The Giants of Rheumatology at Johns Hopkins: Lawrence E Shulman, MD, PhD and Mary Betty Stevens, MD

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KEYWORDS

• Rheumatology • Systemic lupus erythematosus • Johns Hopkins

KEY POINTS

- Drs Lawrence E. Shulman and Mary Betty Stevens were the giants of rheumatology at Johns Hopkins during the latter half of the twentieth century.
- Together, they made immense contributions to our knowledge of systemic lupus erythematosus as well as other systemic autoimmune rheumatic diseases, and provided excellent clinical care to thousands of patients with rheumatoid arthritis, systemic lupus erythematosus, and other systemic autoimmune rheumatic diseases.
- Together, they trained almost 100 postdoctoral fellows, many of whom went on to highly successful careers in academic medicine, including the Directors of Divisions of Rheumatology and the Chairs of Departments of Medicine. Thus, their legacy was carried forward to the current generation of academic rheumatologists.

The history of rheumatology at The Johns Hopkins University School of Medicine and Medical Institution begins with Sir William Osler, the first Professor of Medicine in the School of Medicine and Physician-in-Chief of The Johns Hopkins Hospital who was appointed to these positions in 1889.[1] Among his many contributions to medicine, Osler largely is credited with the description of the visceral manifestations of systemic lupus erythematosus (SLE), based on systematic clinical observations of patients seen either on the wards of the Hospital or in the Medical Clinic, often with medical students and residents.[2] The sixth full-time Professor of Medicine, A McGehee Harvey solidified the reputation of Hopkins as a center for the study of SLE through his scholarly studies of this condition.[3] Dr Harvey established the Connective Tissue Division in 1955 and appointed Dr Lawrence E Shulman, then an Instructor in Medicine, as head. Thus begins our exploration of the contributions of the greats of Hopkins rheumatology, Drs

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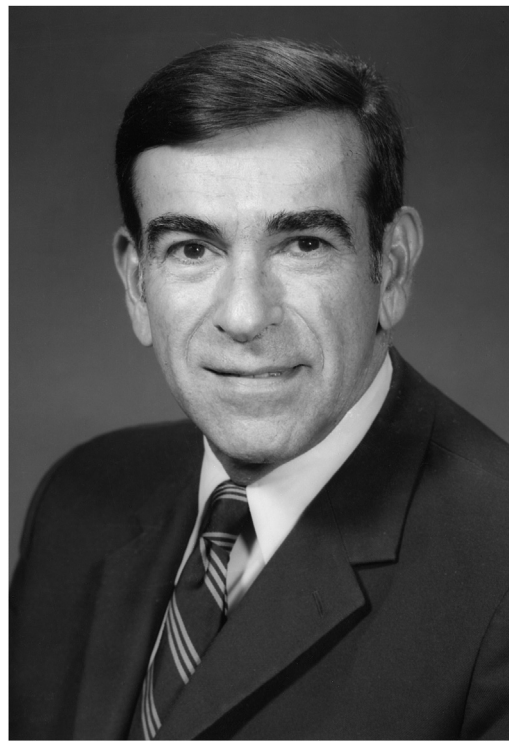

Fig. 1. Lawrence E Shulman, MD, PhD.

Lawrence E Shulman and Mary Betty Stevens, in the latter half of the twentieth century.

LAWRENCE E SHULMAN, MD, PhD

Lawrence (Larry) Edward Shulman was born on July 25, 1919, in Boston, MA, and raised in Brookline, MA (Fig. 1). He graduated from Boston Latin School; however, his schooling was interrupted for 1 year when he contracted polio. He matriculated at Harvard College and graduated in 1941. He spent the next 4 years working in the Department of Public Health under Prof Charles-Edward Amory Winslow at Yale University on projects related to the development of protective clothing for military troops operating in extreme cold and hot weather climates; this work was funded by the John B Pierce Foundation and resulted in a PhD in Public Health. Subsequently, he entered the Yale University School of Medicine and received his MD in 1949.

Larry came to Baltimore in 1949 and served as an intern on the Osler Medical Service at The Johns Hopkins Hospital. He later wrote that "This proved to be an unexpectedly exciting, exhilarating, educational and exhausting experience. … I became captivated with clinical medicine and have been ensnared thereby ever since."[4] Dr Harvey identified him as a unique young physician scientist and personally supervised his work on the effects of adrenocorticotrophic hormone (ACTH) and cortisone. Over the next 2 years, first as an Ayerst, McKenna and Harrison fellow in endocrinology, he pursued studies of ACTH and cortisone on hypersensitivity and then, as a Vernon D Lynch fellow, he studied the benefits and adverse effects of these agents in the

collagen diseases, including SLE. He returned to complete his residency on the Osler Service and then joined the faculty of the School of Medicine as an instructor in Medicine in 1953. He was appointed to head the new Connective Tissue Division in 1955 by Dr Harvey and was promoted to the rank of Assistant Professor in 1956 and Associate Professor in 1964. Larry led the Division until 1975, the year before he left for the National Institutes of Health (NIH). I had the privilege and good fortune of being one of his last fellows, spending 6 months from July to December 1975 seeing patients with and learning from him in the Meyerhoff Private Outpatient Clinic and on the medical wards of The Johns Hopkins Hospital; we usually started daily inpatient consult rounds after 5:00 PM

