Pediatric Infectious Diseases: 60 Years of Contributions by Military Pediatricians

To describe the many contributions that uniformed pediatricians have made to the field of pediatric infectious diseases is a complicated task. Part of the difficulty is that for the decades after the end of World War II, a number of talented and brilliant physicians spent short periods of time in the military to fulfill their service obligations. Investigators such as Floyd Denny and Lew Wannamaker published their seminal works on group A β-hemolytic streptococci and rheumatic fever while on active duty in the US Air Force. Some of the early work on vaccines for common childhood infections was done by investigators who, at least for a portion of time, wore a military uniform. In addition, many of the contributions of military physicians were often made alongside and in concert with their civilian colleagues.

In an attempt to illustrate some of the more significant contributions of military pediatricians to the field of pediatric infectious disease, however, a good starting point would be the work of Colonel Ogden Bruton. His early work performed over 60 years ago in many ways began the military legacy of clinical research in a variety of important areas of pediatric infectious disease but in particular those areas where the disciplines of clinical immunology and infectious disease have overlapped.

SERENDIPITY AND THE BEGINNING OF A LEGACY

While evaluating children at what was then known as Walter Reed General Hospital in 1951, Colonel Ogden Bruton observed an 8-year-old boy with recurrent pneumonia. Dr Bruton noted the unusual pattern of this child's pneumonias, and while analyzing the child's immune system, noted a lack of serum immunoglobulin. Dr Bruton's observations eventually led to his reporting of the first primary immunodeficiency disease ever to be described, Bruton's agammaglobulinemia. Both Dr Bruton's discovery of the disease as well as his attempts at treating it with specific immunotherapy in the form of intramuscular immune globulin would herald the dawn of modern clinical immunology. Although Dr Bruton was a brilliant clinician and researcher, he also was a visionary leader who established the pediatric residency program at Walter Reed and who also served as department chairperson there for over a decade. His clinical discoveries and the leadership that he provided to military medicine in the following decades led to his becoming one of the most beloved pediatricians to serve in this capacity. Over the past half century, many other prominent military pediatricians have built upon Dr Bruton's legacy in the field of pediatric infectious disease and immunology and have also been exceptional leaders and educators in their own right.
EMERGING DISEASES AND OUTBREAKS BRING OPPORTUNITY

Military infectious disease physicians are often at the forefront of emerging diseases and the study of new pathogens due to the global reach of the military health care system. The study of cat-scratch disease (CSD) is a microcosm of such endeavors. CSD was first reported in the medical literature in 1951, and the first pediatric description was published in 1953. Captain Andrew Margileth, who spent 24 years on active duty in the US Navy, concentrated a great deal of his scholarly work on the recognition, diagnosis, and treatment of clinical manifestations of CSD. In 1957, Dr Margileth was the first clinician to describe Parinaud oculoglandular syndrome due to CSD.4 An additional clinical observation attributed to Dr Margileth was his recognition of a constellation of systemic symptoms and fever first associating CSD as an etiology of “fever of unknown origin.”5 His fascination with this disease led him to try to decipher the etiology of these clinical syndromes. In 1984, Dr Margileth et al6 first reported the identification of organisms within the cat scratch papule at the site of inoculation. Ironically, the military was the first to isolate an organism from a patient with CSD, and the organism was named for the organism from a patient with CSD, and the organism was named for the organism from a patient with CSD. In the ensuing years, several investigators, including clinicians from the army and air force, demonstrated that Bartonella henselae, not Aflipia felis,7 is the primary etiology of CSD. All told, Dr Margileth published 25 articles concerning various aspects of CSD in the peer-reviewed medical literature over 5 decades.

