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Human Pathology Perspectives in Pathology “On Being a Pathologist”

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Introduction

It has been 50 years since I completed my undergraduate training in the College of Literature, Science and Arts at the University of Michigan. I was admitted to Medical School in the fall of 1955 after three years of undergraduate training. I immediately began doing research in the Department of Microbiology/Immunology under Professor Arthur Johnson and in the Department of Pathology under the tutelage of Professor Murray Abel, trying to figure out how lipopolysaccharide (LPS) derived from *Escherichia coli* causes enhancement of the immune response (1). After the first two years of Medical School, I was persuaded to accept a U.S. Public Health Service Post-Sophomore Research Fellowship in the Medical School, being the first medical student to follow this route at the University of Michigan. My classmates were aghast that I would temporarily drop out of Medical School to undertake such a daring task, but I was determined to pursue a full year of research while also taking some undergraduate courses in the College of Literature, Science and Arts in order to complete requirements for the Bachelor of Science degree, which was issued in the summer of 1958. Most Pathology Departments in those days were focused on Surgical and Autopsy Pathology and, while the clinical diagnostic laboratories were just beginning to become organized under the leadership of pathologists, Laboratory Medicine (Clinical Pathology) was a nascent part of Pathology in the late 50's. Specialty clinical diagnostic laboratories were often fragmented, being under the control of individuals who were either basic scientists or physicians with a particular interest in a diagnostic laboratory specialty. For example, at the University of Michigan Hospital, Microbiology was headed by a surgeon with an interest in post-operative infections, tissue typing was supervised by a Ph.D. in the Department of Surgery, and much of hematopathology was supervised by the hematologists in the Department of Internal Medicine. This fragmentation ultimately became moot in 1985 when, under President Ronald Reagan, the Tax Equity and Fiscal Responsibility Act (TEFRA) was passed, effectively abolishing financial incentives for these special, limited function clinical laboratories. At Michigan, this resulted in the transfer of nearly all such laboratories into the Pathology central clinical laboratories. Hospital officials embraced this change, since it took away from them financial decisions that had to be negotiated separately with each one of the “splinter” laboratories.

In the 1960's and 70's, the attitude in Pathology was that a really capable surgical pathologist could cover nearly every aspect of surgical pathology efficiently and reliably. The inexorable trends towards sub-specialization in both Surgical Pathology and Laboratory Medicine would

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accelerate as it became clear that pathologists could no longer be all things to all people, either in the setting of Surgical Pathology or Laboratory Medicine. Even within these two areas, there would be an inevitable super-specialization as new information and progress made it nearly impossible for one person to master all of the data in either arena, at least in the setting of hospitals with large bed capacity (>500).

After Medical School (1960–65)

Upon completion of Medical School in the summer of 1960, I was unable to decide if I wanted to end up in Internal Medicine because of my interests in Immunology or in Pathology because of my research experiences. I decided to pursue a “Straight Medical Internship” at Bellevue Hospital, on the Third Medical Division (New York University). This essentially was a first year of residency in Internal Medicine, although it also featured some brief stints in areas such as surgery and obstetrics. Being a house officer in Medicine at Bellevue Hospital was especially inspiring because of the Medicine Chair, Lewis Thomas (Figure 1). Thomas was becoming revered as an incisive author of publications dealing with biological phenomena. He became widely known for his short articles on “Notes from a Biology Watcher” appearing monthly in the New England Journal of Medicine. In the year at Bellevue, I decided that I would be more comfortable pursuing a Pathology residency rather than one in Internal Medicine, so in the summer of 1961 I returned to Ann Arbor to pursue a two-year program in Anatomic Pathology under Jim French and his colleagues. I was able to continue doing some research during that period of time, but I realized that I would best be prepared for the future by doing a post-doctoral fellowship someplace other than in Ann Arbor. I was torn between a post-doctoral fellowship at NYU, which had a very strong Department of Pathology and Immunology, versus going to the relatively new institute (established in 1961) in La Jolla, California (Scripps Clinic and Research Foundation, SCRF) headed by Frank Dixon. Ultimately, I decided to undertake a post-doctoral fellowship in La Jolla and settled into that beautiful part of Southern California in the summer of 1963. For the next two years I worked with Charles G. Cochrane (Figure 2), my chief mentor and Hans J. Müller-Eberhard (Figure 3), my co-mentor, trying to define the role of complement activation products in the emigration of blood neutrophils into extravascular locales. We induced deposition of complement-fixing IgG immune complexes in venular walls (“reversed passive Arthus reaction”) as well as using Boyden chambers for in vitro chemotaxis. We clearly established in the vasculitis model that blockade or consumptive depletion of the complement system prevented the influx of neutrophils (2). We were able to determine that the complement dependent chemotactic factor was C5-derived. SCRF at that time was a relatively small institute with approximately 5 full time senior scientists and about a dozen post-doctoral fellows, a tiny fraction of its future size. Nevertheless, the time in La Jolla was exhilarating, and the scientific progress I was making there was extremely satisfying.

