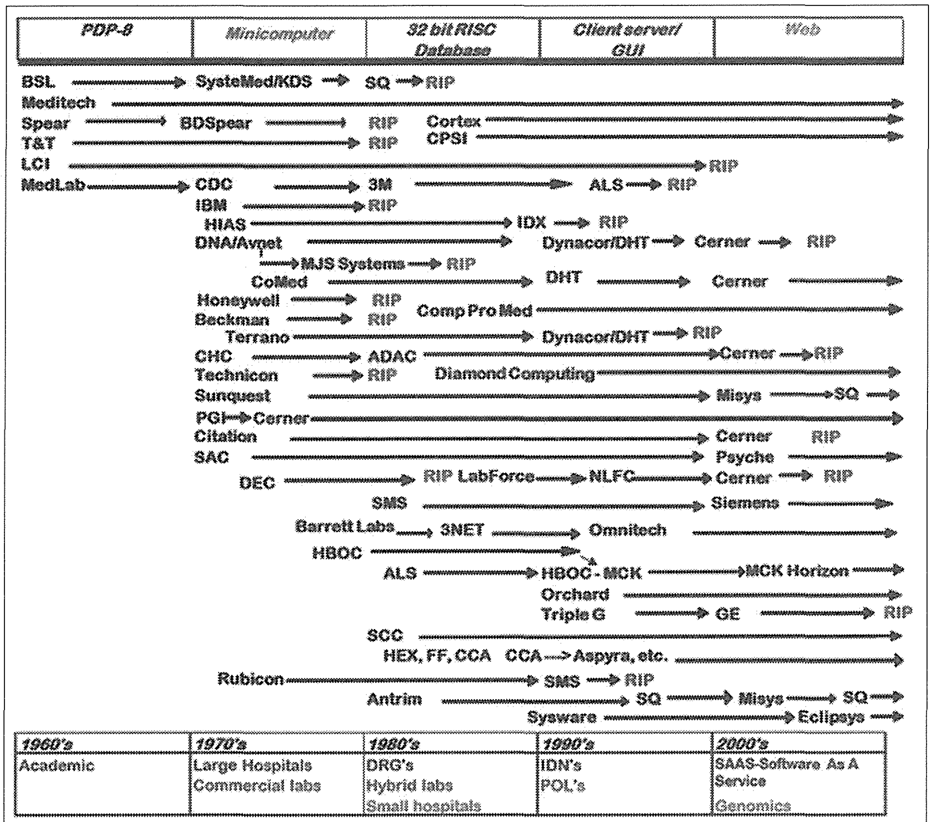


Figure 5: A timeline of selected Laboratory Information Systems (LIS) vendors from 1960's to the present. It is important to note that this is a sampling and not an exact account of the full history of LIS vendors. ALS = Advanced Laboratory Systems; BSL = Berkeley Scientific Laboratories; CCA = Creative Computing Applications; CDC = Control Data Corporation; CHC = Community Health Computing; DEC = Digital Equipment Corporation; DHT = Dynamic Health Technologies; DNA = Diversified Numeric Applications; FF = Fletcher-Flora; HBOC = Huff, Barrington and Owens; IDX = IDX Systems (acquired by GE in 2006); KDS = Knowledge Data Systems; LCI = Laboratory Consulting, Inc.; MCK = McKesson; MJS = Michael J. Selner Systems; NLFC = New Lab Force Corporation; PGI = Patterson, Gorup, Illig; SAC = System Analysis Corporation; SCC = Soft Computer Consultants; SMS = Shared Medical systems; T and T = T and T Technology (Peter Tong). Image courtesy Weiner Consulting Services and Dennis Winsten and Associates

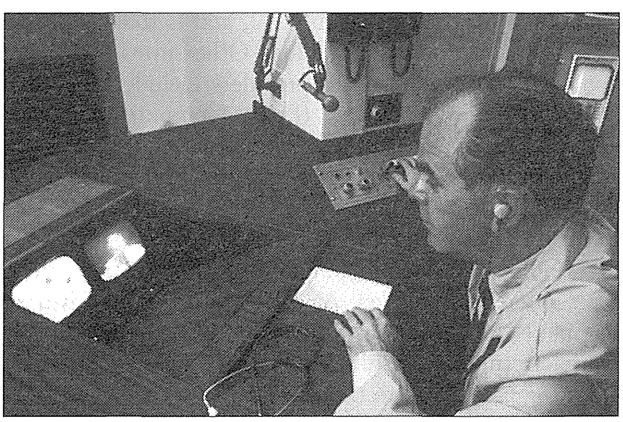


Figure 6: The live telepathology system connecting Boston Logan Airport and the Massachusetts general hospital in action. This is widely considered the first working telepathology system in history

for image-based pathology informatics to have a positive effect on the practice of surgical pathology, cytopathology and hematology. With the advent of increasingly affordable digital imaging technologies,

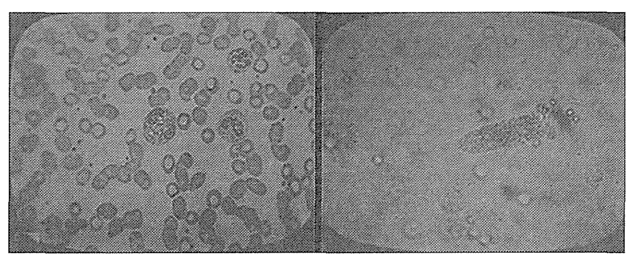


Figure 7: Examples of the video streams the first telepathology system could generate. Left: peripheral blood smear; right: Urine cytology

such early analog efforts paved the way for the emergence of digital pathology. The first publication describing the use of dynamic robotic telepathology occurred in 1986 [Figure 8], and an early publication describing a "virtual microscope" prototype which included the concept of WSI was published 10 years later. This publication forecast correctly that digital slides would not only conveniently emulate a physical microscope for clinical interpretations and teaching,

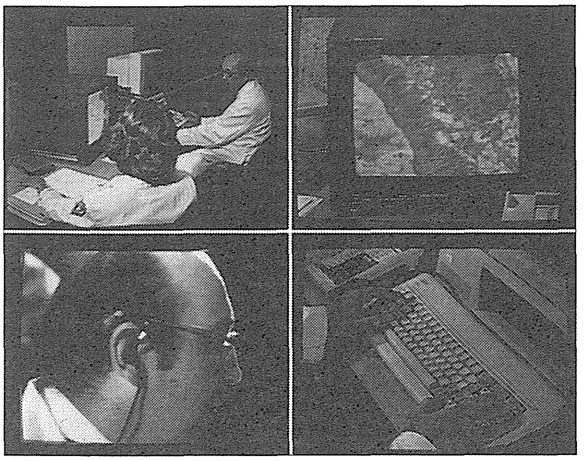


Figure 8: Live demonstration (in 1986) of the first operational robotic telemicroscopy system in history. Top left: Dr. Alexander Miller and associate operating the robotic telemicroscopy system; top right: example of the video feed from the system; bottom left: Close-up of videoconferencing gear worn by participants; bottom right: Close-up demonstrating keyboard control of remote robotic microscope

but also that digital images would be used to better screen and characterize malignancies, generate three-dimensional (3D) reconstructions, and permit image analysis using various special stains that revealed the presence or absence of biochemical markers.[104,105] Over the ensuing years the field of digital pathology continued to evolve with faster and better whole slide scanning technologies and computational algorithms to analyze the images. The first national course on digital pathology led by Mariano Alvira, Peter Shireman and John Minarcik was presented by the ASCP both at its national meetings and at its Chicago headquarters beginning in the early 1990's. Early efforts in image analysis can also be attributed to researchers in pathology informatics.[106,107] Automated slide scanners with image analysis algorithms on board were designed to screen cervical cytology smears for abnormal cells. Such instruments first began to receive clearance for clinical use by the FDA in 1995.[108] FDA clearance for image analysis algorithms enabling quantitative analysis of immunohistochemical cancer markers for estrogen receptor, progesterone receptor and others first occurred in 2003.[109] Research continues with extensions into parallel and grid-based systems capable of supporting digital slide sign out in routine surgical pathology practice, computer-aided diagnosis, content-based image retrieval, and 3D image reconstruction.[104,110-112] As the use of WSI evolved, the need for imaging standards specific to pathology emerged. The Digital Imaging and Communications in Medicine (DICOM) standard was initially developed to house radiological images, but in 2005, the Working Group 26 (Pathology) was added to specifically incorporate WSI into the specification. Since that time, Working Group 26 has published two supplements to the DICOM standard.[113,114]

