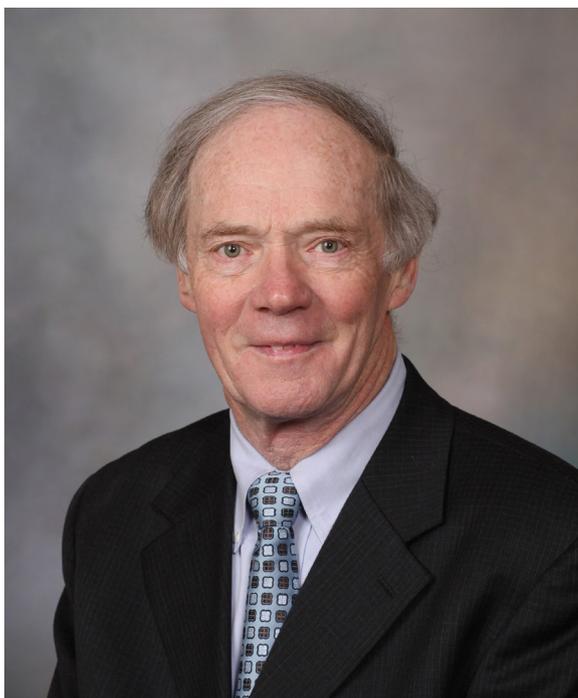




Biographical Feature: Thomas F. Smith, Ph.D.

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In 2012, *Journal of Clinical Microbiology* began publishing quarterly biographical features of pioneers and innovators in clinical microbiology. Of the more than 15 microbiologists who have been profiled as of the date of this writing, strong and common threads among this cohort include expertise in antimicrobial agents and antimicrobial susceptibility testing (1–4), novel automation systems (5–7), and appropriate utilization of the clinical microbiology laboratory (8, 9), just to mention a few. The following career summary of Thomas F. Smith, Ph.D., is unique in that it represents the initial *Journal of Clinical Microbiology* biographical feature primarily focused on a diagnostic virologist. For some *Journal of Clinical Microbiology* readers, the following text may represent a significant trip down memory lane to the days when cell lines and cytopathic effects (CPE) were mainstays of the clinical virology service. On the other hand, insight from a leading clinical virologist of the past 5 decades may provide profound educational benefit for a younger readership that may not possess such perspective.

Thomas F. Smith was born in Mason City, IA, in 1939. His father was employed in auto sales, auto parts distribution, and farm management, while his mother was a nurse. Both were strong advocates of education, and Smith attended local elementary

and high schools. During high school basketball season, he played point guard (the basketball correlate of the football quarterback), which may have provided a foreshadowing for future leadership. Smith characterizes his upbringing as in part traditional yet allowing for freedom of expression. At a basic level, he was taught to “be on time and have a strong work ethic.”

Smith furthered his education by moving out of state to attend St. John’s University in Collegeville, MN. He was graduated in 1961 with a baccalaureate degree in biology. During Smith’s undergraduate studies, the inevitable question that plagues flocks of biology majors today also entered his mind: “What are you going to do with a B.S. in biology?” Smith remembered subsequently sorting out areas of biology with which he was comfortable. Through the counsel of key microbiology faculty members, the field of microbiology was “something that was fostered in my mind.” While at St. John’s University, Smith also completed a Reserve Officers’ Training Corps program, which (unbeknownst to him at the time) would eventually provide a platform to discern future professional goals.