Larry made seminal contributions to our knowledge of connective tissue diseases, particularly SLE and systemic sclerosis (scleroderma), his two main clinical interests. As a clinical research fellow, he worked with Dr Harvey as well as Drs Philip Tumulty, C Lockard Conley, and Edith H Schoenrich on the seminal Hopkins paper based on a careful analysis of 138 cases of SLE[3]; I am pleased to have a copy of the bound reprint of this paper, personally signed by Dr Harvey and given to me before I left Hopkins in 1991. Dr Shulman was the first to apply the life-table method to study the prognosis of patients with SLE; they reported that the 4-year cumulative survival was only 51% in this cohort of patients.[5] During this time, he also worked with Dr Joseph E Moore and helped establish the relationship between the presence of a chronic biologic false-positive test for syphilis and possible, probable, or definite SLE as well as other connective tissue diseases in almost half of such patients.[6]

Dr Shulman mentored the clinical research careers of several postdoctoral fellows focused on SLE; two of note were Dr Mary Betty Stevens, a postdoctoral fellow from 1958 to 1960, and Dr Frank C Arnett, Jr, a postdoctoral fellow from 1970 to 1972. Dr Stevens' work with Dr Shulman will be discussed below; herein, I will briefly comment on the work of Dr Arnett with Dr Shulman to analyze the familial occurrence of SLE. They reported eight families and analyzed 53 cases in 25 families in total.[7] They noted a strong concordance for disease manifestations in identical twin pairs and parent-offspring pairs but not in sib pairs, supporting a genetic contribution to the etiology of SLE. These studies laid the groundwork for Dr Arnett's career as a physician–scientist in rheumatology not only at Hopkins but also at the University of Texas Health Sciences Center in Houston where he was the Director of the Division of Rheumatology, the Chair of the Department of Medicine, and the first Director of the Center for Clinical and Translational Sciences before his retirement.

Dr Shulman's other major clinical interest during his tenure at Hopkins was systemic sclerosis (scleroderma). He and his fellows, Drs William D'Angelo and James Fries, and his colleague, Alphonse Masi, wrote a seminal paper on the pathologic findings in systemic sclerosis comparing autopsies in 58 cases that had died in Baltimore area hospitals between 1948 and 1966 and age, sex, race, and hospital-matched controls.[8] They reported that autopsied cases had more pulmonary involvement, both interstitial fibrosis and pulmonary arteriolar thickening; myocardial fibrosis, particularly in younger patients; coronary arteriolar lesions, fibrinous pericarditis, muscle atrophy, and/or fibrosis in all areas of the gastrointestinal tract; and renal arteriolar disease, similar to that seen in patients with malignant hypertension. Dr Rida Frayha and other postdoctoral fellows worked with him to report the frequency and type of hematologic abnormalities and cranial nerve involvement, most often a sensory trigeminal neuropathy, in large series of patients with systemic sclerosis seen at Hopkins.[9,10]

Because of this clinical interest and his renown as an excellent physician, he was the recipient of many referrals of patients with connective tissue diseases. Of particular relevance, were two men with a scleroderma-like illness characterized by firm taught

skin over the arms and legs but sparing the hands accompanied by peripheral eosinophilia, elevated erythrocyte sedimentation rate, and hypergammaglobulinemia who had striking thickening of the fascia between the subcutis and muscle on full-thickness biopsies. These patients were initially presented at the VIth Pan-American Congress of Rheumatology in 1974 and along with two additional cases, published in 1975.[11] I actually saw one of the latter two patients, Case 4 in this article, with Dr Shulman in the Meyerhoff outpatient clinic during my fellowship.

In 1978, Fu and colleagues described four additional cases and summarized 23 cases reported since Dr Shulman's original paper and coined the eponym "Shulman's syndrome" for the syndrome of eosinophilic fasciitis characterized by eight features (**Box 1**).[12] Dr Shulman commented on these and other subsequent cases and noted that the pathogenesis of eosinophilic fasciitis remained obscure.[13] Later, he compared and contrasted the clinical and laboratory features of eosinophilia-myalgia syndrome and toxic oil syndrome with eosinophilic fasciitis and noted that some patients initially diagnosed with eosinophilia-myalgia syndrome subsequently developed the full picture of eosinophilic fasciitis.[14]

Dr Shulman spent 20 years as the Director of the Connective Tissue Division at Hopkins before transitioning to the next phase of his career at the NIH. The list of postdoctoral fellows that he trained at Hopkins who went on to noteworthy and successful careers in academic medicine includes, but is not limited to, Drs Mary Betty Stevens, Alexander S Townes, Murray Urowitz, James F Fries, Bevra H Hahn, Frank C Arnett, Graciela S Alarcon, and myself.