Education Efforts in Pathology Informatics

Approximately 10 years after the first reports of computer use in a laboratory, the CAP established the first computer course for pathologists at their annual meeting.[99] In 1979, the ASCP began offering the first regularly scheduled course in pathology informatics entitled "The ABCs of LIS." This was offered at every ASCP national meeting, fall and spring, from 1979-1986. Fellowships in medical informatics (this was general informatics – not pathology informatics) began to appear in the early 1980's, funded by the NLM and again spearheaded by Dr. Donald Lindberg.[115] In 1986, the first journal article, which called for pathologists to be medical information specialists appeared in the literature.[116] The first pathology informatics book, called "The ABCs of LIS", was published by Dr. Frank Elevitch and Dr. Ray Aller (based on their ASCP course) in 1986, with a revised edition published in 1989,[117] In 1980, the first article was published on training pathology residents in informatics,[118], but subsequent articles did not appear until a decade later. In 1984, Dr. Frank Elevitch was appointed Chair of the CAP Lab Computer Committee (LCC), subsequently termed the Informatics Committee and more recently the Diagnostic Intelligence and Health Information Technology Committee. Under his leadership, the members of the LCC proposed, prepared, and presented an enormous number of CAP national meeting seminars on pathology informatics. Indeed, for much of the ensuing decade, more than 50% of the courses at the CAP National Meeting were focused on informatics. Although this strengthened informatics expertise at many community practices, academic centers did not appoint sufficient faculty, or permit them sufficient focus, to strengthen residency training. Because of ongoing gaps in pathology informatics expertise at many residency training programs at that time, the CAP began to develop several informatics mini-fellowships in the late 1990's to early 2000's. In 1995, the first formal pathology informatics fellowship in the nation was established by Dr. Michael Becich at the University of Pittsburgh Medical Center.[119] Today there are many more training opportunities (http://www.pathologyinformatics.org/content/training-opportunities-pathology-informatics), but still not enough to meet the emerging demand for skilled informaticists.

Professional Activities for Pathology Informaticists

The first national foci of pathology informatics began with the CAP courses of Rappaport and others in the 60's and 70's, then the ASCP course series of Elevitch and Aller 1979-1986, followed by the CAP seminars from the mid-1980's to 2000. A large amount of focused information was presented at user groups of various LIS vendors, such as Meditech, Sunquest, Cerner, and

Kontron.

The first national pathology informatics conference in the USA took place in 1983 in Ann Arbor, Michigan, entitled Automated Information Management in the Clinical Laboratory (AIMCL). One year later, the American Association for Clinical Chemistry formed a division of the organization dedicated to LIS.[120] A journal called "Informatics in Pathology" was launched that same year, but was unfortunately discontinued 1 year later due to poor subscription and insufficient contributions.[78] In contrast, the AIMCL meeting was quite successful, taking place annually for 21 years. Beginning in 1996, a second conference known as advancing pathology informatics, imaging and the internet (APIII), later renamed Advancing Practice, Instruction and Innovation through Informatics (still APIII), began to be held each fall, usually in Pittsburgh, Pennsylvania. While the theme of AIMCL tended to be weighted toward clinical pathology, APIII was initially more focused on anatomic pathology and digital imaging. The driving forces behind each of these conferences were Dr. Bruce Friedman and Dr. Michael Becich, respectively. As a result of their efforts and those of many others, the first professional organization specifically oriented to pathology informatics called the Association of Pathology Informatics (API) was chartered in 2000. Since its inception, the API has been a driving force behind a number of conferences and activities for pathology informaticists (http://www.pathologyinformatics.org/).

In 2004, AIMCL was replaced by the Lab InfoTech Summit which was held annually in Las Vegas, Nevada from 2004-2009. During this time, several international meetings related to pathology informatics were held including the First World Congress on Pathology Informatics in Australia organized by Michael Legg, Ulysses Balis, and Vitali Sintchenko, and conferences in Europe hosted by the European Congress on Telepathology and International Congress on Virtual Microscopy. The Digital Pathology Association subsequently formed in 2009. Toward the end of 2010, both the APIII conference and the Lab InfoTech Summit combined, in concert with the Histology Image Analysis group, to produce a single pathology informatics mega-event in Boston, Massachusetts, named Pathology Informatics 2010. That same year, a new open-access journal entitled "Journal of Pathology Informatics" was launched under the editorship of Dr. Liron Pantanowitz and Dr. Anil Parwani.[121] Most recently, in August 2011, the first-ever nationwide retreat for pathology informatics fellows was organized by and held at the MGH in Boston, MA.

Mexico, South America, Central America, and the Caribbean

1958-1989

Telepathology

In 1974, static black-and-white images of tissues, peripheral blood and bone marrow smears were transmitted via satellite from a hospital ship docked in Brazil to Washington DC, USA. It was the first time that still images of microscopic slides were transmitted by satellite communication.[122] The same year, Dr. Moacyr Domingos Novelli from the University of São Paulo published a report on the SACI Project (Advanced System in Educational Communication), which broke new ground in the usage of satellite communication in telemedicine in Brazil.[123] In 1981, the same group described its experiences with rendering remote histopathologic diagnosis from analog images obtained with optical microscopes that were then digitized and finally transmitted via satellite communication.[124,125] In 1985, the Mexican Centre for Health Education by Television (CEMESATEL) began transmitting clinicopathologic conferences from the Hospital Infantil Federico Gómez to 18 remote Mexican health institutions via satellite.[126]

Data Management

Computer data analysis in pathology was first reported in the South American literature by Friedrich *et al.* in 1977; their report describes a postoperative staging system for vulvar carcinoma.[127] One year later, Novelli *et al.* published their work on computerized data analysis in oral pathology.[128] Novelli's group would, 4 years later, also report on their research on terminology coding and database management in surgical pathology.[129] In 1985, a group of pathologists and engineers developed an information system for pathology and reported their experiences.[130] The same year, a team of researchers from the Universidad Nacional Autónoma in Zargoza, Mexico described an information system for oral histopathology.[131]

Image Processing and Analysis

Throughout the 1980's, Brazil was a hotbed for microscopic image processing and analysis (mainly focusing on oral pathology) as evidenced by the creation of the Laboratory of Informatics Dedicated to Odontology at the University of São Paulo in 1980.[132] In 1987 in Cuba, the first computer-based morphometric studies were performed on atherosclerotic lesions of the aorta at the Higher Institute of Medical Science of La Habana. In these studies, data was gathered with a digitizer interfaced with a NEC 9801 personal microcomputer. These data were then processed on a GDR EC-1040 minicomputer using SPSS (a statistical software package).[133] In 1989, studies on computer-aided morphometric analysis were published by the Laboratory for Cell Biology and Pathology of the University of São Paulo.[134]

Teaching and CME

In 1958, the University of Santa Maria (Río Grande do Sul, Brazil) utilized closed-circuit television for undergraduate pathology education.[135] This was considered a pioneering use of that technology in the worldwide literature at the time. In 1986, Dr. Fernando Augusto Soares of the Ribeirão Preto Medical School of the University of de São Paulo published practical recommendations for pathologists on the use of computers.[136]

1990-1999

Telepathology

In 1993, the Department of Pathology of the Hospital of Hermosillo, Mexico (Roberto de León Caballero, Jorge Platt Garcia, and Minor Cordero Bautista) participated in 63.5% of all cases processed by the Arizona International Telemedicine Network that year. This network utilized static telepathology methods to reach hospitals across the world. Even with the technological limitations (static telepathology only; relatively low-resolution images), an 88.3% absolute concordance between telepathologic diagnosis and glass slide diagnosis was seen – with an astonishing 96.5% concordance for clinically significant diagnoses.[36,137]

Brazil and Mexico were avid users of the AFIP's Telepathology Service between 1994 and 1999. This service – described in section: Telepathology in South Africa – utilized static telepathology only in that time period and recorded a telepathology-to-glass concordance rate similar to that of the Arizona International Telemedicine Network (73% absolute concordance; 97% concordance for clinically significant diagnoses). These early static telepathology experiences highlighted the need for increased technical expertise on the part of both the referring pathologist and the telepathology consultant and increased training in the selection of appropriate regions of interest on the part of the referring pathologist.[138,139]

In 1994, RESINTEL's TRANSPATH network – briefly described in section: Telepathology (Africa) – had operational telepathology sites in Martinique and Guadeloupe Island. Unfortunately, by 1998 this network had to be shut down due to lack of funding. The ultimate fate of these sites is not known, but they are thought to be currently non-operational.[7]

On October 11th, 1996, Dr. Sergio González (Department of Pathology, Hospital Clínico of the Pontificia Universidad Católica de Chile) reported on the usage of a telepathology station that connected his institution with the Hospital Dr. Sótero del Río, also in Chile. This study concluded that the 10 Mbps connections afforded by their network offered good image quality for online S-video transmission from microscopes using a Silicon Graphics workstation to digitize and compress video signal from a Sony DXC-C1 camera mounted on the Olympus BH-2 light microscope.[141,142]