The U.S. Army Medical Corps and the A.F.I.P. (1965–71)

In 1965, at the beckoning of the U.S. Army, I left La Jolla and became Captain in the U.S. Army Medical Corps with assignment to the Armed Forces Institute of Pathology (AFIP) at Walter Reed Army Medical Center in Washington, D.C. For the first two years I was an active duty Medical Officer, essentially spending most of my time as Chief of the Immunobiology Branch where research was the primary effort. In 1967 I resigned my commission as an Army Medical Officer and switched to a relatively high level civil service position in research at the AFIP. While at the AFIP, much work was done to further define mechanisms of chemotactic motility of neutrophils and the chemical nature of factors that were chemotactic for neutrophils as well as for other types of leukocytes (especially lymphocytes). In the case of lymphocyte chemotaxis, we showed that in vitro stimulation of these cells produced a soluble chemotactic factor that could be responsible for accumulation of the bulk of non-antigen specific lymphocytes in allograft reactions or in delayed type hypersensitivity reactions (3).

U Conn Health Center (1971–80) and the University of Michigan (1980–present)

In 1971 I became Professor in the Department of Pathology at the University of Connecticut Health Center at Farmington, Connecticut, one of the new medical schools opening between the late 1960's and 70's. In 1973 the then Chair of the Department of Pathology, Irwin Lepow (Figure 4), left the Department of Pathology to become the Chair of the Department of Medicine at the same institution. Previously, Lepow and I collaborated on studies defining biological functions of anaphylatoxins as well as chemotactic factors (for neutrophils) released from bacteria in the log phase of growth (4). Soon after Lepow's departure from the Department of Pathology, I became Chair of the Department of Pathology at the U Conn Health Center until 1980. During the 70's, my research efforts focused on regulation of chemotactic factors, defects in chemotactic responsiveness in humans, and related topics.