Dr Shulman was appointed as the first Associate Director for Arthritis, Musculoskeletal and Skin Diseases at the National Institute of Arthritis, Metabolism and Digestive Diseases in 1976. He was named the Director of the Division of Arthritis, Musculoskeletal and Skin Diseases at the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases in 1983 and was the inaugural Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases when it was formed in 1986. He retired from NIH on October 1, 1994, at the age of 75 years. Following his retirement, the late Dr J Claude Bennett wrote the following regarding his tenure at the NIH: "In his scientific leadership role, Larry has demonstrated the utmost commitment not only to advancing our understanding of the pathogenetic, diagnostic, therapeutic, and rehabilitative aspects of these diseases but also to rapidly and effectively transferring

Box 1
Features of Shulman's syndrome[10]

- Rapid onset
- Recent history of exertion
- Sclerodermoid skin changes
- Absence of Raynaud's phenomenon and visceral involvement of progressive systemic sclerosis
- Hypergammaglobulinemia G
- Peripheral blood eosinophilia
- Histologically nonspecific inflammatory reaction involving fascia, with extension into the adjacent muscle and subcutaneous tissues
- Dramatic response to systemic prednisone therapy

useful knowledge directly to practicing physicians, to patients and their families, and to voluntary health organizations and other lay and professional groups championing the cause of general or specific medical research."[15]

Dr Shulman was the President of the American Rheumatism Association (now American College of Rheumatology [ACR]) from 1974 to 1975 and the President of the Pan American League of Associations of Rheumatology from 1982 to 1986. He received numerous honors during his career; the two that he was most proud of were the Heberden Medal in 1975 and the Presidential Gold Medal from the ACR in 1996. Dr Shulman passed away in 2009 from bladder cancer; he is survived by his daughters Kathy Shulman and Barbara Shulman-Kirwin and grandchildren. Dr Bevra H Hahn wrote that "The world of rheumatology has lost a great man. We miss him, honor him, and continue to draw inspiration from him."[16]

MARY BETTY STEVENS, MD

Mary Betty Stevens was born on January 11, 1929, in Cambridge, New York, and raised in Granville, a small town in upstate New York bordering Vermont (**Fig. 2**). She matriculated at Vassar College and graduated in 1948. After 1 year as a teaching assistant at Mount Holyoke College, she came to Baltimore in 1949 with plans to become a research scientist and served as an Assistant in Chemistry at the School of Hygiene and Public Health before deciding to matriculate at the School of Medicine in 1951. She received her MD in 1955 and completed her internship and residency on

Fig. 2. Mary Betty Stevens, MD. (Hahn BH: In memoriam: Mary Betty Stevens, MD, FACP, FACR, 1929-1994. Arthritis Rheum 1995;38:444.)

the Osler Medical Service from 1955 to 1958 and postdoctoral fellowship in the Connective Tissue Division from 1958 to 1960.

Mary Betty joined the faculty of the School of Medicine as an instructor in Medicine in 1960. She rose through the faculty ranks, eventually being named Professor of Medicine, and remained on the faculty until her death in 1994.

As a fellow and junior faculty member, Mary Betty worked with Dr Shulman on clinical research studies in patients with lupus and other connective tissue diseases, including the importance of the finding of extracellular material on LE cell preparations and the association between esophageal dysmotility and Raynaud phenomenon.[17,18] As an Assistant Professor, she became the Director of the Hopkins Outpatient Arthritis Clinic and implemented nurse management programs for patients with rheumatoid arthritis receiving intramuscular gold injections and patients with gout receiving prophylactic colchicine and urate-lowering therapy. During this time, she also developed her remarkable bedside teaching skills which were recognized when she received the George J Stuart Award for best clinical teacher from the Hopkins' graduating class of 1971. Ted Rose, President of the class, stated "A lot of people are brilliant in their field, but they can't seem to get their thoughts across. Dr. Stevens manages both, and at the same time she shows great concern for the students."

