Practice beyond the microscope, a memoir: My years as a doctor's doctor

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February 2021—When I entered the practice of pathology the role was described as being a "doctor's doctor." That reflected the fact that physicians turn to the laboratory for so many tests that define diseases and determine the response to treatment, a reality true today. But my memories are of the more personal interactions with clinicians over the years as I pursued the practice of pathology beyond the microscope, and often beyond the laboratory.

Today, medicine is highly specialized with subspecialties in every field. These physicians are so well trained that it may seem as though there is no need for the pathologist beyond the walls of the laboratory. Indeed, many common medical problems are so well researched that standard practices in diagnosis and treatment are universally available. Although I have been retired and removed from the modern hospital environment, I wonder about the complexities of molecular diagnostics today, CAR T-cell therapies, diagnostic tests for COVID-19 and its antibodies, and other breakthrough areas of medicine. I suspect there remains much that the doctor's doctor can contribute. You just have to look, stick your neck out, and become involved.

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My experience along these lines began as a young resident at Walter Reed Army Medical Center during the Vietnam War in its early stages, the '60s. Many young men were being admitted to "Reed" with severe trauma and infected wounds, often presenting with spiking fevers, which raised the question of whether that was due to an infected wound or malaria, a disease we had not had much experience with since World War II. On my hematology rotation, I encountered many clinicians pressing us to find the malarial parasites on blood smears. Our lab had lost the art of the "thick and thin" smears formerly, the traditional way to diagnose the presence of diagnostic forms of the parasite. Thick smears were designed to layer the red blood cells so that one could hemolyse them, making it possible to see low numbers of these parasites that would establish the diagnosis. At the time, our lab was measuring the white blood cell count by an advanced method that used saponin to lyse the red blood cells, permitting a particle counter to enumerate the remaining white blood cells. It didn't take much experimentation to devise the conditions to provide a method to detect very few parasites by centrifugation, allowing the clinicians to rule out malaria and rule in other forms of infection. This test endeared us to the trauma surgeons and infectious

disease physicians challenged with the differential diagnosis of many patients. The method led not only to my first publication in a medical journal but to active participation with the clinical malaria team approach at Reed.

In a later phase of my training, while rotating in immunology, I had the good fortune to assist a young, recently drafted pathologist who had just completed his training at Columbia University. He was setting up a new test for systemic lupus erythematosus. After learning how to spell it, and marveling that my mentor had traveled to Baltimore to a meatpacking plant to obtain a calf thymus gland, I assisted him in cutting the tissue into 1-cm cubes and freezing them for subsequent use in making imprints on slides to establish the first antinuclear antibody test at Reed. We used immunofluorescent antibodies to identify patterns of nuclear staining along with the titer of the antibodies found to be virtually diagnostic of a disease that was readily recognized in its full presentation but difficult to recognize in the majority of patients with early or partial features. Rheumatologists were generous in extending appreciation for this advance, including the progressive sophistication of our recognition of different patterns of nuclear fluorescence in lupus and related collagen diseases. It was a lesson that there is much more to communication with clinicians beyond the printed result on a laboratory report.

After my service in the Air Force, I was privileged to enter private practice in South Carolina with an outstanding group of young colleagues, led by Joe Black, MD, who had established a reputation for high professional standards. Among their innovative practices was the inclusion of an admission complete blood count and, the classic for its time, the 12-test biochemical profile with review of each abnormal blood smear and the pattern of the biochemical tests by a pathologist. Each afternoon, the pathologist of the day would sign out abnormal blood smears and the abnormal biochemical scans. Often, the findings were correlated between the morphology and biochemistry. When striking findings would be recognized, a personal call would be made to the admitting physician informing her or him of the potential diagnoses raised by these findings. There were numerous cases of iron deficiency, vitamin B12 deficiency, hemolytic disease, leukemias, sepsis, hypothyroidism, hepatitis, occult myocardial infarction, and many other diagnoses raised for early confirmation and other related tests. While many of these were suspected, many were not, and it became apparent to us that many clinical problems were not recognized without our interventions.

The experiences with recognizing silent or atypical myocardial injury at a time when nonspecific tests such as the total creatine kinase, transaminases, and lactic dehydrogenases were the predominant laboratory tests to complement the electrocardiogram led us to pursue the more reliable creatine kinase isoenzymes early in their availability. I had set up the first total creatine kinase test at Reed in my rotation on clinical chemistry while a resident. We had thought at the time that it was a marvelous advance over the other tests, and it was, but only after later establishing the isoenzymes did we recognize how misleading the total was in isolation. This was a quantum leap in diagnostic sensitivity and specificity. It would lead later to my early investment in developing the cardiac troponin test while in Dallas at the University of Texas as director of the medical laboratories at Parkland Hospital. Finally, the test was truly sensitive and specific, sufficiently so that one prominent cardiologist, mockingly and skeptically, referred to our troponin results in a patient as a “Joe Keffer 5 gram Infarct.” It really was. He was wrong. Once again, there was demonstrated a need for an intimate investment in collaboration with the clinicians.

