History of the Infectious Diseases Division at UTSW

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Introduction:

The Infectious Diseases (ID) Division at UTSW has been in operation for 65 years, from 1953 through 2018. There is probably no other specialty in Medicine that has experienced greater changes in terms of events and pathogens. This history seeks to tell about the major personalities in ID at UTSW and to relate some of the problems encountered by them and the Division.

Timeline:

1953. Dr. Donald W. Seldin as Chief of Internal Medicine at UTSW recruits Dr. Abraham Braude to become Chief of Infectious Diseases. Dr. Braude is the first Chief of the Infectious Diseases division. He later is to become President of the Infectious Diseases Society of America. His predominant investigative interests are related to the pathogenic potential of endotoxin in gram negative bacterial infections.

1957. After four years, Dr. Braude leaves Southwestern for Pittsburg but had recruited Jay P. Sanford to the Division. Dr. Sanford had been a junior medical student studying the effects of bacterial endotoxin under Dr. Braude at the University of Michigan. Dr. Sanford recruits Jack A. Barnett as a Fellow in Infectious Diseases. After Dr. Barnett had finished his training, which included one year in the laboratory of Dr. Frank Dixon at the University of Pittsburg, learning immunologic techniques, he becomes a faculty member and together from 1957-1975, Drs. Sanford and Barnett train forty physicians who complete their

fellowship training in ID. About one-half of these fellows eventually would become full professors in Infectious Diseases and Internal Medicine.

1965. Drs. Sanford and A.K Pierce in Pulmonary Diseases and others (Dr. James Allen Reinarz, Benita M. Mays) establish that the humidifying apparatus in ventilators or the main-stream reservoir nebulizer is a major source of gram negative rods (GNRs) causing pneumonia in patients on ventilator therapy. This phenomenon is recognized first at Parkland Memorial Hospital (PMH) but is proven to have occurred in multiple hospitals in Dallas and presumably throughout the country (1).

1966. St. Louis encephalitis in Dallas necessitating aerial insecticide spraying. In 1966, Dallas becomes the site of a major epidemic of St. Louis encephalitis which causes 145 cases and 14 deaths. The first cases are discovered early and its extent predicted. Ninety-five of the laboratory documented cases are seen at PMH. For the clinical studies, a group of these patients were followed prospectively by Dr. Paul M. Southern and James W. Smith and compared with the features of patients not followed in this manner. The full series of investigations of the disease involved 16 faculty members and fellows and eventuated into a three paper series appearing in the Annals of Internal Medicine on its clinical manifestations, pathophysiology and interferon response (2,3,4).

1966. A new fellow, Dr. Waldemar (Buzz) Johanson is recruited to the ID and Pulmonary Divisions and begins to study pneumococcal colonization of hospitalized patients at PMH. His mentors (Drs. Sanford and Pierce) and he are surprised to find that hospitalized patients with severe illness but not normal controls or psychiatric patients have their nasopharynx colonized with GNRs and that this furnishes the basic science observation underlying the occurrence of infections with these organisms in hospitalized patients. Somehow, gravely ill patients develop receptor sites for GNRs and that influences the nature and course of the infections that complicate their illnesses (5,6).

1968. A large outbreak of Serratia marsescens infections occurs at PMH related to contaminated multiple dose respiratory medication vials. Many asymptomatic patients are colonized and the path of the organism can be traced from a

respiratory source to urine to surgical wounds and blood-stream invasion. The epidemic occurs in the setting of a surveillance system designed to detect pneumonia caused by GNRs. The epidemic also illustrated the necessity of multiple exposures before colonization in individual patients (7).

1970-1971. Resurgent measles (Rubeola) in Dallas County. Ridding a classical infectious disease from the community requires continuing efforts and multiple disciplines which include Pediatrics, Internal Medicine, the Dallas County Health Department and Hospital Administration. Between December 1970 and May 1971, 1071 cases of measles including 3 deaths occurred in Dallas. Immunization rates in school-age children were low and students already in school were not subjected to an entrance requirement that September requiring rubeola immunization. The epidemic was controlled by a special immunization campaign centered in schools. Again, from December 1989 to June 1990, 2300 cases of rubeola occurred in Dallas County including 6 deaths. The epidemic spilled over to involve 33 adults working at PMH who incurred their disease from contact with sick children. Eight of the employees were older than 30 years and were born before 1957. A hospital-based mandatory immunization campaign ended the personnel epidemic.

1975. Dr. Sanford is recruited to become Dean of the Uniformed Services Medical School. He had been Chief of the ID Division at UTSW from 1957-1975. He headed the Clinical Microbiology Laboratory at Parkland Memorial Hospital and chaired the Infection Control Committee at PMH, which was one of the first to be established in the U.S. He was an expert in urinary tract infections; with Drs. James W. Smith, Jim Lehman, Lee Hand and Tom Miller, he was involved in the study of the local immune response in pyelonephritis (8). He was particularly interested in the quantitative urine culture and in antibody coated bacteria as a means of studying diagnosis and clinical impact (9). He was elected president of the American Federation of Clinical Research and later president of the Infectious Diseases Society of America. He is best known and remembered for his authorship of the Sanford Guide to Antimicrobial Therapy, which has gone through 47 editions, beginning in 1970 with a Parkland Hospital Grand Rounds and

progressing with changes through multiple teaching sessions with resident physicians and fellows in Infectious Diseases.