Colonel James W. Bass began his medical and army careers simultaneously, and he had a profound effect on pediatric medicine as well as military pediatrics. His scholarly work began while in his first tour as a general pediatrician at Tripler Army Medical Center in Hawaii. He and his colleagues undertook some of the first clinical trials on the use of ampicillin for the treatment of otitis media.9,8 Shortly thereafter, Dr Bass began formal fellowship training under Dr Margaret H.D. Smith at Tulane University. A pertussis outbreak in New Orleans during his time there afforded the opportunity for breakthrough work on the carrier state10 and antibiotic treatment11,12 of pertussis. He continued his interest in pertussis over the next 3 decades with a dozen more reports and articles. Dr Bass was eclectic in his infectious disease interests, contributing advances in penicillin therapy of streptococcal disease, evaluation and management of occult bacteremia, as well as cutaneous manifestations of infectious diseases. The military pediatrics’ interest in CSD was continued by Dr Bass, with the only placebo-controlled antibiotic trial for the treatment of CSD13 ever published. Although this litany would lead one to believe that Dr Bass was primarily involved in clinical research, his greater calling was as a teacher and leader of military pediatrics. His role as the first chairman of the Department of Pediatrics at the Uniformed Services University of the Health Sciences (USUHS), his service on the American Academy of Pediatrics (AAP) “Redbook” Committee, and his long-time service training scores of pediatricians in the legacy of Dr Bruton at Walter Reed in Washington, DC, and Tripler in Hawaii left a great legacy for all those that follow.

NEW UNIVERSITY, NEW FELLOWSHIP, NEW CHALLENGE

Upon the charter of what was then the new USUHS in 1972, Dr James Bass was chosen as the chair of the fledgling Department of Pediatrics. One of his first executive decisions was to bring then Army Lieutenant Colonel Gerald W. Fischer on board to lead the division of pediatric infectious diseases. Soon thereafter, they decided to establish a fellowship in pediatric infectious diseases that would be jointly sponsored by the USUHS and Walter Reed Army Medical Center. The fellowship is now part of the National Capital Consortium for military graduate medical education and has trained over 30 pediatric infectious disease specialists in 25 years. The members of the fellowship were some of the earliest clinicians involved in pediatric HIV care and discovery. One of Dr Fischer’s early fellows, then Army Major Dennis Shanks, saw an unusual case of an infant with Toxoplasma encephalitis.14 The group began to see additional patients who had a spectrum of opportunistic infections very similar to adults who were afflicted with AIDS. It was suspected that these patients too must have had an immunologic basis for their susceptibility to unusual infections. Ultimately, they became one of the early groups to recognize the spectrum of disease associated with pediatric HIV infection.

As the military was developing rapid and robust HIV testing for force protection, Dr Fischer’s group was quickly able to identify a large cohort of children who were infected via vertical transmission. Dr Fischer recalls an early presentation of this group of patients to a National Institutes of Health working group on the subject. He noted that Dr Antonia Novello, future US Surgeon General, was present and helped the group develop a multidisciplinary clinic to study this cohort of patients (G.W. Fischer, MD personal communication, 2010). Through these early efforts of the newly named Military Pediatric HIV Consortium, Air Force Major David Ascher, Army Major William Raszka, Army Major Merlin Robb, and Navy Lieutenant Commander Norman Waecker published early articles on the immunologic phenomena that occur in young children infected with HIV15-17.
This early work also led to the involvement of the Military Pediatric HIV Consortium in many early collaborative efforts. In particular, Dr Fischer remembers working very closely with the National Institutes of Health group led by Dr Phillip Pizzo. In this arrangement, military dependents were some of the first children enrolled in studies to examine the use and efficacy of trimethoprim-sulfamethoxazole and zidovudine in children (personal communication with Dr Fischer). Pediatric infectious disease physicians continue to have a prominent role in the military research efforts directed at understanding the immunologic phenomena and the development of treatments for HIV. Dr Robb is now retired from the US Army but presently is a key investigator in military efforts with industry to develop novel vaccines to fight HIV.

WORKING TO HELP CHILDREN WORLDWIDE

The military has worked on many projects in its overseas research laboratories where great strides in the treatment of “orphan” diseases have been made. The work at Naval Medical Research Unit 3 (NAMRU-3) in Cairo is an excellent example of such work. One of the greatest accomplishments of this institute was the invention of oral rehydration solution for the treatment of cholera in Egypt. Oral rehydration solution is now used as the mainstay of diarrhea treatment worldwide. For this accomplishment, Navy Captain Robert Phillips was awarded the Lasker Award, considered the American corollary to the Nobel Prize.