South America experienced a wellspring of telepathology activity in 1997. That year, the "Europe-Latin America Telepathology Initiative" – a pilot telepathology exercise – was funded by the European Union, with the participation of the Netherlands and the Belgrano Public Hospital in Buenos Aires, Argentina. It employed ISDN technology for its network connectivity.[143] Also in 1997, the Hospital de Clínicas de Porto Alegre in Brazil conducted a comparison study on tele-consultation in cytopathology of serous effusions.[144] Finally for 1997, the Enlace Hispano Americano de Salud (EHAS) Project as created to offer low cost radio (HF and VHF) links, with solar energy systems, in rural areas and other areas in South America where conventional telephony was not available. For instance, in the province of Alto Amazonas, Peru, this allowed for sending and receiving of E-mails between healthcare providers – a first for that geographically isolated province.[141]

Telepathology in South America continued to be strongly developed in 1998 and 1999. A videoconference session on telepathology, using three ISDN telephone lines (384 Kbits/s), between Santiago de Chile and Buenos Aires took place in 1998, during a Congress organized by the Hospital de Clínicas de Buenos Aires.[145] In October of 1998, a telepathology workshop was organized in Peru, between Lima (Universidad Federico Villarreal) and Arequipa (Universidad San Agustín). Its subject matter included tele-consultations, Internet, as well as image capture and processing.[146] Finally, in 1999, the Universidad Nacional de Colombia (UNC) implemented a remotely-managed robotic microscope – a first for this region of the world.[147]

Data Management

There were two notable events in pathology data management in South/Central America and the Caribbean, both of which took place in 1995. The Mexican National Epidemiological Surveillance System (SINAVE) was created that year, including an information system for the histopathologic records of malignant neoplasia.[148] Meanwhile, in Cuba, SARCAP – an automated registry and control system for pathology – was developed by the pathology department of the Hospital "Dr. Luis Díaz Soto." It was initially designed as an information system for both autopsies and biopsies but has since then expanded into a national database for registry and coding clinical autopsies in Cuba.[149]

Image Processing and Analysis

An Argentinian group from the Medical School of the University of Buenos Aires published a digital pathology image processing study in 1990.[150] In the same timeframe, another Argentinian group studied the morphometric determination of AgNORs in breast carcinoma.[151] Also in 1990, Novelli *et al.* created software called IMAGELAB for image processing and analysis of microscopic images.[152] Though Novelli's group was the most prolific it was far from the only Brazilian effort in digital pathology image analysis at the time; there were also active research groups at the Evangelical Faculty of Medicine of Parana, Brazil and the Adolfo Lutz Institute, São Paulo, Brazil.[153,154] In 1993, The Institut Pasteur de Guyane, Hopital Jean Martial, Cayenne, French Guiana published a paper on the use of computer-aided image analysis in the study of inflammatory cells in skin lesions of chromomycosis.[155] Finally, in 1994, the Department of Biomedical Engineering of the Universidad Nacional de Asunción (Paraguay) began a full-blow research initiative on biomedical images and cancer pathology.[156]

Teaching and CME

In 1994, Infomed – a Cuban health telecommunication network that supports Internet connectivity and web editing – was brought online. It became a very popular resource for anatomic pathology in that country and still enjoys considerable activity today (http://www.sld.cu/sitios/scap/). The first Virtual Hispano-American Congress of Pathology (http://www.conganat.org/) took place in 1997, with the participation of Argentina, Brazil, Cuba, Dominican Republic, and Mexico.[157] Since then, there have been 10 further convocations of this virtual Internet congress. Dr. György Miklós Böhm, a Professor of the Department of Pathology, Faculty of Medicine, University of São Paulo, created the first Brazilian Telemedicine and Medical Research Laboratory in 1998.[158] Finally, a multinational virtual health library known as Biblioteca Virtual en Salud (http://regional.bvsalud.org/) was created in March 1998 as an initiative of the Pan-American Health Organization (a WHO affiliate). Its mission was to improve access to reliable, locally relevant information on health and health sciences. Pathology journals from Ibero-American countries were included as part of this library.

2000-Present

Telepathology, WSI, and Image Analysis

The year 2000 was a highly significant year for telepathology in South America. Early that year, the UNC, the Instituto Tecnológico de Electrónica y Comunicaciones and TELECOM (National Company of Telecommunications in Colombia) began a pilot study on telemedicine. This study connected the San Andres Islands, Amazonas, Bogotá and other centers. Telepathology services were based on the use of the Nikon Coolpix 995 digital camera and Nikon and Leica microscopes.[141] The inaugural Telemedicine Meeting in Panama took place in August 2000, with the collaboration of Dr. Ronald Weinstein. In this meeting, the National Program of Telemedicine, with the participation of the Medical School of the Universidad de Panamá presented a telepathology project led by Dr. Silvio Vega that connected the Universidad de Panamá with the Hospital El Vigia in Chitré.[159,160] Finally, in October 2000, an international randomized telepathology study was performed between Instituto Materno Infantil de Pernambuco in Brazil and St. Jude Children's Research Hospital in Memphis, Tennessee, USA. The main objective of this project was to improve the diagnostic accuracy of pediatric cancer using static telemicroscopy. It was concluded that telepathology is an efficient second opinion method and that it also allows for an improvement of quality and speed of diagnosis, resulting in a better treatment of cancer in children.[161]

In 2001, tele-consultations utilizing static telepathology only were performed between the Arias-Stella Pathology and Molecular Biology Institute in Peru and the Instituto Nazionale per lo Studio e la Cura dei Tumore in Milano, Italy. These tele-consultations were a success, with concordance rates similar to previous studies on static telepathology.[162] The Arias-Stella group continues to be a driving force for telepathology in South America to the present day.

Between 1st October 2003 and 30th September 2006, the European Union funded the T@lemed project. This project – which promoted evidence based telemedicine for remote and rural underserved regions in Latin America using e-health platforms – included fast transmission of microscopy images from local hospitals to high-level referral hospitals, in order to improve the diagnosis of malaria. There were 14 institutions from many different countries that participated in this project, notably the Universidad Santiago de Cali, Universidad Nacional, Centro Internacional de Vacunas and Cámara de Industría y Comercio Colombo-Alemana of Colombia and the Fraunhofer Society of Germany.[163]

In 2004, Dr. Mauricio Ribeiro Borges of the Pontifícia Universidade Católica do Rio de Janeiro published a comprehensive thesis on telepathology.[164] This thesis would later be recognized as a classic in the field, and now serves as one of the cornerstone texts in the understanding of telepathology in Latin America.

In 2005, the ABC Hospital of Mexico was formally recognized as a private institution with one of the highest technological levels in telepathology and digital medical imaging services in the Latin American sphere. It has remained a regional superhub for pathology informatics endeavors ever since.[148] Also in 2005, two microscopes with attached digital cameras were installed at the National Cytology Program of El Salvador, allowing quick consultations between pathologists in remote areas of the country and experts in San Salvador.[4]

In 2005 in Colombia, a telemedicine network between Cali (Universidad Santiago de Cali) and Costa Pacífica was developed for the tracking of infectious diseases. Microscopic images containing blood and urine samples were exchanged utilizing a custom store-and-forward architecture. This network is still in operation today.[165]

In 2006, the Amazon Telemedicine Project developed a tele-health system using satellite-based networking to reach Amazon Indians in Northern Brazil, with applications in the areas of telecardiology, teleradiology, teledentistry, telepathology, and videoconferences. The telepathology component of this project largely focused on the transmission of high-resolution static images of Pap smears. The satellite communication system – said by its creators to be highly robust, and cost-effective – is still in operation and actively use today.[166]

In 2007, a Peruvian project known as PAMAFRO (Control of Malaria in Border Areas of the Andine Region) began installation of wide-area networks utilizing IEEE 802.11 (Wi-Fi) technology in remote areas of the country. One of the networks – which spans a 447 Km segment along the Napo river, allowing an uplink to the Hospital Regional de Iquitos – is notable as being the single longest known Wi-Fi network in the world.[167]

In 2007, the BioIngenium Research Group of the UNC in Bogotá, Colombia was formed. It has since then made virtual microscopy, image compression, and image analysis its main research foci.[168] One of its notable projects has been on the automatic programmatic detection of malaria parasites in thick blood films stained with haematoxylin-eosin.[169]

In 2008 in Cuba, a national network for telediagnosis in anatomic pathology was established by a National Reference Center for Anatomic Pathology (CENRAP) in the Hospital "Hermanos Ameijeiras" in La Habana, Cuba.[170] That same year, in Cuenca, Ecuador, a private hospital known as the SOLCA Institute began to utilize a WSI scanner for tele-consultation and primary remote diagnosis. To the best of our knowledge, this is the first – or at least one of the first – mentions in the South American literature of WSI for primary diagnosis.[171]

