-review of urinary bladder cancer surgical pathology diagnosis by the CPL, before therapy became moot, at least for the time being.

**Introduction of Telepathology to the Health-care Industry and the General Public**

In 1986, Corabi International Telemetrics, Inc. developed a four-pronged product rollout and marketing strategy for robotic-dynamic telepathology systems. These activities were envisioned at a strategic planning meeting in Bethesda, MD, in late 1985. They were executed in parallel and in highly coordinated fashion for maximum market impact and to attract investors.[28‑30]

The Corabi strategic plan was to (1) introduce the scientific term “telepathology” into the English language; (2) organize the first national demonstration of satellite-enabled robotic telepathology, working with the US Department of Defense and COMSAT Corporation, for the demonstration; (3) have Dr. Weinstein author and submit the first telepathology US patent application; and (4) create an academic literature on telepathology.[20‑27,31]
The event was organized and moderated by Dr. R. S. Weinstein, and his sister Beth Newburger, President and CEO of Corabi International Telemetrics, Inc. Following a press briefing in a nearby conference room, the telepathology demonstration took place in the COMSAT Corporation’s Board Room, in downtown Washington, DC [Figure 3]. The plan was to have the telepathologist, Dr. Alexander Miller III, flown in from Chicago for the demonstration, and seated at a telepathology workstation at the front of the COMSAT Board Room, render the pathology diagnosis on a 66-year-old female patient’s breast biopsy which was mounted on a glass slide that was, in turn, mounted on the stage of a Corabi robotically controlled motorized light microscope at the William Beaumont Army Medical Center, in El Paso, TX. Dr. Miller viewed the slide as an “unknown” although the case had actually been signed out the day before by another person [Figure 3]. As Dr. Miller analyzed the images of the breast biopsy on a video monitor, he controlled the movements of the robotic motorized light microscope in TX 1800 miles away. The biopsy viewing lasted 20 min. After Dr. Miller rendered his diagnosis of “invasive ductal carcinoma” and shared his findings with the surgeon and the pathologists in El Paso, TX, the audience of academic leaders from Washington, DC area medical schools, and nearby Johns Hopkins, AFIP staff, and the Assistant Surgeon Generals of the US Army and Air Force rose in unison to give Dr. Miller a large round of applause. They sensed that they were participating in an event representing the future of pathology. The demonstration was reported by many newspapers, including the International Wall Street Journal and the Washington Post, and was carried on NBC television news [Figure 3].

**Competing Telepathology System Designs**

Since 1986, dozens of independent telepathology equipment companies have introduced and marketed an impressive range of telepathology products. Many of the new telepathology equipment companies popped up as exhibitors at pathology meetings in various countries, showcased novel features on their systems, and were never heard from again.[33] Before the year 2000, numerous descriptions of telepathology services and validation studies had been published.[24,29,30,34-38] Some of the telepathology systems had been incorporated into clinical practices that remain active today.[30,34,35] On the other hand, before 1990, the number of telepathology equipment companies, telepathology validation studies, and active telepathology service entities could be counted on one hand. A PubMed (including MEDLINE) search of “telepathology” for papers published before 1990 lists just 3 papers, all from Dr. Weinstein’s group in Chicago.[21,22,24]

Efforts have been made to reconcile the similarities and differences between the various telepathology system designs.[199] Common threads can be followed through the years by conceptualizing telepathology system designs in terms of two competing options for telepathology imaging, static imaging, and real-time imaging.[40-49] Today’s WSI builds on the original static imaging concept in which small individual digital
images were electronically stitched together into progressively larger composite static images until an entire histopathology or cytopathology WSI was represented in one giant digital pathology image. Dynamic-robotic telepathology is based on a different concept. Whereas WSI telepathology can be performed asynchronously as a giant store-and-forward image modality, dynamic-robotic telepathology is performed in real time with the specimen/glass slide on the motorized stage of the remote light microscope.

Reconciliation of Telepathology System Designs

Both dynamic-robotic telepathology and WSI (virtual slides) telepathology evolved out of the work of a single medical imaging research group active at Rush Presbyterian St. Luke’s Medical Center and Rush Medical College in the late 1970s and early 1980s. James A. Bacus, PhD, was a research professor in Rush’s Section of Hematology in the Department of Medicine. His collaborator, Dr. Weinstein, was Chair of the Department of Pathology, Director of the CPL of the NBCG, and founder of Corabi International Telemetrics, Inc. They shared interests in pathology imaging but from different perspectives and had earlier collaborated on one of the last NIH grants to develop an automated PAP smear screening device. Dr. Bacus founded Cell Analysis Systems (CAS) which produced an automated blood cell analyzer, which was acquired by Beckton Dickinson, Inc. after CAS brought their digital scanner to market. Dr. Weinstein’s Corabi patents were licensed to Apollo Telemedicine, Inc., another family-owned company, which marketed robotic-dynamic telepathology systems in the United States and Canada. Drs. Weinstein and Bacus became stiff competitors once they relocated their respective high-tech startup companies to the Chicago’s West Side Technology Park.