More recently, pediatricians have played a large role in the research performed at NAMRU-3. One of the major missions of NAMRU-3 was to study the evaluation and treatment of “enteric” or typhoid fever. Under the direction of Navy Captain Robert Frenck, multiple studies were conducted on the treatment of typhoid fever with azithromycin. Ultimately, this treatment has become the therapy of choice in most situations. An additional focus of research at this institute involved the study of enterotoxigenic *Escherichia coli* (ETEC). Vaccinology has been a particular emphasis in an attempt to understand and prevent diseases due to ETEC. Navy pediatric infectious disease specialist Stephen Savarino headed a team that established a diarrheal disease field site in Abu Homos, Egypt, an agrarian community in the Nile River. Dr Savarino conducted 4 studies of the ETEC vaccine culminating in a large-scale efficacy trial of the vaccine in Egyptian infants and young children. As part of the preparation work for the vaccine trials, Dr Savarino established diarrhea surveillance in the community and was able to describe the epidemiology of the major pathogens including ETEC, shigella, *Campylobacter*, rotavirus, and norovirus. At this time, Dr Savarino continues to work as the military’s head of enteric disease research and continues to search for improved ETEC vaccines.

FROM THE BEDSIDE TO THE BENCH AND BACK

The role of the military in the development of products, in particular vaccines, that would end up in commercial production has been well documented. Most of these products were developed with the concept that they would directly benefit the active duty populations serving the United States. Military pediatricians played key roles in laying the ground work leading to many of these discoveries. One recent series of product development strayed somewhat from the usual path taken. The products leading to the respiratory syncytial virus (RSV) prophylaxis of high-risk neonates were developed through the efforts of the previously mentioned Dr Fischer and Air Force Colonel Val Hemming at USUHS. Both Drs Fischer and Hemming had research interests centering on the use of passive immunotherapy to prevent childhood diseases such as group B *Streptococcus* in neonates. Drs Fischer and Hemming ran a laboratory at USUHS studying passive immunization with the help of Mr Samuel Wilson and Ms Sally Hansen. The observations regarding RSV were the result of a clinical trial where a colleague, Army Colonel Leonard Weisman, noted unexpectedly rapid improvement of a child with presumed group B *Streptococcus* disease after the administration of intravenous immunoglobulin. In the end, this child was found to have RSV. From these findings, the researchers postulated that immunoglobulin may have a therapeutic benefit to children with RSV diseases (G.W. Fischer, V. Hemming, MD personal communications, 2010).

The search for further development of this theory led to work with Dr Gregory Prince, a civilian pathologist and dentist with experience studying paramyxoviruses. Dr Hemming worked with Dr Prince to use an animal model, *Sigmodon hispidus*, the cotton rat, to further study this disease. Their work resulted in the discovery that passive antibody treatment prevented pneumonia in this animal model.

From this point, a unique consortium of diverse research groups worked together to develop this hypothesis. Dr George Siber of the Massachusetts Public Health Laboratory was able to provide pooled, high-titer, anti-RSV neutralizing antibody for clinical testing. A multicenter evaluation of these lots was run with the help of Dr Carol Heilman (National Institute of Allergy and Infectious Diseases) and Dr Jesse Groothuis (University of Colorado at that time). Dr Hemming’s laboratory at USUHS and Dr Prince’s laboratory at Virion Systems continued to work on neutralizing plaque assays of infant
specimens and animal models, respectively. Finally, through a complex arrangement facilitated by the Henry M. Jackson Foundation for the Advance-ment of Military Medicine in collaboration with MedImmune, Inc, the first major clinical trial was completed and published in 1993.25 This initial study demonstrated a significant reduction in the number of hospitalizations, hospital days, and ICU days for high-risk infants who received prophylactic intravenous immunoglobulin with a high titer of RSV neutralizing antibody. After a second study, the PREVENT study, which showed similar results, Respi-Gam, the polyclonal anti-RSV immunoglo-bulin product was released.26 Further work and the development of monoclonal antibody technology led to the development of a second-generation product, Synagis, which could be delivered more effectively as a monthly intramuscular injection.27