Finally, in 2009, a telepathology pilot using digital slides created with Aperio ScanScope was performed with the participation of the Arias-Stella Pathology and Molecular Biology Institute in Peru, the Department of Pathology of University of Sao Paulo in Brazil, the Hospital Británico de Buenos Aires in Argentina, and Centro Consulenze Anatomia Patologica in Milano, Italy.[172]

Teaching and CME

In 2000, a website containing a comprehensive collection of histopathologic images with a special focus on oral pathology was published by the Fundação Odontológica de Ribeirão Preto, Universidade de São Paulo.[173] Also in 2000, the University of Cauca served as a mirror site for the 6th Internet World Congress for Biomedical Sciences, organized by the Pathology Department of Hospital de Ciudad Real in Spain.[174] Since June 2002, autopsies have been broadcast online on a weekly basis, with the participation of 12 Brazilian medical schools.[175]

In 2004 in Uruguay, the Pathology Department of the Medical School of the Hospital de Clínicas "Dr. Manuel Quintela" in Montevideo, Uruguay started publishing online study material for medical students.[176] In 2005, the Virtual Hispano-American Congress of Pathology began utilizing WSIs instead of static images in its presentations. Finally, at present, iPath hosts the Telemedicina Sur telemedicine network, active in South-American countries for medical discussions, including pathology CME and consultations.

LISs

In the last 5 years, significant improvements have been made in data management in pathology departments in Central and South America. Several commercial vendors (e.g., Labsoft Tecnologia Ltda.) are distributing products in Argentina, Brazil, and other countries. System integration and interoperability solutions for pathology are also available in products like data innovations (Austria and Brazil), Tesi Pathox (Italy and Brazil), CSC Patwin, Vitro Novopath and Esblada Gesapath (Spain and Ibero-America). Tracking and laboratory connectivity solutions from Dako (DaloLink, TPID) are also distributed in Brazil and other Ibero-American countries.

ASIA

The progress of pathology informatics in Asia has been much like the phenomenon of watching ripples spread across the surface of a once-placid pond after a pebble has been thrown into it. The pond in this metaphor is Asia; the pebble represents progress in telepathology and WSI from the West. Although this historical review of informatics in Asia is focused largely on advances in digital imaging, much progress has been achieved in these countries utilizing computers to establish LISs. In general, development of digitized telepathology was supported by the development of computers, and improvements in the performance of digital cameras. In the modern era, WSI have been a primary focus of pathology informatics activity across the world. Asia is no different in this respect. In some Asian countries (e.g., Japan), where network infrastructure and high-speed Internet-based telemedicine are well-developed WSI systems are in heavy use. In other Asian countries (e.g., China), there are significant bottlenecks to further penetration of telepathology, including (i) low levels of understanding in society in general about the importance of pathological diagnosis, (ii) physical constraints, including infrastructure development not keeping up in large geographic areas, (iii) high prices of WSI systems, (iv) lack of mutual trust between pathologists in different areas, and (v) regulatory issues.

The story of digital imaging in pathology was, in its earliest years, confined largely to the USA and Europe.

With the development of the Internet came the possibility of sending and receiving digital images across the world; most historians of our still-nascent field trace the lion's share of the evolution of the current state of telepathology – and indeed pathology at large – to this singularly disruptive event. Many organizations – such as the AITN – sprang up in the so-called "Web 1.0" era, providing platforms for diagnoses and consultations based on international telepathology involving not only the USA, but also many other nations, including China and Japan.[177] While these early efforts uniformly used static telepathology as their primary diagnostic modality, in the modern era we have seen a shift to the usage of WSI instead.[178] In Asia, the story of true digital pathology has just begun; it currently lags far behind the more developed state of digital pathology among the Western nations. However, Asian nations – particularly those with advanced network infrastructures like Japan and South Korea – are making more and more use of digital pathology as broadband saturation in these countries have reached (and indeed by now have exceeded) 100%. More recently, fast-growing economies like China and India have been pushing forward with digitization. Iran and Uzbekistan are also promoting digital pathology.[179,180]

Telepathology options differ from country to country: Offerings run the gamut from relatively slow transfer of static images taken by digital cameras via digital subscriber line to nearly-instantaneous transfer of WSIs via fiber optic networks.[181-183] Governmental support for telepathology and digital pathology is also quite variable – some countries have embraced these new technologies as quickly as they are introduced, whereas others have applied heavy regulation that has effectively stifled the growth of digital pathology in those nations. A case in point is the comparison between Japan and South Korea: Although both countries have impressive network infrastructures (South Korea's broadband penetration approached 100% as of 2012), the uptake of digital pathology in South Korea has been relatively slow due to an onerous regulatory environment. Compare this to the governmental policies of Japan, which openly promote a "standardization of cancer medical services" based on WSIs as well as other medical advances. It should therefore, come as no surprise that Japan's growth in telepathology and WSI adoption is outstanding as compared to that of South Korea – a nation that not only has a smaller landmass, but also an arguably better-developed network infrastructure [Figure 9].[184]

Japan

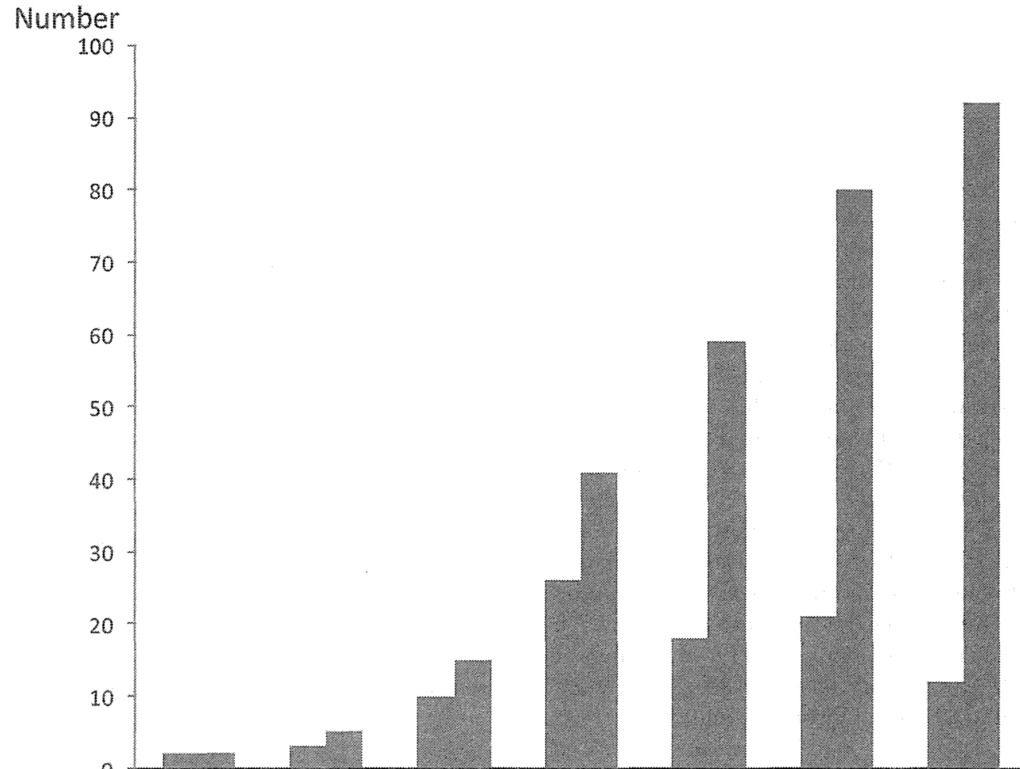
Japan's network infrastructure is among the best-developed in the world. Population coverage and network speeds also rank among the highest in the world-it is worth noting that fiber optics is a common connectivity option even among general households! High-speed network-based telemedicine has been developed to such a level that intraoperative rapid diagnosis and consultation take place actively in the field of pathological diagnosis. The first reports of digital pathology in Japan date from the first half of the 1990's. At first, static images were the major telepathology modality; now, real-time remote control of robotic microscopes and access to WSI is the norm. The essential driver of this change is widely accepted to have been the government's policymaking.