Smith earned his master’s degree from the University of South Dakota in Vermillion in 1963. He investigated growth characteristics of influenza virus in Madin-Darby canine kidney epithelial (MDCK) cells. Smith then entered the U.S. Army as a commissioned lieutenant in the Medical Service Corps and was stationed at Fort Baker, CA (an outpost of the Presidio in the San Francisco, CA, area). He served in the Sixth U.S. Army Medical Laboratory. In retrospect, this provided introductory experience to the reference laboratory paradigm, as this laboratory provided basic offerings for several clients, including military operatives in Washington, Oregon, California, and Arizona. The laboratory at Fort Baker was split into disciplines such as chemistry, hematology, pathology, and microbiology; it also provided rabies and other virology testing as well as virology research. Smith additionally noted that within the realm of bacteriology, primary specimens were plated to primary media at satellite clinics and transported to Fort Baker in candle jars. The Sixth Army Medical Laboratory also supported efforts to control sporadic outbreaks of *Neisseria meningitidis* in Fort Ord (Monterrey Bay, CA), Fort Lewis (Tacoma, WA), and Fort Huachuca (southeast Arizona). Smith further remarked that, during his tenure, “Colonel Adrian Mandel [Ph.D.] in our lab encouraged me to get a Ph.D., as a master’s degree may limit opportunities to direct a clinical laboratory. This was a big influence for me to return to graduate school.”

Smith earned a U.S. Army Commendation Medal in 1965 and returned to the University of South Dakota for doctoral studies from 1966 to 1969. While basic virology research was pursued, with his dissertation project investigating the influence of influenza virus on MDCK cell membranes under the mentorship of Dr. Charles R. Gaush, it was during this time that Smith’s professional interests experienced a transition. “I always had an interest in diagnostic virology,” he said. The influential Dr. Mandel was connected to respiratory viruses and preventive medicine researcher Elliot Dick, Ph.D. (studying at the time at University of Wisconsin—Oshkosh), and was able to facilitate postdoctoral fellowship opportunities for Smith in Wisconsin, Georgia, and Rochester, MN. As most wise individuals would do, Smith acted on the advice of his spouse (wanting to reside closer to Iowa) and began a postdoctoral fellowship at Mayo Clinic in 1969. Smith entered the Mayo Clinic fellowship with the expectation of being trained in classical diagnostic virology. Much of the pioneering work in cell culture, cultivation of viruses, and cytopathic effect in the Mayo Clinic laboratory was established by Ernest C. Herrmann, Jr., Ph.D., in the early 1960s. This was a paradigm shift away from reliance upon inoculation of embryonated eggs, inoculation of suckling mice and other animals, and characterization of distinctive tissue patterns and inclusion bodies by pathologists. Smith wrote that the Herrmann laboratory was “the first nonpublic health laboratory (at that time) to offer routine, rapid, and specific diagnostic virology services based on the use of cell cultures. His laboratory was patterned after the prototypical bacteriology in that diagnosis, not epidemiology, was focused for patient management. Cell cultures in virology were similar to differential media in bacteriology; similarly, cytopathic effects were analogous to colonial morphology.”

When Smith joined the Mayo Clinic Division of Clinical Microbiology faculty in 1971, the future of diagnostic virology was not firmly established, as most offerings were relegated to public health laboratories. Questions regarding the role of clinical virology (whether for a separate clinical laboratory department, an independent laboratory, or outsourcing) even surfaced within the largest clinical microbiology laboratories. Smith possessed the vision of fully integrating the diagnostic virology service into the clinical microbiology laboratory, stating "I could enhance what was already present at the end of my fellowship by setting up a virology laboratory the way I thought it should be run. I had a basic background in virology, so I didn't have to carve out a place in the microbiology lab. I could make a career as being a virologist." Goal number one was to increase the volume of specimens processed by the virology service (which, at that time, was staffed by four full-time equivalents [FTE]). Smith therefore established diagnostic systems in his laboratory for pathogens that were not adaptable to conventional bacteriologic media. "When there was a bacterium that was ignored, it was funneled into my lab." Most of these adaptations were based on cell culture (*Mycoplasma* spp. from past laboratory experience at the University of South Dakota and *Clostridium difficile* cytotoxin assays), although Smith remarked that the refinement of *Pneumocystis carinii* (now *Pneumocystis jirovecii*) immunofluorescence microscopy techniques was timely during the advent of the AIDS epidemic in the early 1980s. These innovative means to an end subsequently afforded Smith the revenue stream to both develop additional virus assays in his laboratory and promulgate research efforts.