In South Carolina, an unusual patient presented to our outpatient laboratory, a Champion Stud Spaniel. Obviously old, yet regal, he was miserable with a seemingly untreatable ear infection with creamy pus draining from both ears. In spite of numerous injected and oral antibiotics administered by multiple veterinarians, there had been no relief. His loving master could no longer watch him suffer with endless pawing at his ears. He was scheduled to be put down. One of our doctors directed them to me and my pathology laboratory with kind words of hope. The first task was easy: Discover the bacterial cause of this obvious infection. We knew from the exam that it was a virulent bug and one not likely responsive to common antibiotics. Our cultures quickly confirmed that suspicion, identifying a potentially effective therapy, but we were reminded to respect the basics of dealing with infection: Drain when possible and irrigate the wound, if possible, to physically lift the infection and its products from the site. The hero in this case would be simple hydrogen peroxide and patiently, gently, and wisely wielded Q-tips. This classic approach quickly gave us encouragement during our daily visits. Our revered canine’s caring master learned the lessons with dedication. As the debris cleared, now we could directly administer the carefully selected topical antibiotic of choice for the *Pseudomonas* bacteria into the ear canal. The lessons learned: When challenged, go

back to basic principles. They are, after all, basic because they are truth.

One fascinating case in my early practice involved a young Black male who was bleeding profusely into his urine. We became involved in transfusing him. We learned that the urologist was planning to resect one of his kidneys that had been identified as the source of the hemorrhage because there was no other known approach. His problem was that he had sickle cell trait and it had been learned that, not uncommonly, such patients, owing to the low oxygen concentration in the renal papillae, would develop sickling in the capillaries, leading to infarction and renal papillary necrosis with life-threatening hemorrhage. It was a no-win situation. Further, upon reading recent literature on the subject, it became apparent that after resection of one kidney, it was known to recur in the sole remaining kidney. Resection of both kidneys was not an option. A treatment had been devised that was experimental and potentially life-threatening involving the gradual infusion of epsilon-aminocaproic acid. This would inhibit the enzymatic fibrinolytic activity in the renal papilla, which promoted the bleeding and prevented fibrin from stanching the flow by clot formation. At that time, there were few subspecialists in that community, and when the urologist declined to administer the critical infusion, which required constant monitoring and termination as soon as the bleeding was controlled, I became the default clinician. It worked. The young man recovered completely. Later, I read that the drug had been withdrawn for safety reasons. It is now approved as Amicar for treating intravascular fibrinolysis. I had become the doctor who needed a doctor's doctor.

In the early years of my practice, it became apparent that the field of endocrine testing was a frequent problem. In those days, screening for adrenal abnormalities typically relied on highly imperfect collections of a day's urine for the measurement of "hydroxy and ketosteroids." When dealing with perplexing patients in response to clinicians' queries, I realized we were measuring metabolic degradation products of the hormones that really mattered, cortisol and other specific steroids such as testosterone. This became possible in a timely fashion as the technique of the radioimmunoassay was just evolving. We had begun exploring the utility of direct cortisol measurements using fluorometry. While this was an advance over the older methods, it remained limited. With the specificity and sensitivity introduced using the radioimmunoassay, we now had rapid and specific assessment of the hormone level. What became apparent was that the static level of one measurement was not sufficient. We learned of the value of obtaining a baseline followed by administration of a stimulus, the ACTH testing protocol, which was the prototype for a range of testing strategies of either stimulation or suppression for many common endocrine disorders. Our experience evolved into a stimulating partnership with an endocrinologist whose office we served with our outpatient laboratory, Nelson Watts, MD, now professor of medicine at the University of Cincinnati. Together, we published a practical guide to endocrine testing through several editions.

The experience with adrenal testing was paralleled with even greater efficacy in thyroid disorders by the progression from measuring the protein-bound iodine to measuring thyrotropin (TSH) eventually with the highly sensitive TSH assay, which came to define both hypo- and hyperthyroidism.

Another unusual aspect of being a consultant to other physicians came in my time at Miami Beach's St. Francis Hospital. The large retirement community of the elderly became lovingly known to our nurses as "God's waiting room." Death and dying were issues needing attention in the '70s, and Elisabeth Kübler-Ross addressed them well in a secular form. We dealt with the ethical issues of disease and dying in the elderly. While dealing with death, usually the pathologist is principally involved with the autopsy. Our role in the medical staff, however, is central to the practice of medicine in a hospital environment; consequently, I became involved from the medical ethics perspective of death and dying. When is a person dead as opposed to experiencing profound depression of the brain, and what are the signals of the dying process? How are we, as a civilized society, to respond? Fortunately, having been trained in ethics at Villanova and later at Georgetown, I had a foundation upon which to develop. By good fortune, our chaplain held an advanced degree in bioethics, as the term became known. We formed a multidisciplinary team with nurses and administrators, and this team created an Institute of Bioethics for the Florida community. Presenting many conferences and grand rounds provided us a platform for contributing on this subject, again outside of the usual pathology environment, but responding to the call of other doctors for the "doctor's doctor."

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