The focus and priorities of Dr. Weinstein’s companies and the Bacus companies were different and produced highly differentiated products. Dr. Weinstein’s goal was to improve the diagnostic accuracy and reproducibility of surgical pathology results, especially with respect to the inadequate up-and-down focusing issue that was a possible source of interobserver variability. Dr. Bacus was less interested in the focusing issue and more interested in imaging mono-layers of blood cells on glass slides. Dr. Weinstein’s instruments would be robotically controlled by a telepathologist at a distant location and Dr. Bacus’s products would be totally automated and without requiring a pathologist-operator.

What is interesting from the prospective of university technology transfer is that as soon as Dr. Weinstein and Dr. Bacus set up their companies, their scientific collaboration at Rush Medical College came to an abrupt halt. Although their companies were tenants of the same innovation building in the West Side Technology Park and they frequently saw one another in Chicago and at national meetings, they never spoke to one another again. Participating in university spin-out companies can be highly polarizing. Information sharing may be nonexistent. The principals of the companies find themselves competing on many levels: for attention at their home university, for claims on intellectual property and patents, investors, and for local “bragging” rights.

Sustainable Deployments of Dynamic Robotic Telepathology Before the Year 2000

In the 1990s, static image telepathology’s main use was in education, as medical schools began to replace their student light microscopy laboratories with WSI. In addition, there were dozens of relatively short-lived static-image telepathology services worldwide by the year 2000. There were, however, noteworthy implementations of dynamic-robotic telepathology for rendering provisional primary surgical pathology diagnoses. Two well-documented, sustainable, dynamic-robotic telepathology programs were located in Tromsø, Norway, and Milwaukee, WI.

In 1991, a landmark paper was published in Human Pathology, by a group of Norwegians, including Ivar Nordrum, MD, a pathology resident, and Tor Eide, MD, Professor, and Chair of Pathology at the University of Tromsø. The Norwegian telepathology frozen section service remained in operation for decades. Following the publication of the 1991 Norwegian paper, Human Pathology became a “go to” journal for publishing telepathology papers for the next two decades.

Figure 4: Public recognition of telepathology. (a) Dr. Weinstein being honored at Armed Forces Institute of Pathology for his pioneering work in creating the field telepathology, on May 22, 1986. (b) American and European pioneers in robotic telepathology meet for the first time at the University of Tromsø, in Tromsø, Norway, in 1993. L to R - R. S. Weinstein, K. J. Bloom (United States), and I. Nordrum (standing) and T. Ide, M. D. (seated) (Norway). (c) Drs. A. Bhattacharyya and R. S. Weinstein, in Tucson, AZ, rendering the first USA-China static-image surgical telepathology diagnosis in Hangzhou, China, on October 3, 1993. (d) Bruce E. Dunn, M. D., in Milwaukee, WI (3rd from the left, white lab coat) in 1996 receiving a US Department of Veterans Affairs “Hammer Award” for innovation in telepathology from US Vice President Al Gore (5th from the left)
Furthermore, by the early 1950s, television microscopy was introduced and found its first clinical application, its use for the remote evaluation of blood smears, and urine sediments mounted on glass slides.

**The Year 2000 and Beyond**

Around the year 2000, which we arbitrarily designate as the “end” of the “early history of telepathology,” the number of telepathology equipment companies appeared to be nearing a peak. There was already a sorting out of the various system designs and system options driven by market forces. At the Kyoto International Forum for Telepathology and Regional Medicine, there was a sense that the key product missing from the arsenal of available WSI glass slide digital scanners was a 1-min slide digitizer. Lack of a “1-minute slide scanner” emerged as the critical bottleneck in laboratory slide digitization.

Upon return from Kyoto Japan, Dr. Weinstein and a group of optical engineers at The University of Arizona, College of Optical Sciences, invented and produced a novel array microscope-equipped ultrarapid glass slide digitizer that drastically reduced the WSI glass slide digitizing throughput times, from 30 to 45 min, to under 1 min.[11] Basically, they devised an optical array light microscope system that increased the functional “field-of-view” for WSI light microscopy, at ×20 magnification, from 1 mm to 2 cm. This improved glass slide digitizer throughput time by over an order of magnitude. Other organizations, such as Philips, approached the problem a different way. Apparently, they increased the efficiency of the CMOS-enabled digital cameras in their glass slide scanners while retaining a single optical pathway layout for their lens.
system. This was in comparison to the 80-miniaturized lens system approach introduced by The University of Arizona scientists. The Arizona group and their spin-out company, DMetrix, Inc., were first to digitize 100 glass slides, the entire glass slide production workload of the typical histopathology laboratory, in a single day. This became the aspirational glass slide digitizer throughput target for laboratory histopathology slide digitizing equipment. After 2004, the number of WSI slide digitizer throughput target for laboratory histopathology declined. Some consolidation of the industry took place through acquisitions of smaller companies by the larger companies, such as Roche and Ventana. Today, the glass slide digitizer market is dominated by a handful of large companies. Market leaders offer ultrarapid WSI equipment with a dual dynamic-robotic/static imaging telepathology option for their top-of-the-line instruments. Some hospital-based laboratories are going entirely digital, based on this hybrid technology.

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Conflicts of interest
There are no conflicts of interest.

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