Infrastructure

Telepathology in Japan was first conducted on an analog system. It started shifting to digital modalities in approximately 1996 by using the ISDN protocol, which was the first step toward full implementation. In 2001 and 2002, asymmetric digital subscriber line (ADSL) and fiber optics, respectively, were implemented in telepathology. The advances in transmission technology combined with wide spread digitization made it possible to transfer still images and videos of tissues for pathological diagnosis. With the more recent addition of Hi-Vision (HDTV) technology, intraoperative rapid diagnosis is performed utilizing dynamic methods with full remote control of a robotic microscope.[185,10] WSI is also utilized for consultation and second opinions while their application in medical education is expanding. In 2009 and 2010, the high-speed satellite "Kizuna" was used for the first-ever Japanese fully dynamic/WSI telepathology study via satellite; this study allowed for simultaneous live telepresence across three sites (Iwate, Tokyo, and Okinawa).[186]

Digitization

In Japan, the static, dynamic (live video feed without control of the microscope), fully dynamic (live video feed with direct control of robotic microscope), and WSI methods of digital pathology are all in use. As of today, two Japanese providers offer fully dynamic and/or WSI methods. The Ministry of Health, Labour and Welfare has provided (and continues to provide) half of the funds necessary to procure WSI scanners and other such equipment at institutes and hospitals across the nation. The total number of WSI systems deployed in Japan is approximately 400, most of which are provided by Hamamatsu Photonics and Olympus. The use of WSI has taken root not only for pathological diagnosis, but also for education. The usage rate in medical faculties of Japanese universities for teaching histology and pathology is 46%.[187] Most of the universities utilize WSI in combination with existing microscopes; however, depending on the content of the lectures, some have fully shifted to WSI.[188] Although a complete shift from microscopes to WSI still requires validation of their educational effectiveness, WSI has been highly praised by students and researchers alike as they allow more than one user to look at a specimen simultaneously and to conduct discussions among themselves. WSI is also more flexible compared with traditional microscopes.



	2004	2005	2006	2007	2008	2009	2010
Number of Introduction/yr.	2	3	10	26	18	21	12
Total Numbers	2	5	15	41	59	80	92

Figure 9: Growth in Japanese telepathology installations, 2004-2010

China

Expectations for telemedicine including telepathology are very high in China, which is a country with an extensive national territory. Telepathology, however, is not currently actively practiced because (i) the infrastructure has not developed fast enough to cover all areas, (ii) hardware cost is still high, (iii) digital imagery is not fully trusted, (iv) people have a strong attachment to traditional optical microscopic diagnoses, (v) not enough physicians engage in telepathology, and (vi) state regulations concerning remote diagnosis are inadequate. In terms of infrastructure, digital subscriber line (DSL) is still the dominant technology, but more recently some cases of telepathology are reported as using fiber optics and WSI.

Infrastructure and Equipment

Along with its recent outstanding economic growth, China has been rapidly expanding its infrastructure. The speed of development can be exemplified by the number of Internet users reaching 400 million in 2011 and the number of cell phone users reaching 900 million.[189,190] Nevertheless, China's overall network infrastructure remains less developed than that of the USA, Japan, and South Korea. Although the absolute number of people who have access to the Internet is the highest in the world, if divided by China's large population, the penetration rate remains as low as 36.3% as opposed to 100% in South Korea, 78.3% in North America, and 78.4% in Japan.[191] Moreover, the digital divide in terms of Internet use between urban and rural areas is significant.

Digitization and Telepathology

Pathologists are scarce in China, particularly in the southwest region. To ascertain the telepathology situation in the country, we performed a PubMed search with the keywords, '"Telepathology" and "China."' There were five hits, three of which were related to consultation using the AITN as reported by Weinstein. These telepathology cases utilized static telemicroscopy over the Internet. Telepathology efforts indigenous to China, however, began in the first half of the 1990's.[177] Since the early 2000's, telepathology studies have been conducted based mainly on employing digitized still images and live video feeds without direct microscope control. These two diagnostic modalities appear to be the current mainstream in China. More recently, however, telepathology using fiber optics and WSI has tentatively begun between

Peking University and its first hospital. The most popular way of currently conducting telepathology in China is to either share WSI on a server with a trusted partner or to send an E-mail with a WSI as an attached file in the file transaction hub (FTH) format via DSL. In this format, the sender observes an image enlarged by a factor of four, extracts his/her area of interest into a 40-times-larger WSI, attaches the image as an FTH file to an E-mail, and sends it to the consulting pathologist. The advantage of this process is that the WSI files are of relatively small size, between 2 MB and 30 MB. This represents a middle ground between WSI-based and static image-based approaches. The attempt started with validating the result of this mode of telepathology by comparing it to conventional optical microscopy using biopsy cases; the diagnoses were reported to show good agreement for all cases.[182,183] Nevertheless, the use of static telepathology still remains more prevalent than dynamic methods. In addition, the issue of disparity between urban and rural areas remains unsolved in terms of limited infrastructure development and utilization of Information Technology (IT) in hospital facilities. As such, the practice of telepathology in China is currently limited to certain institutes only.

India

Telepathology in India is generally limited to static telemicroscopy utilizing the Internet.[181] Similar to China, constraints include the size of the country, the gap between urban and rural areas, startup cost, a power grid electrical supply system that is subject to occasional blackouts, and also the complex human relations among several groups.

Infrastructure

Due to India's historical background, the Indian people exhibit a high level of proficiency in English and mathematics, and the implementation of IT, mainly in enterprises, has been well positioned in a global society since the 1990's due to the government's policies. As of June 2010, the number of subscribers to wired Internet services was 16.72 million and that to broadband services was 9.47 million. The most popular connectivity type is DSL.[192] At the same time, the number of cell phone users reached around 635 million. The (what?) coverage was approximately 53.8% in 2010.[193] The country is pushing forward the construction of a wireless communications infrastructure in rural areas, with increasing adoption of third-generation (3G) wireless telecommunication and WiMAX technology.

The implementation of IT in medical settings is observed in the connection of the three major municipal hospitals in New Delhi with their affiliated hospitals, and communication with local cities was experimentally attempted in the Hyderbad District in the Southern part of the country.[194] Transmission of surgery-related images and other interactions on remote images in other districts have not been reported.

Digitization

According to the 50th Annual Conference of the Indian Association of Pathologists and Microbiologists held in Mumbai in 2001, the static (store-and-forward) method of telepathology relying on the Internet was used for consultation.[181] This static approach is still the mainstream method of practicing telepathology, but is used only by very few pathologists. Desai *et al.* successfully obtained effective tele-consultation outcomes by connecting the Tertiary Cancer Center (Tata Memorial Hospital) and the Rural Cancer Hospital (Nargis Dutt Memorial Cancer Hospital). However, these consultations were performed with a 56 kbps modem, which is not broadband. Still, concordance rates from this trial were 90.2%, and such time- and labor-consuming efforts are contributing to the rise in the level of confidence in telepathology.[195] In 2011, Kanthraj reported the application of store-and-forward teledermatology and mobile teledermatology.[196] The scope of this application, however, mainly covered macroscopic observation and treatment and addressed pathology images only in part. The promotion and utilization of WSI in the country awaits better infrastructure and other issues are overcome.

South Korea

The adoption of IT in South Korea is characterized by the highest levels of high-speed Internet coverage in the world, cloud computing, and active applications in the medical sphere. Conversely, due to a heavy regulatory environment and the high number of diagnostic pathologists to the number of hospitals, social need for and interest in telepathology seem marginal. The number of WSI scanners is approximately 30, which is fewer than Japan has, and most are being used for educational purposes.

Infrastructure

The country has been developing its infrastructure for high-speed Internet based on advanced DSL technology, as part of its initiative promoting IT projects since the mid-1990's. A great portion of the South Korean population is concentrated in Seoul and its metropolitan area, where many people reside in housing complexes. This is an appropriate environment for ADSL, and its coverage has expanded due to its low pricing, which since its introduction has fallen even further as a result of fierce competition among providers. Today, more than one-half of wired broadband subscribers use fiber to the home and optical LAN with sustained transfer speeds of greater than 50 Mbps.[197]

In general medicine, receipts (medical fee bills) and other documents have been increasingly digitized, such that the nationwide digitization rate for medical billing was already 88% in 2006 and almost 100% of this information has been made available online at dispensing pharmacies.[198] Nevertheless, telemedicine is observed only in the government's primary-level research and not in practical settings due to legal constraints.

South Korea is a rapidly aging society, just like Japan. Thus, the "u-healthcare" industry, which combines information and communication technology with medicine, garners much attention for future healthcare services. This concept includes telemedicine and also remote health control. It is most likely that, once the regulations are relaxed, services at an international standard will immediately be available in South Korea, where the IT infrastructure is well established.

Digitization

Though the number of WSI systems in South Korea is smaller than that in other Asian nations, WSI is being applied in educational conferences, but rarely for telepathology. Factors contributing to this include the South Korean medical laws and also the perceived lack of need for telemedicine considering the relatively large scale of South Korean hospitals and the presence of local pathologists. WSI for educational applications, on the other hand, are widely observed and enthusiastically adopted in the hands-on training of students and for self-study. WSI is highly appreciated by students and positioned as an important tool for pathological education.[199] It is likely that the WSI-based learning style will be common in the country, where onsite LAN is well developed in educational settings.