In 1980, I was recruited back to Ann Arbor to become Chair of the Department of Pathology after 25 years of Jim French's tenure as chair, who decided it was time to retire. While Connecticut was an exciting and beautiful place, the opportunities at Michigan would allow me to lead an effort to develop a large immunopathology program and acquire resources for program expansion in the ensuing years. From the summer 1982 to the summer of 1985, I was also Interim Dean of the Medical School at a time when construction of the replacement University Hospital was underway, the Medical School class size reduced by nearly 30% (to 175), and many new research programs in the Medical School and in the Department of Pathology were initiated. During this time, we had to adjust to continuously changing federal reimbursement regulations, especially under TEFRA the onset of disease-related grouping (DRGs) which capped the Medicare reimbursement for each DRG. It was assumed that this would initiate a wave of cost containments. This did not occur. In addition, as Interim Dean, we established the Howard Hughes Medical Institute in the University of Michigan Medical School and four newly recruited faculty members in Pathology were the early members of that Institute. The clinical programs in Pathology continued to expand with ever increasing demands for highly specialized services in the areas of Surgical Pathology and Laboratory Medicine. In the 70's and 80's, the cloning techniques emerged as powerful research strategies, ultimately with many clinical applications. In the 80's at Michigan, for instance, Francis Collins and his colleagues described the mutations in cystic fibrosis and defects in the cystic fibrosis transmembrane conductance regulator (CFTR) (5). This was but one of many disease related studies in which the inherited basis of the defect was defined. Against strong pressures to remain in the Dean's office, I decided in 1985 to return full-time to the Department of Pathology and continue to recruit both diagnostic and research faculty, take a leadership role in establishing a Ph.D. program in Pathology, assist in recruitment of extremely highly qualified MD/PhD students into Pathology research laboratories, and continue to pursue my own research interests. In the 80's and 90's my research included defining the role of oxygen metabolites in inflammatory tissue damage as well as the emerging field of cytokines and chemokines as important mediators of the inflammatory response, with the research having a special emphasis on the lung. Over the past 8–10 years, our focus has continued in several of these areas as well as trying to define the molecular mechanisms of sepsis using polymicrobial sepsis (after cecal ligation and puncture) in rodents. Part of the reason for this focus in sepsis research was related to the very large and unresolved clinical problem, with nearly 600,000 sepsis cases per year in North America and with a death rate from 30–50%. There was also accumulating evidence that sepsis was a disorder in which regulation of the inflammatory response had been lost (6). In the summer of 2005, I stepped down as chair after 25 years at Michigan to move full-time into research and enjoy getting away from the numerous administrative duties related to the chair position.

Changes in Pathology Over 50 Years

Changes in the field of pathology over the past 50 years have been remarkable. As indicated above, there has been steady and inexorable increasing sub-specialization both in Anatomic Pathology and Laboratory Medicine. In the 1950's, Anatomic Pathology was the chief clinical endeavor. In the past 20 or so years, Laboratory Medicine has come into its own. In some academic Departments of Pathology, Laboratory Medicine is preeminent in terms of academic and research excellence. Soon after my arrival in Ann Arbor in 1980, it became apparent how transformative Pathology was becoming, as more and more monoclonal antibodies were available for immunostaining, causing this technology to become a powerful tool for obtaining additional information that had important bearing on diagnostic decisions. An example of one unexpected outcome was that, prior to this period of time, expensive and time-consuming transmission electron microscopy (TEM) had been used in cases when it was difficult to define the nature of a tumor. Features such as cytokeratin or tight junctions would allow one to more accurately identify the type of tumor (sarcoma versus carcinoma, subtype of lymphoma, etc.). With the advent of monoclonal antibodies capable of detecting multiple surface and intracellular markers, most of the clinical applications of TEM vanished. Currently, TEM continues to be an integral part in renal diagnostic pathology, in certain disorders of the central nervous system, to list a few important applications for TEM in the clinical setting.

With an ever expanding database in molecular biology, (including genomics and proteomics) and with molecular markers such as single nucleotide polymorphisms (SNPs), chromosomal translocations, etc., new strategies can now be employed for more effective diagnosis and understanding of diseases. It has become impossible for one person to master all the new knowledge and to integrate it into a diagnostic decision. In the space of the past several decades, it has become apparent that many diagnostic areas (such as cytopathology, neuropathology, dermatopathology, renal pathology, molecular diagnostic pathology, infectious diseases, etc.) require pathologists with highly specialized expertise.