One additional bacterial pathogen brought into the realm of the diagnostic virology laboratory in the 1970s was *Chlamydia trachomatis*. Smith noted that "chlamydia was not recognized as an established STD at that time. Laboratories in California and Washington did have an interest in trachoma. However, military personnel returning from Southeast Asia had signs and symptoms of STD, but the diagnosis was being made largely by epidemiology, rather than the clinical laboratory. When *Chlamydia* testing was brought into the laboratory, it eventually became recognized as an STD." Laboratories on the west coast began to determine that *in vitro* host cell susceptibility to *C. trachomatis* could be enhanced by irradiation or by chemical agents. Smith then made the discovery that *in vitro* detection of *C. trachomatis* could be significantly enhanced by utilizing McCoy's cells cultivated on coverslips placed in 1-dram glass shell vials (10), so that the testing could be adaptable to the clinical laboratory. In retrospect, Smith remarked that the subsequent combination of low-speed primary clinical specimen centrifugation into chemically treated shell vial cell culture plus iodine staining was the "gateway to allow for the clinical laboratory to diagnose *Chlamydia* with a routine diagnostic test with a turnaround time of 1 to 2 days." Patrick R. Murray, Ph.D. (11), senior director of worldwide scientific affairs, BD Life Sciences, who began a Mayo Clinic fellowship in 1974, provided commentary on the significance of this work: "I think what was remarkable about Tom's early career was his systematic approach to defining optimum culture conditions for *Chlamydia* and viruses and then integrating this into his diagnostic virology lab. I was impressed by the fact he was never satisfied with the status quo." Such adaptations allowed Smith's laboratory to become the first in the United States to offer testing for *C. trachomatis*.

A second major professional achievement in Smith's career involved extrapolation of shell vial technology to laboratory diagnosis of viral infections in 1983. Many of the techniques learned from culture and detection of *Chlamydia* were applied to the detection of human cytomegalovirus (CMV) and other viruses using the shell vial technique. Such accomplishments fed his continued passion for virology. Jaber Aslanzadeh, Ph.D., director of microbiology, Hartford Health System, recalled that even though his own past research interests were related to mycology and tuberculosis, "Tom affected me with his enthusiasm for viruses. You could see how he enjoyed it. He would do virology for free if he wanted to." As stated by Smith, the impetus for conversion of conventional cell culture to shell vial culture was simple. "Nothing is more important to physicians than to rapidly report accurate results," he said. The validity and

improved analytical sensitivity of this emerging application were ascertained in simplistic fashion by blinded studies (12–15) involving independent sections of his laboratory performing conventional cell culture and shell vial culture, respectively. With respect to detection of CMV intermediate-early antigen, Smith related, “the role of shell vial for reducing average time of infection to 16 hours from the median 8 days in the past allowed for rapid detection.” This advancement did not go unnoticed in the clinical community. The advent of shell vial-based detection of CMV also paralleled the early years of the AIDS epidemic. Marie-Louise Landry, M.D., director of the clinical virology laboratory at Yale New Haven Hospital, identified this discovery as being transformative and revolutionary. “CMV had been a major untreatable cause of morbidity and mortality in transplant patients, and conventional culture methods required 1 to 4 weeks for a result. When ganciclovir became available, the shell vial method provided a CMV diagnosis in 1 to 2 days that was critical to delivering effective therapy.” Dr. Landry went on to comment that the application of the shell vial paradigm to other viruses was extremely beneficial to viral diagnosis because viral antigens could be detected prior to CPE. In addition, this “was not only faster but a much easier method for those not trained in classical virology. You do not necessarily need to know the CPE. You just perform the monoclonal antibody stain.”