AUSTRALIA

Australia's Council for Scientific and Industrial Research Automated Computer Mark 1 (CSIR MK1), which ran its first program in 1949, was the fourth stored program computer in the world. This and the replacement machines in Sydney, SILLIAC and KDF9 were used for medical and pathology research including Fourier analysis of pressure and displacement waves to understand the elasticity of arteries. Between 1969 and 1971 three Australian preventive healthcare organizations began using computers for EHRs. All these systems included a pathology LIS. Those organizations were Medicheck and Preventicare in Sydney and the Shepherd Foundation in Melbourne. Medicheck, modeled on the Kaiser Permanente Multiphasic Health Screening Centre led by Morris Collen (after whom the American College of Medical Informatics Prize is named), had its own pathology laboratory and installed the IBM 1800 while Preventicare, which developed into New South Wales' largest private pathology laboratory, used the IBM Call 360 time-share service. Both developed their own software. This was front-page news at the time and seen as a threat to good medicine. Around the same time an LIS written in assembler on ICL hardware (Hospro) was developed and became the dominant system in private pathology practices in Australia. These LISs were later replaced by one of the world's first LISs that used a high transaction relational database-Triple G's Ultra (so-called after the three Australian developers who called one another George but were actually Mike, Peter and Brian). Triple G sold in Canada and the USA, and the company was subsequently acquired by GE.

Other LISs developed in Australia of note are:

- MGH Utility Multi Programming System (MUMPS) based system first developed by Détente in 1970's and now known as ISS-Omni-Lab installed in the United Kingdom and New Zealand. This was redeveloped by Sonic into their Apollo system which is now in use in their laboratories around the world.
- Pick based system from last resort support which is sold into the United Kingdom.
- Delphi and HL7 based kestral and medical objects LISs-both organizations at the vanguard of informatics standards development and recognized for having contributed significantly, especially to HL7.

The first electronic transfer of pathology reports from laboratories in Australia was in 1969 using teletypes on the Preventicare IBM Call 360 network. In the early 1970's, this network got as large as 250 sites in four states and was reputed to be the third biggest network of its kind in the world.

The first pathology transfer using the Internet was in the early 1990's, but the most common method then was modem to modem communication. In 1993, a *de facto* standard for this purpose was introduced with an agreement between two dominant Queensland laboratories. This was a FORTRAN like message called Pathology Information Transfer (PIT) that was and still remains in wide use. In 1996, a Standards Australia Committee (IT 14-6-5) was established ostensibly to answer which was the best Standard for Australia to adopt for pathology results reporting-PIT, EDIFACT or HL7?

In 1997, Standards Australia established a relationship with HL7.org (and later HL7 Australia) and in 1998 Australian Implementation Standards AS4700.1 ADT and AS4700.2 for Pathology Orders and Results were published. A detailed handbook for pathology messaging (HB262) followed in 2002. The Standard pointed to a subset of LOINC codes as the recommended terminology for the test name (OBX3). This standard for electronic communication was taken up in the National Pathology Accreditation Advisory Council "Requirements for Information Communication" publication in 2007, and so forms an integral part of the requirements for laboratory accreditation in Australia. It is estimated that there are around 100 million pathology messages a year and it is now the usual manner for delivering a report, and in some places now also used for ordering.

In 1993, the Australasian Association of Clinical Biochemists sponsored a satellite meeting of the International Federation of Clinical Chemistry and Laboratory Medicine dedicated to pathology informatics at Uluru in the middle of Australia. Among the eminent invited speakers were Dr. Octo Barnett from the MGH, who was instrumental in designing and programming one of the first comprehensive HIS. This was followed by a meeting a decade later sponsored by the Health Informatics Society of Australia and in 2007 the first World Congress in Pathology Informatics co-sponsored by the API, the Health Informatics Society of Australia and the Royal College of Pathologists of Australasia (RCPA).

Pathology informatics research and projects reported at these meetings and subsequent ones included:

- The application of ripple-down rules in pathology decision support (1993)
- Privacy in community pathology (2002)

Government Quality Use of Pathology Committee Projects (2003-2007):

- The chain of information custody
- The role of pathology informatics in a quality framework
- The influence of computers on ordering
- Terminology
- Electronic reporting and ordering
- Natural language processing of surgical pathology reports
- Evaluation of pathology order entry systems in hospitals
- A seminal work on Infectious disease informatics (2009).

Unlike teleradiology, where Australia is a major player, telepathology has not yet become routine. Virtual microscopy, using Aperio, has however been a component of the RCPA Quality Assurance Programs since 2008. In 2007 a national workshop on safety and quality in pathology identified workforce and smart requesting and reporting as three of the top five issues that should be addressed in Australia. This set the agenda for funding through the Quality Use of Pathology Program of the Australian Department of Health and Ageing. The role of the health informaticist was recognized in the 2008 report entitled 'The Australian Pathology Workforce Crisis' and has been included in workforce considerations since. In 2012, the RCPA established a formal Informatics Advisory Committee of the same status as other sub-disciplines in pathology after having had ad-hoc taskforces for many years.

EUROPE

Stereography and the Infancy of Pathology Informatics

In the infancy of pathology informatics in Europe (1945-1970), much effort was focused on measuring sizes and numbers of nuclei, cells, vessels, glands and nerves by projecting microscopic images on a light screen equipped with a suitable grid.[200] This technique – later to be called stereology – would allow three-dimensional approximations to be extrapolated from two-dimensional measurements.[201] The history of stereology in pathology can be traced back to the 1950's, when H. Elias analyzed the structure of the mammalian liver,[200] and Tomkeieff and Campbell investigated in the structure of the mammalian lung.[201,202] Later, Cruz-Orieve applied rigorous mathematical algorithms to stereology, and Gundersen and Jensen published their ideas of the "fractionator", "nucleator" and "rotator" – statistical sampling techniques that allowed the observer to estimate particle volume and distribution in an unbiased manner.[203-205]

At that time, European research in pathology informatics was largely focused on attempting to associate stereological data with clinical findings, for example, morphological changes with cancer cell types, or to predict the survival of cancer patients.[206,207] Although several significant associations were reported initially, clinicostereologic correlation never made it past the experimental phase. On the other side, such experiments promoted further investigation and understanding of semi-quantitative methods in image evaluation, as well as research in classification, coding, and nomenclature.

Coding Standards and Natural Language Processing

Once the first computers became available, two important areas of research and development emerged: The standardization and codification of clinical nomenclatures (e.g., SNOMED, ICD) and natural language processing (and auto-coding) of free-text pathology reports.[208-213] These efforts quickly bore fruit and were integrated into routine pathology services. At the Institute of Pathology at the University of Heidelberg, for instance, there were projects to (a) enable "just-in-time" free text translation of autopsy findings and (b) pursue complete digitalization of all autopsy records back to 1841.[214]

The advent of computerized tomography technology in the 1980's induced a sharp decrease of autopsies. For instance, at the Institute of Pathology at the University of Heidelberg, the number of autopsies dropped down from 1200/year in 1970 to approximately 350/year in 2000; other European and German Institutes of Pathology displayed a similar trend.[215] It was around this time that interest in natural language processing for the automation of pathology reports waned, instead being supplanted by research in molecular biology and genetics.[216-218]

The drop in autopsies did not diminish the workload of pathologists. In fact, the concurrent rise in biopsies, fine needle aspirations, and surgical specimens created an overwhelmingly heavy workload for pathology departments throughout Europe, along with the need for sophisticated logistics, financial analysis, and clinician-facing electronic communication tools in the laboratory.

Laboratory and HIS

In Europe, the increase in biopsies induced research in different aspects of pathology informatics. Questions on to handle the enormous number of biopsies and other specimens, how to classify the obtained diagnoses, and how to correctly manage issues of reimbursement arose,[219] eventually resulting in the need for the first precursors of modern LISs.[220] Advanced tissue testing modalities, most notably immunohistochemistry and DNA sequencing, drastically increased the complexity of routine tissue handling, in turn requiring a standardization of laboratory techniques and performance.[221] It was soon recognized that LISs themselves require regulation and standardization, which gave rise to formal certification of LISs. Such certification is now considered to be mandatory since the beginning of this century.[222,223]

At the same time, similar factors in the health care industry at large forced hospitals to introduce electronic record-keeping systems, and thus HIS were increasingly adopted in the 1990s.[224] In Germany, LIS and HIS are strongly controlled by obligatory insurance companies: employees who earn less than a certain salary per month are mandatorily insured by one of these companies. These companies provide reimbursement for care which is calculated by so-called reimbursement codes (codes for diseases, therapeutic and diagnostic examinations, all of which correspond to a flexible, fixed amount of Euros). The financial value of each code is locally and periodically regulated and depends mainly upon the local and momentary contribution of the insured workers to the insurance company. Thus, the management and maintenance of LIS and HIS in combination with the demands of certification is highly region-specific. Commonly, these systems require an update every 3 months.