A second theme of change has been related to the constant changes in reimbursement policies involving governmental and private insurers, and managed care systems, as each group has tried to cope with the increasing demand for services in the face of escalating costs. The dilemma continues to this day, with a battle between federally funded programs (such as Medicare), and federally and state funded programs (such as Medicaid). With increasing demand for new and expanded clinical services, with federal and state budgets growing at a much slower pace, with escalating costs of drugs and diagnostic procedures such as imaging, this has created tremendous tensions between states and the federal government in a scramble to try to contain costs and figure out how to reimburse new modalities (such as angiostatic drugs for cancer, implantable defibrillators, etc.) that add significantly to the cost of medical care. As indicated above, the passage of the TEFRA legislation (1985) initiated the era of DRGs in which it was assumed that managed care approaches would predominate in medicine and would contain costs. For many reasons, this has not happened, and costs of medical care have continued to escalate, representing an increasing portion of the annual gross national product. A little appreciated provision of the TEFRA act was the fact that, for governmental and academic employees, the traditional retirement limit at the age of 65 was abolished, creating interesting opportunities and challenges for both the federal government and the academic sector.

At the turn of the last century, completion of the human genomic sequence, followed soon by genomic animal sequences created a whole new world of opportunity and challenge, to the point that, with the cost of genomic sequencing dropping dramatically, individuals with adequate cash can now afford to have their own genomic sequence completed, although precisely what to do with such information and how to access the bioinformatic systems that

can accurately interpret the massive data are tremendous challenges. Connected with these changes are developments of “personalized medicine” in which genomic sequence information may be used for more effective diagnostic and therapeutic decision-making. However, before the use of genomic information becomes common-place, the issue of confidentiality and concerns about whether or not insurers will use this information to preclude individuals from insurance programs or charge considerably higher premiums will have to be worked out in a way that is acceptable to the public.

Such changes are also leading to a greater emphasis on interdisciplinary research in pathology. For instance, geneticists, biochemists and pathologists work together in order to interpret phenotypes in genetically manipulated mice in order to understand what changes have occurred and why. The complexities of this type of interdisciplinary research should not be underestimated. For instance, quite a few years ago when the human CFTR mutation of cystic fibrosis was produced in mice, these animals had no intrapulmonary defects although they did demonstrate changes in the pancreas (7). It is still not clear why the CFTR mutations in humans lead to such striking changes in lungs whereas in mice with the same mutations the lungs have no phenotype. Other areas of interdisciplinary research include the broad area of biomedical engineering with device development, requiring participation of basic scientists as well as clinician researchers. It is only through this type of collaborative interaction that the most efficient research can result in development of effective products that can be used in humans.

Finally, it is interesting to note a new wave of expansion of medical schools, involving increased sizing of existing schools and development of new schools (some via increased state funding and some evolving as a consortium between private hospitals and non-public organizations). In a sense, we are seeing something akin to what happened in the 1960's and 70's, although this time around the driver is not the federal government but rather state governments and private agencies. Another determinant relates to geographic need for new medical schools. For instance, in a rapidly growing state like Arizona, the single state medical school is in Tucson, the home base for the University of Arizona. The Tucson area currently comprises approximately 300,000 individuals while the Phoenix area comprises of over a million, with many highly regarded hospitals. Not surprisingly, Arizona has decided to establish a second state-related medical school in the city of Phoenix. In La Jolla (CA) there is a move to establish a new medical school at the Scripps Research Foundation that would emphasize the traditional training of medical students together with intensive training in bench research. In the state of Michigan, a new medical school linked to Michigan State University in East Lansing is being established in the city of Grand Rapids, in the Western part of the state, in a thriving city and with support from private organizations. Because of the fact that the federal government is not actively involved in providing significant financing for such ventures, it is likely that expansion of medical schools in the U.S. in the next decade will not come close to the scope of new schools established in the 60's and 70's. Nevertheless, what is currently going on indicates that there are considerable pressures locally and within the states to expand medical educational opportunities.