Yi-Wei Tang, M.D., Ph.D., chief of the clinical microbiology service at the Memorial Sloan Kettering Cancer Center, identified Smith as “a great microbiology crystal ball player,” implying that he possessed a unique talent to predict where the field was headed, despite not being a day-to-day bench technologist. When asked about this skill, Smith replied, “As you grow in knowledge and experience, you are able to discern what is important and what is not. I knew what was important down the line; I knew what would work and what wouldn’t.” Such thoughts characterized the next major paradigm shift driven by Smith: the conversion of shell vial and conventional cell culture to nucleic acid amplification-based methods in the 1990s. Dr. Tang put it succinctly: “If no Tom Smith, no modern clinical virology laboratory.” One of the first clinical scenarios benefiting from this change involved detection of herpes simplex virus from cerebrospinal fluid in patients with signs and symptoms of encephalitis. Once again, this paradigm shift was simply related to accuracy and turnaround time. “More rapid and more accurate results—that’s why we made the conversion to shell vials and later to molecular diagnostics,” noted Smith.

In conversations that this writer was fortunate to have experienced with Smith and several of his colleagues, the concept of “data driven” was constantly drilled home. “If you make decisions based on data, they won’t ask questions,” stated Smith. Robin Patel, M.D., current chair of the Division of Clinical Microbiology at Mayo Clinic, learned the importance of the data-driven paradigm during her postdoctoral training with Smith. “This was back in a day when things were more subjective and descriptive. Less data were available.” Mark J. Espy, M.S., long-time research and development technologist for Smith at Mayo Clinic and coauthor of more than 60 peer-reviewed publications through this collaboration, added, “If you do not have the data, you cannot just make assumptions.” Using this logic, Smith, largely with the assistance of LightCycler technology (16–18), converted approximately 95% of the assays offered by the clinical virology laboratory at Mayo Clinic to molecular methods performed by a staff that now approximates 40 FTE. (Today, the Division of Clinical Microbiology at Mayo Clinic includes a staff of more than 250 FTE [including 8 research and development technologists], many of whom continue to perform the assays developed by Smith.) This paramount contribution to diagnostic virology is viewed by Richard B. (Tom) Thomson, Jr., Ph.D., director of microbiology laboratories at NorthShore University HealthSystem, as follows: “In the 1990s, the clinical laboratory spoke to the promise of PCR, but very few were doing it. In the middle 2000s, commercial companies started selling the assays. Tom spearheaded this whole effort but never really took credit for it. At the same time, he didn’t want to retire until it was accomplished.”

When clinical scientists who were interviewed for this biographical feature were asked to cite lasting contributions and innovations of Smith, to a person the two paradigms that arose were the aforementioned shell vial culture optimization and conversion of the clinical virology laboratory to molecular diagnostics. Steven Specter, Ph.D., professor of molecular medicine at University of South Florida Health, offered a third: "Tom's lab was one of only a handful of labs to offer quality training in clinical virology, and he produced a large number of trainees in clinical virology." Early during his tenure, Smith assumed directorship of the second-oldest American Society for Microbiology Committee on Postgraduate Educational Programs-approved fellowship program (CPEP) in the United States and fostered the program through a number of reaccreditation exercises. He estimates having directed the program for 12 to 15 years and having trained more than 2 dozen fellows (most of whom currently direct clinical microbiology laboratories). Smith noted that the fellowship experience also proved to be of benefit to faculty, as "these people were already trained as Ph.D.s and were capable of bringing another (laboratory) method into Mayo. These individuals were always very bright and challenged us. They made the laboratory more exciting." In addition to CPEP, Mayo Clinic facilitated an American Board of Pathology training program in medical microbiology, with Smith serving in a mentorship capacity for dozens of additional fellows. Qualities that Smith attempted to instill in these world-wide trainees included honesty and fairness, integrity, a strong work ethic, and patient-centered care. "If the patient comes first, then decisions are easy. It takes you (and your interests) out of the equation, other than being the judge of the best test." Dr. Aslanzadeh noted that his 2 years with Smith and the Mayo Clinic CPEP were "two of the most wonderful years of my life."