With only a few exceptions, all patients in Europe have been equipped with an insurance card. These cards commonly integrate a solid-state electronic storage component that contains the patient's personal identifiers and the patient's insurance company. While these cards have carried no medical records up until now, trials are now underway to include comprehensive medical records on insurance cards.[225] In most cases, these data can be electronically transferred into the HIS, and afterwards into the LIS in hospitals, or into the local administration system of private pathology institutions. This allows for true portability of a patient's personal health records, as well as easy billing and reimbursement on the part of the institution.[225]

LIS and HIS are well developed in nearly all Western European countries including Belgium, Denmark, Finland, France, Great Britain, Iceland, Ireland, Italy, Norway, Portugal, Spain, Sweden, and the Netherlands. Those in former socialistic EU countries such as Estonia, Latvia, Lithuania, and Poland have introduced well developed LIS and HIS in combination with the mandatory renovation of their bigger hospitals.

The implementation and maturation of LIS and HIS was forced by the demands of public health and the government. Standardization of image transfer (in radiology) and medical records inside and in between different hospitals were considered to be prerequisites for success. The implementation of PACS and that of DICOM standards occurred in the middle to end of the 1990's. At present, more than 80% of hospitals and private institutions (radiology practices) are assumed to be equipped with such systems to the best of our knowledge.

Image Analysis

The development of measurements at a light microscopic magnification was characterized by three milestones in the 1980's-1990's, namely the development, implementation and standardization of DNA cytometry, syntactic structure analysis, and communication in diagnostic pathology.

DNA cytometry was the first and to our knowledge only pathology measure that introduced fixed, reliable, and commonly agreed measurement standards and error limitations, for example, a standard deviation of less than 5%, and others.[226-229] It is a crude measurement procedure of genetic abnormalities in a nucleus (total amount of DNA) and is based upon the stoichiometric light absorption of Feulgen stained DNA. The analyzed parameters include ploidy, S-phase, and 5C exceeding rate.[226-229] In recent years, DNA cytometry has been replaced by genetic examinations that permit a more detailed insight into chromosome, genes, DNA sequences, and proteins.

Syntactic structure analysis is a measure of structures present in cells (or nuclei). It utilizes graph theory to successfully analyse and annotate properties between nodes (edges) in combination with properties of nodes (vertices). It can be considered as a direct successor to DNA cytometry.[230-234] The reported results and derived data (e.g., Structural Entropy) have been shown to be of prognostic significance for certain patient populations, most notably lung cancer patients with intra-pulmonary metastases.[235-237] At present, the technique has been expanded to IHC images, and reported being suitable for determination of so-called areas of interest in WSI.[238-241]

Telepathology

Early Events Prior to the Internet

The history of telemedicine is closely associated with the technological development and progress in medical diagnosis and treatment.[242,36] Most efforts focused on diagnosis (teleradiology, telepathology, teledermatology, tele-endoscopy, etc.), and only a few investigations were devoted to teletreatment such as telesurgery.[242,36,243-246,178,247] The floodgates of telemedicine were opened by the National Aeronautics and Space Administration of the USA in the 1960's.[245,178,248-251,177,252-255] Telemonitoring systems had to be implemented in order to monitor the health condition of astronauts.[256-263] These included continuous monitoring of cardiovascular functions as well as those of brain functionality.[242,253,264,265] Based upon these experiences, earth-bound telemedicine trials were performed in the USA first. One of the earliest events was the video transmission of black and white blood smears from the Logan International Airport, Boston to the MGH by W. Beck and K. Bird in 1968.[245,254,266,267] Despite some tele-education and distant cytology consultations done at John Hopkins Hospital, Baltimore, USA (J. Frost)[268-271] in 1979, it took about another 20 years until further investigations in telemedicine followed. They started with USA-based trials.[266,140,272,273] European investigations followed about 3-4 years later.[248,274-279] At that time, telemedicine was based mainly upon still images, and those that were performed using the remote control systems (mainly for intra-operative frozen section). These considerations are based upon the three different types of tissue–based diagnostic needs (pre-, intra- and post-operative diagnostics.[36,280-286] With the exception of cardiology, most investigations regarding telemedicine trials included still images.[247,248,252,287-299] Still images for telemedicine investigations were seen also in radiology (including ultrasound examinations), surgical pathology, and dermatology.[247,276-278,295,298,300-311]

Telecardiology, however, did not include still images, as it relied on the transmission of analogue signals. In fact, the first telecardiology trial was reported by Wilhelm Einthofen (1860-1924), who in 1905 transmitted heart beats by telephone.[312-315]

This historical event remained silent for more than 50 years until the need for bridging long distances of inaccessible heart functions was evident for astronauts. In Europe, the electronic transmission of electrocardiogram signals to specialized clinics took place in the 1980's. The analogue signals were acquired by specific electronic devices (frame grabbers) and the patient could be monitored for at least 24 h.[295,313-316] Ultrasound telemedicine devices had already been suggested in 1978.[313-320] However, it was only in the 1990's that these emergency devices were available for patient care in Europe.[250,264,265,310]

The common telecardiologic devices included ambulatory Holter monitors and loop event recorders, or event-triggered monitors. Similar to other telemedicine fields the preferred solutions have been an end to end connections, i.e., a fixed client – observer line.[250,265] In addition to telecardiology, the development of telemedicine applications in Europe was formed by other medical fields that use images for diagnosis, such as dermatology, pathology, and radiology.[177,316,321-325,327-341]

Intensive research to explore the potency of this new technology was remarkably enhanced by the on-going technological development. Here, three different "coordinates" have to be mentioned:

- Velocity and the kind of line (telephone) connections available,
- Systems of image acquisition and display, and
- Electronic communication systems.

To start with, telecommunication in Europe was characterized by a unique situation in which state owned telecommunication companies dominated the market. Private telephone companies did not exist at the beginning of the telemedicine era. Therefore, the analogue lines could be replaced by digital line connections without major difficulties or without dealing with (intra-state) different digital standards. The ISDN was created by the European Telecommunication Standards Institute in 1989 and implemented as a European Telecommunication Standard in 1993.[342]

European efforts with telepathology started, however, prior to this development. Of particular interest was the immediate transfer of a (primary) diagnosis in surgical pathology during frozen section. This involved the replacement of specimen transportation from smaller hospitals, which were not equipped with an Institute of Pathology, by the electronic transfer and remote control of microscopic images.[121,343-351] Several specific telepathology systems have been developed for this purpose.[343,350,352-357]

In 1988, a routine telemedicine service was started by T. Eide and I. Nordrum to provide three smaller hospitals with an intra-operative frozen section service.[334,350,358] The hospitals were located at a distance of 300-400 km from the Institute of Pathology of the University of Tromsö, Norway. A specific end-to-end user (store-and-forward) system was developed. By 1993, more than 150 intra-operative frozen section diagnoses had been reported through this service.[275,122,359] At the same time, the University Hospital of North-Norway performed trials in teleradiology, teledermatology, tele-otorhinolaryngology (remote endoscopy), remote gastroscopy, tele-echocardiography, remote transmission of electrocardiograms, telepsychiatry, teleophthalmology, teledialysis, tele-emergency medicine, tele-oncology, telecare, telegeriatrics, teledentistry, and maritime telemedicine.[291]

Telepathology trials confirmed the following:
Intra-operatively obtained microscopic images could be acquired with an image quality that was sufficient for reliable diagnostic purposes.

The velocity (bandwidth) of the (analogue) telephone line connections permitted a stable transfer of images.

The diagnostic error rate of this technology was in the same range as that of conventional light microscopy frozen section technology, which served as the gold standard.

Patients greatly benefited from this technology by being treated in accordance with the latest guidelines, by avoiding the need to be transported over a long distance, and minimizing their risk of potential repeat surgical treatment.

The costs of this technology could be compensated by using reliable intra-operative diagnostic statements that translated into potential financial reimbursement.

The impact of the Tromsö trials on the development of European telemedicine (pathology) cannot be overstated.[242,360-363] Several telepathology teams followed suit with their own investigations on the use of this technology to support a remote frozen section service, and reported similar results.[298,332,343,346,351,357,364-381] This applied technology seemed to be promising, and was considered to increase the reputation of smaller hospitals, helped to establish larger institutes of pathology which would take over the services of smaller institutions, and provided patients with the latest technology for medical diagnosis and treatment. At about the same time, in 1990, Kayser *et al.* reported on different aspects of telepathology.[36,249,285,338,360,382] They performed the first expert consultation trials in Germany between Darmstadt, Heidelberg, and Mainz, three cities each with about 120,000 inhabitants [Figure 10], which was followed by the first quality control board examination of lung cancer cases using telemedicine in 1992.[36,362,383] The year 1992 can be considered to be one of the milestones of early telemedicine in Europe because:

- The Tromsö telepathology group reported their successful trials
- A unique telepathology network was installed in France by E. Martin, P. Dussere, and G. Brugal
- The first European conference on telepathology was held in Heidelberg
- The first international conference of telemedicine took place in Tromsö, Norway.