CONTINUING TO LEAD THE WAY

Many military pediatric infectious disease experts have continued to further the field of scientific discovery. Dr Martin Ottolini, a retired US Air Force Colonel, was the long-time pediatric infectious diseases fellowship director at the Uniformed Services University. He trained more than 15 specialists in all 3 services in this role, one of the largest contingents nationally during that period. Additionally, he worked closely with the RSV group and helped develop multiple small animal viral models utilizing the cotton rat, S his-pidus.28,29 He presently serves as an integral program manager in a unique National Institute of Allergy and Infectious Diseases-sponsored research endeavor, the Infectious Disease Clinical Research Program. This program sponsors multicenter prospective clinical research utilizing the robust military medical center conglomeration. In this role, Dr Ottolini is presently implementing research aimed at elucidating the role of emerging pathogens such as H1N1 influenza. Navy Captain Judith Epstein has been working extensively in the search for possible immunizations to fight the malaria plague confronting much of the developing world. In her role as US Military Malaria Vaccine Program Director, she is presently overseeing the first human trials of an irradiated sporozoite immunization that has been developed in collaboration with Dr Stephen Hoffman and Sanaria Incorporated.30,31 Army Colonel Julia Lynch served as Director, Division of Viral Diseases at the Walter Reed Army Institute of Research. In this role, she has overseen the US Army’s efforts to understand the immunologic response associated with dengue fever and to ultimately develop a safe and effective vaccine. Additionally, these laboratories have been integral in the development of new oral adenovirus type 4 and 7 vaccines to help protect active duty troops. The adenovirus vaccines are presently under consideration for approval by the Food and Drug Administration. Most recently, Dr Lynch has been named the Director of the Military Infectious Disease Research Program. In this position, she manages all efforts to protect the US military against naturally occurring infectious diseases.

In addition to the many pediatricians who have made significant contributions to the field of infectious disease during their careers in the military, there are many examples of renowned physicians who continue to lead and educate as they transition into civilian life. Dr Russell Steele did his residency at Tripler under Dr Bass and subsequently served in many roles as a US Army pediatrician. To the present day, he is highly regarded as one of the leaders in the field of pediatric infectious diseases, having published over 300 peer-reviewed articles, multiple textbooks, serving as editor-in-chief of Clinical Pediatrics, and having served on the Redbook Committee for many years. Another one of Dr Bass’ key pupils, retired Colonel James Brien, is also a well-recognized figure to many pediatricians. Dr Brien’s career in the military included active duty tours at Brooke Army Medical Center and Walter Reed Army Medical Center. Dr Brien has mastered the art of teaching through instructive cases. He is a frequent speaker at many pediatric conferences and reaches tens of thousands of pediatricians with his publications of cases that pose a diagnostic or therapeutic quandary. Another contemporary of these physicians is retired Colonel Richard Lampe. Dr Lampe was the chief of pediatrics at multiple army medical centers and pediatric residency director at Walter Reed Army Medical Center. Since retiring in 1992, he has led the pediatricians department at Texas Tech University Health Sciences Center. He has chaired the AAP’s Uniformed Services Section Executive Committee and now serves as the President of the Texas Pediatric Society. It should be noted that Drs Steele, Brien, and Lampe all served their countries and deployed to the Middle East in support of either the First Persian Gulf War, Operation Enduring Freedom or Operation Iraqi Freedom.

SECTION RECOGNIZES THE LEGACY OF THEIR COLLEAGUES

The AAP Section on Uniformed Services Pediatric Seminar and Scientific Awards Competition to recognize the contributions of many of the founding fathers of pediatrics in the military, with the majority of these awards named in honor of pediatric infectious disease specialists. The top pediatric basic science researcher and keynote
teaching exploits of Dr. Bass, the James Bass Challenge Bowl is a college bowl medical trivia contest pitting pediatricians from the army, air force, and navy against each other at the annual Uniformed Services Pediatric Seminar meeting.

CONCLUSIONS

The Medical Corps of all 3 branches of the military have a proud tradition of service and excellence in pediatrics and pediatric infectious disease. In fact, the study and treatment of infectious diseases within the military in general can be traced back to some of the earliest investigators in the field such as army physicians Bailey K. Ashford and Walter Reed for their studies of hookworm and yellow fever, respectively. Military pediatricians and pediatric infectious disease specialists presently work and practice in an environment that has been nurtured by the careful hands of many of the leaders presented in this article; however, it would be impossible to enumerate the many other contributions made by those not listed. With this tradition in mind, military pediatric infectious disease physicians continue not only to proudly treat the children of military service members wherever they may reside but continue to make advances to the science of medicine for the benefit of children both locally and globally.

REFERENCES


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