In the setting of Chairs of clinical departments, in many ways Pathology offers unique opportunities. In most clinical departments, especially those involving surgical subspecialties, Chairs need to be active in the operating rooms in order to be considered as peers by their clinical colleagues. In Pathology departments, Chairs are often little, if at all, involved in diagnostic Surgical Pathology or Laboratory Medicine, yet they earn acceptance and respect from their departmental colleagues. This means that Chairs of Pathology have special opportunities to pursue areas of academic endeavor, such as in education (authoring authoritative textbooks) or in research. In some situations, academic pathology departments have become enmeshed in the extramural laboratory business of generating “outside” income to supplement intramural income. This has occasionally taken the form of assuming administrative and

staffing oversight of non-academic hospital pathology units in the same or nearby geographic regions. In such situations this may compel the sitting chair to spend significant amounts of time on the extracurricular business. However, such situations are exceptional in academic Departments of Pathology in the U.S. In the past several decades, appointment of new chairs of Pathology departments has usually involved individuals with strong research credentials rather than those with superlative diagnostic skills in Surgical Pathology or Laboratory Medicine. Whether this trend will continue remains to be seen.

Conclusions

Pathology is in a “golden period” when the rapid advances in molecular biology, genomics, proteomics and informatics are going to have profoundly important impacts on medicine as well as in diagnostic and research activities. Such changes will have enormous influences on diagnostic decisions and therapeutic interventions. Many of the new molecularly based microbial and viral diagnostic tests will allow rapid and reliable interpretations of the invading infectious agent. Genomic and proteomic markers will likely allow more reliable classifications of tumors and in many cases may allow predictions regarding the most effective therapeutic interventions. The possibilities for important advances in the medical setting are endless. In all of these endeavors, Pathology will play a key role. We should all embrace and accept the new order.

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Biography

Brief Summary of Career of Peter A. Ward

- 1960 – MD, University of Michigan Medical School
- 1960–61 – Straight Medical Internship (Bellevue Hospital, NYC, Third Medical Division – NYU)
- 1961–63 – Residency in Anatomic Pathology, University of Michigan Hospitals
- 1963–65 – Post-doctoral fellow, Scripps Clinic and Research Foundation (La Jolla, CA)
- 1965–67 – Captain, U.S. Army Medical Corps, Armed Forces Institute of Pathology (Washington, DC)

- 1965–71 – Chief, Immunobiology Branch (AFIP)
- 1971–73 – Professor, Department of Pathology, University Connecticut Health Center (Farmington, CT)
- 1973–80 – Professor and Chair, Department of Pathology, University Connecticut Health Center (Farmington, CT)
- 1980–2005 – Professor and Chair, Department of Pathology, University of Michigan Medical School
- 1982–85 – Interim Dean, University of Michigan Medical School
- 2005 – present – Stobbe Professor, Department of Pathology, University of Michigan Medical School

Figure 1. Lewis Thomas, M.D. (1913 – 1993)

Lewis Thomas occupied a number of important positions (Dean at NYU and Yale Medical Schools, CEO of Memorial Sloan-Kettering Cancer Center). He was widely known as a poet-philosopher of medicine and for his monthly articles (“Notes of a Biology Watcher”) in the New England Journal of Medicine.

Figure 2. Charles G. Cochrane, M.D. (1931 – present)

Charles Cochrane was my chief mentor while I was a post-doctoral fellow at Scripps Clinic and Research Foundation (SCRF) in La Jolla, CA. He is widely known as an immunopathologist and for his studies of the inflammatory response.

Figure 3. Hans J. Müller-Eberhard, M.D. (1927 – 1998)

Hans Müller-Eberhard was my co-mentor at SCRF from 1964–65 and was widely acknowledged for putting complement on a solid biochemical basis.

Figure 4. Irwin H. Lepow, M.D., Ph.D. (1923 – 1984)

Irwin Lepow was a scientific collaborator and was widely known for his work in defining pathways and products of complement activation, especially the anaphylatoxins. As Chair of Pathology, he recruited me in 1971 to the U Conn Health Center Department of Pathology.