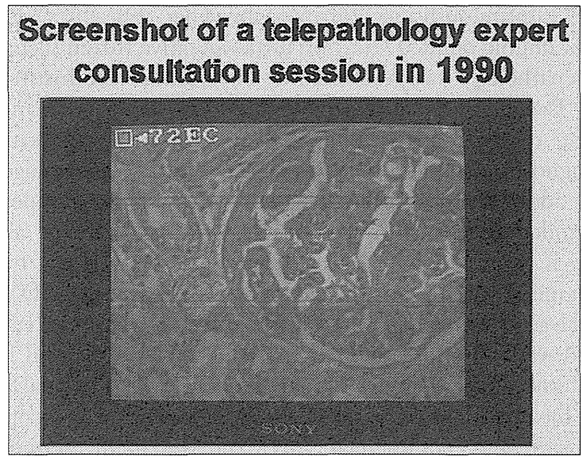


Figure 10: Demonstration of image quality of first expert telepathology trials in Germany, 1990. Note the breaks of line connections

These two aforementioned conferences solidified the acknowledgement of telemedicine in Europe, and all subsequent annual national conferences of pathology since 2002 included telepathology in their themes. Bi-annual European telepathology conferences were held without exception in:

- Heidelberg (Germany, 1992)
- Paris (France, 1994)
- Zagreb (Croatia, 1996)
- Udine (Italy, 1998)
- Aurich (Germany, 2000)
- Heraclion (Crete, Greece, 2002)
- Poznan (Poland, 2004)
- Budapest (Hungary, 2006)
- Toledo (Spain, 2008)
- Vilnius (Lithuania, 2010)
- Venice (Italy, 2012)

During the decade 1990-2000, there were several innovative European trials, some of which were successful, others not. Innovation by itself, however, does not assure success. The technological environment has to be mature in order to accept disruptive efforts, and to provide the "soil of success".[384] One successful application was the implementation of telepathology in a modern pathology laboratory in Cambodia, where a Cambodian-Thai-German pathologist team formed a working group (DIAG_AID) and trained Cambodian colleagues in diagnostic surgical pathology.[242,380,385] Only three experienced Cambodian pathologists were working in Cambodia at that time. A telepathology system was implemented at the Sihanouk Hospital Center of HOPE in 2002. It relied on the iPATH servers and was in use until the termination of the overarching iPATH system.[14,386,387] This infrastructure served for both assistance with immediate diagnoses and continuous education of young colleagues. The European assistance was continuously accompanied by Thai colleagues. The first double blinded study on intra-operative frozen section telepathology was performed by H. Guski at the Institute of Pathology, Charite.[242,383,394,395] This study confirmed that digital images could be judged with the same diagnostic accuracy as conventional microscopic images. An additional innovative successful trial was the European founded Europath project headed by Dr. G. Brugal and Dr. K. Kunze.[388-393] To our knowledge, this was the first telemeasurement system in cytology (using static DNA analysis of Feulgen stained nuclei). It was started in 1996 and was fully implemented in 1999. It was employed for determining individual measurements, as well as analysis of measurement accuracy of both submitted microscopic images and commercial DNA measurement systems. A less successful trial was the introduction of the PARIS project (pathology and anatomy review international score) in 1999. The focus of this project was to peer review potential scientific articles and to provide the authors with an internationally acknowledged score independently from the journal in which the authors wanted to publish their article. Only a few authors participated in this free service. The project resulted in the first solely electronically published medical journal (the electronic Journal of Pathology and Histology), which was eventually cancelled due to lack of subscribership.[36,328]

The Internet Era

The advent of the Internet significantly influenced the development of telepathology in Europe.[344] Contemporary with the development and implementation of the Internet, preliminary development of the first WSI scanners started.[327,396-403] Both technologies impacted the application and distribution of telepathology; the Internet made telepathology easy to use which levelled the playing field between expert and non-expert computer telecommunication users.[242,327,368,404-409] Whereas in the pre-Internet era the implementation and maintenance of a telepathology network required high technical expertise and financial investment – thus sharply limiting the number of sites that could support telepathology – the Internet changed this allowing groups to implement telepathology platforms built from open-standards roots.

iPATH – developed by Brauchli and Oberholzer at the Institute of Pathology, University of Basel – is perhaps the most successful of these platforms.[387,14,13,410] It was first implemented in 2002, and has served over 150 user groups around the world. More than 15,000 telepathology cases have been examined using this system. Its success can be attributed to the basic operating principle or iPATH: the development of an easy to use system optimized for diagnostic consultation in pathology that also permits the creation of individual "working groups" (for example, specialized for cytology, lymphomas, or countries such as Cambodia, etc.).[386,387,13] Participating experts were notified about a client's request to remotely view a case via E-mail, and after rendering their opinion, the client was in turn notified via E-mail. The iPATH system was built using only open source software; due to this, local iPATH server installations were located all over the world.[39] Two similar Internet-based telepathology platforms were created during this time period, one in the USA at the AFIP (Washington, DC),[411-414] and the other at the Institute of Pathology, Charite, Berlin, Germany, sponsored by the Union Internationale contre le Cancre (UICC), Lyon, France called UICC-TPCC (UICC Telepathology Consultation Center).[396,407,415,416] All of these systems – including iPATH – have since been terminated. Two of them (iPATH, AFIP) have been replaced with commercial software packages. iPATH was the first telepathology platform to offer such tremendous flexibility, and as such enterprising individuals soon realized that it was possible to formulate something akin to a virtual department of pathology around it.[242,36,384] To accomplish this, administrators and pathologists were recruited; administration and duty plans were drawn up, and the first ever Virtual Pathology Institution (VPI) was born.[384] This VPI served the total tissue – based diagnostic needs of the Salomon Islands for several years.[417] Oberholzer and Brauchli implemented a pathology laboratory in the Solomon Islands and trained technicians to perform gross examinations on excised tissue create H and E glass slides and submit corresponding microscopic images to the VPI. Usually, a telediagnosis could be rendered within 24 h.[417] Prior to this solution, all tissue had to be sent to Australia, with an average turnaround time of roughly 2 months. This VPI was in operation for more than 5 years. It was, however, unfortunately terminated due to the fact that neither the Salomon Islands Government nor charity organizations were willing to consistently fund it. Nevertheless, this remarkable experience can be considered as proof that functional VPIs can be implemented.[384]

The recently (2011) released telepathology forum called Medical Electronic Consultation Expert System (MECES) is an example of a platform that has tapped into Web 2.0 and WSI technologies.[418] It focuses on performances experienced from iPATH and UICC-TPCC in combination automated electronic measurements (EAMUS™), still image acquisition, and WSI. In combination with an internationally well-known expert team, MECES will probably become a new milestone in the history of European telepathology.

CONCLUSION

The history of clinical (medical) informatics, a relatively new domain of computers and information science in healthcare, has been previously described.[419-421] However, to the best of our knowledge, this article represents the first account of the history of pathology informatics from a global perspective. Significant progress in our field has occurred in many countries around the world, and this rate of progress seems to be increasing. Progress in pathology informatics has been tied closely to developments in technology, particularly the advent of computers, the Internet and more recently digital imaging. It is apparent that major drivers in the field included the need for pathologists to comply with national standards for health information technology and for telepathology applications to meet the scarcity of pathology services and trained people in certain countries or underserved regions. Our predecessors are acknowledged for their insight, enduring investigations and trials to show us what works and what failed, and helping us solidify the current field of pathology informatics. This is a time of great excitement and opportunity for our discipline. Advances in genomic, molecular, diagnostic, imaging, and data analytic techniques have allowed – perhaps for the first time – a glimpse into a future in which hidden patterns embedded in our visual (e.g., WSI) and numerical (e.g., laboratory tests) data will be brought to light and exploited for the benefit of patient care. For us to face the challenges, and capitalize on the opportunities the "digital decade" of personalized medicine, it is imperative that we face our challenges and overcome ever changing barriers with the same vigor and excitement displayed by those who have gone before us. The history of pathology informatics is the story of us all. Those who have gone before us have left a rich foundation for us to build upon, but this story is not yet finished. We can be visionary leaders, bold explorers, and drivers of positive change throughout our healthcare systems; in doing so, we have the opportunity to take the destiny of medicine into our hands. Or we can be content to be followers or even ignore the disruptive changes that this history so clearly points out are looming before us; this being the path of diminishment and relegation to eventual irrelevance. We have the ability to write the end to this story. Where we go from here, is up to us.

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