Smith is widely credited with expanding the pedagogic knowledge base of diagnostic virology with his more than 230 peer-reviewed publications, five coauthored books, 51 book chapters, and hundreds of abstracts. Richard L. Hodinka, Ph.D., chair of the Department of Biomedical Sciences at the University of South Carolina School of Medicine in Greenville, stated, "Tom was right at the ground level of diagnostic virology. He was one of the first to write about the clinical use of the diagnostic virology laboratory and one of the first to speak and write about viral rapid diagnostics as they came of age over the years." One hallmark publication was the *Diagnostic Molecular Microbiology* textbook, published in 1993 (19). Dr. Patel noted, "Tom looked at molecular diagnostics not just as a research tool but also in terms of delivery of care to patients. This book is reflective of his vision to apply molecular diagnostics to clinical medicine." Dr. Hodinka added, "At that time, lots of people in academia were starting to do molecular biology, but there was no book. You had to go to someone's lab or you had to go to a workshop. This text provided a very useful service to everyone who was doing molecular. It provided a basis for quality control and quality improvement that was involved in molecular testing." Smith has also served on several editorial boards, including those for *Journal of Clinical Microbiology*, *Laboratory Medicine*, *Diagnostic Microbiology and Infectious Diseases*, and *Clinical Microbiology Reviews*, and served numerous times as a virology section editor for *Manual of Clinical Microbiology*. He has been elected to fellowship in the American Academy of Microbiology and has achieved diplomate status on the American Board of Medical Microbiology. Drs. Hodinka, Landry, and Specter hailed Smith's advocacy of clinical virology at a professional level through his decades-long association with the Pan American Group for Rapid Diagnosis of Viral Infections and the Clinical Virology Symposium.

Despite the aforementioned burgeoning list of revolutionary accomplishments, Smith is largely described as a soft-spoken and humble gentleman. "Tom really embodied that term," stated Dr. Specter. "Even when taking an opposing view in public, he always represented himself in a way that was considerate and professional. He engendered relationships with colleagues." Dr. Thomson related, "He was a diligent, patient scientist. In a very organized way, he decided what needed to be done and did it. He was always very honest about what he was doing." To this day, Dr. Thomson remarks, "Tom has never really aged. He is like a wonderful doting grandfather; he

always had time for you.” In addition, Dr. Thomson provided the anecdote that, following his retirement, Smith was commissioned by Mayo Medical Laboratories as “a good will ambassador” who would travel to microbiology laboratories within Minnesota and Wisconsin and assist them in their preparation for upcoming College of American Pathologists inspections. Mr. Espy remembered that Smith “wasn’t much on doing things just to see if we could do it. Whatever we did was for the benefit of the patient.” Dr. Aslanzadeh remarked that at local and national meetings, Smith always acknowledged those who contributed to a project. “The audience was clear where this idea came from. He never missed anyone.” Dr. Murray described Smith as “a man of high integrity—a genuinely warm individual. He was always supportive of fellows and visitors to the laboratory and always sharing his knowledge.” One comment intimated to this writer especially seems to personify Smith. When asked about the potential abandonment of conventional cell culture and shell vial culture in the clinical virology laboratory (he emphatically declares “definitely”), Smith selflessly opined, “I’ve never been possessive of a technique I’ve developed. Rather, I let new data determine if these things can be improved. Let the data make the decision, rather than be subjective.”

Dr. Smith retired from the Mayo Clinic in 2009. He continues to reside in Rochester, MN, with Connie, his wife of 56 years. Four daughters and 10 grandchildren (several of whom have gone on to careers in nursing, teaching, law, and business) live 70 miles to the north in the St. Paul/Minneapolis metropolitan area. He golfs twice per week, is an avid baseball fan, and takes in at least one Iowa Hawkeye football game each November (50-yard-line, row 37, at Kinnick Stadium). True to form, this humble, forward-thinking clinical virology pioneer provides these parting words for the classical virologist: “Keep an open mind and be data driven.”

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