In 1970, Dr Stevens was appointed as the Director, Division of Rheumatology and Head of a new 36-bed inpatient Rheumatic Disease Unit (RDU) at the Good Samaritan Hospital. In this position, she pioneered the multidisciplinary team approach to the care of patients with rheumatoid arthritis and other rheumatic diseases involving orthopedic surgery, physical and occupational therapy, social work, nursing, and nutrition in addition to rheumatology. Serving as a subintern on this unit became one of the most popular elective rotations for senior medical students almost immediately after the RDU was established. Several of my classmates and I completed this elective; indeed, five members of my graduating class of 1973 (Drs David Borenstein, Marc Hochberg, Joseph Scarola, Stuart Silverman, and Dennis Torretti) became rheumatologists. I spent 6 months of my first year of fellowship from January to June 1976 covering the inpatient RDU, alternating call with either the Hopkins or Maryland Senior Resident and learning on rounds and at the bedside from not only Dr Stevens but also Drs Frank Arnett, Carole Dorsch, Abdullah Shams, and Thomas Zizic.

Dr Stevens was promoted to Associate Professor and appointed as the Director of the newly renamed Division of Rheumatology in 1975 by Dr Victor A McKusick, succeeding Dr Shulman. She was the first woman to become the Division Director in the Department of Medicine at Hopkins. In the same year, she was named the Director of the Division of Rheumatology at the University of Maryland School of Medicine by Dr Theodore Woodword; this provided an unique opportunity for the amalgamation of clinical teaching of medical students and residents from both academic institutions in Baltimore under one combined faculty. During this period, under her leadership, the inpatient RDU and the outpatient practice at Good Samaritan Hospital developed an international reputation for multidisciplinary patient care and training of not only rheumatology fellows but also arthritis-related health professionals, including nurses and physical therapists. She was assisted in these latter efforts by Ms Joan D Sutton, a clinical nurse specialist in rheumatology who held faculty appointments at both the School of Medicine and School of Nursing until her death in 1991.[19]

Dr Stevens supervised original clinical research in SLE by her postdoctoral fellows and faculty colleagues including descriptions of central nervous system involvement, ischemic necrosis of bone, abdominal vasculitis and colonic perforation, ocular involvement, and a comprehensive summary of racial/ethnic and sex/gender differences in 150 patients with SLE.[20–27] She also supervised original clinical research in

other systemic autoimmune rheumatic diseases, including polymyositis, rheumatoid arthritis, and Sjogren syndrome, among others that resulted in a total of more than 50 peer-reviewed publications.

Dr Stevens stepped down as the Director of the Division of Rheumatology at the University of Maryland in 1985 and at Johns Hopkins in 1987 but remained the Director of the RDU until her death in 1994. The list of postdoctoral fellows whom she trained who went on to successful careers in rheumatology includes, but is not limited to, Drs Thomas M. Zizic, David Borenstein, Dennis Torretti, Frederick Wigley, Joan Bathon, and myself.

Dr Stevens was the Second Vice-President, American Rheumatism Association (now ACR) and elected as Master of both the ACR and American College of Physicians. She received numerous honors during her career; the two that she was most proud of were the George J Stuart Award (vide supra) and the Distinguished Rheumatologist Award from the ACR in 1990. Dr Stevens passed away in 1994 from complications of a stroke. Dr Bevra H Hahn wrote that "Dr. Stevens was unfailingly enthusiastic about teaching, patient care, and the creation of new information. She inspired patients, students, residents, fellows, and colleagues to reach higher, to push back the barriers of our limited knowledge, to excel. She was the ultimate role model and mentor."[28]

PERSONAL REFLECTIONS

I was fortunate to have been a student and fellow under both Drs. Shulman and Stevens during my training at Johns Hopkins. As mentioned above, I completed the subinternship on the inpatient RDU at Good Samaritan Hospital during my senior year and got to witness first-hand the excellent patient care delivered by Dr Stevens and was the recipient of her bedside teaching. I particularly recall watching her sit on the edge of a patient's bed to discuss their symptoms, diagnosis, and treatment, a unique bedside manner that I continue to emulate when I make consult rounds with our fellows.

I spent the first half of my first year of fellowship working with Dr Shulman at Hopkins covering the inpatient consult service and seeing his patients in the private outpatient clinic. The second half was spent on the inpatient RDU working with Dr Stevens and her colleagues. During my second year, after Dr Shulman had transitioned to his new position at the NIH, he came to dinner at our apartment and charted my future career path with the recommendation that I obtain formal training in epidemiology to become a researcher in public health. When I approached Dr Stevens with this idea, she agreed to support me as a part-time student at the School of Hygiene and Public Health when I joined the faculty as an instructor in Medicine. I then spent 2 years studying for an MPH while working half-time seeing outpatients and attending on the RDU and covering the inpatient consult service at Hopkins.

I owe the success of my career to their combined mentorship that continued as I rose through the faculty ranks at Hopkins before leaving to join the faculty at the University of Maryland. The current internationally recognized rheumatology division at Hopkins stands on the shoulders of these giants.

DISCLOSURE

The author has no potential conflicts of interest to disclose.

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