When Dr. Sanford left the Medical School, other faculty members also left. Dr. Jack A. Barnett was an integral member of the Division from 1960-1975. He was an outstanding clinician and teacher and served as a balance to Dr. Sanford who loved to travel and was highly regarded as an excellent, inspiring visiting professor. His tours as visiting professor attracted outstanding potential recruits for the fellowship at UTSW. Dr. Barnett was a more stay at home type who had great practical wisdom with regard to patients, enjoyed their day to day care and was an excellent teacher. Dr. Barnett eventually became Chief of Infectious Diseases at the Methodist Health Care System in Dallas. Drs. Sanford and Barnett co-authored multiple papers often in conjunction with a fellow in Infectious Diseases. Dr. Sanford could visualize the important clinical implications of problems that extended outside the realm of patient care and delved into problems that might have national or even military aspects. For example, he was intrigued about the micro-organisms involved in tornado-associated wounds that he observed during a 1957 tornado epidemic in Dallas and organized a study of the nature of these wounds occurring after the 1968 Lubbock TX tornado and which required going to that city and enlisting the assistance of local physicians and patients to study tornado associated wounds (10). Dr. David Gilbert, a fellow in ID was the first author of the paper detailing this experience and he went on to become a Professor of Infectious Diseases at the University of Oregon and later to become president of the Infectious Diseases Society of America. Dr. Randall Holmes did his fellowship at UTSW and left the medical school in 1975 to become Chief of Microbiology at the Uniformed Services Medical School. His area of expertise was in the microbiology of cholera and diphtheria toxins. Dr. Holmes was elected to membership in the American Society for Clinical investigation in 1977.

1975. Dr. James P. Luby becomes chief of the Division. He graduated from Northwestern University Medical School and had been an EIS officer who was assigned to Houston during their 1964 St. Louis encephalitis epidemic and had

spent the summer there seeing patients with this disease at Ben Taub Hospital (the charity hospital) in Houston. He became the Chief Medical Resident at PMH in 1966. In 1975, the ID Division consisted of Drs. Luby and Southern at PMH and Dr. Smith at the DVAMC. Dr. Luby became the head of the Virology Laboratory at PMH, the chief of Infection Control at PMH and later in 1979 became the medical director of a CDC sponsored STD Prevention and Training Program. Dr. Smith worked with Drs. Tom Miller and James Lehman on the local immune response in pyelonephritis and with Dr. Steven Jones in studies defining the clinical significance of antibody coated bacteria in the pathogenesis of kidney infection. Dr. Southern became Director of the Clinical Microbiology Laboratory at PMH with multiple projects in Clinical Microbiology and developed interests in Tropical Medicine. He also plays an important role in Clinical Microbiology at the University Hospitals (St. Paul and Clements University Hospitals) and has been aided in this regard by Drs. Rita Gander, Dominick Cavuoti and most recently by Dr. Francesca Lee. After their second fellowship year, two ID fellows, Drs. William Baine and Kevin Murphy joined the Division as faculty. Dr. Baine worked in the Laboratory to study the pathogenesis of Legionella infections with which he had worked at CDC. While as a faculty member, Dr. Baine was regarded highly as a superb and energetic teacher and given multiple awards by students and resident physicians.

Dr. Robert Munford joined the faculty in 1978 as did Dr. Philip Mackowiak who worked primarily at the DVAMC with Dr. Smith. Dr. Munford continued working on the role of endotoxin in the pathogenesis of Infectious Diseases. Before becoming a faculty member, Dr. Munford did his residency at PMH, spent 2 years at CDC, a year of ID fellowship at the Massachusetts General Hospital and a year studying gram negative bacterial endotoxin at The Rockefeller University with Dr. Emil C. Gotschlich. Dr. Mackowiak also was at CDC, worked on multiple projects and became interested in fever and in medical history, topics to which he devoted himself when he became Professor of Internal Medicine and the Chief of Internal Medicine at the University of Maryland VA Medical Center in 1988. Two other faculty members became associated with the division. Dr. Justin Radolf joined the Division in 1986 and studied infections due to Treponema pallidum (syphilis) and

Borrelia burgdorferi (Lyme disease). He left the Division in 1999 for a position at the University of Connecticut. Dr. John Carpenter joined the Division in 1986 and stayed until 1998 when he left to become director of the ID Division at Scott & White Medical Center in Temple, Texas.

A large nation-wide epidemic of St. Louis encephalitis occurs in 1975 causing approximately 2500 laboratory documented cases but Dallas only sees a small number of cases.

1976. A second Dallas epidemic of St. Louis encephalitis. Again, cases are documented early with enhanced mosquito control bringing about a shortened epidemic. Antigenuria in PMH patients is described in St. Louis encephalitis during the 1976 epidemic and was the first flavivirus in which that phenomenon had been determined (11). It now has been shown to occur in all other flavivirus infections that have been studied (WNV, dengue, Zika, yellow fever and others).

1978. MRSA Hospital Acquired Infections. Parkland Memorial Hospital had its first outbreak of MRSA infections in the Burn Intensive Care Unit (BICU) in 1978. Fifty-six patients ultimately became colonized. A quiescent period followed and the next outbreak occurred in 1981. Cases have occurred on a continuing basis since that time until the present. In 1981, the Surgical Intensive Care Unit became involved as did the newborn and special-care nurseries (SCNs). The BICU was free of cases from 1979 to 1981 but colonization became a persistent problem from 1981 onward. At times during the ensuing period, all new patients became colonized within 72 hours of admission into the Unit. The Surgical Intensive Care Unit outbreak was thought to be primarily related to crowding and the problem was lessened by construction of a new ICU. The Nursery epidemics were ameliorated most by improved nursing to patient ratios (12). The BICU problem generated the greatest number of cases. The BICU was over-crowded and it could be demonstrated that burn wound dressing changes resulted in aerosolization of MRSA throughout the patient's room and into the halls of the unit. Space considerations precluded door closure during dressing changes. Multiple determinations of nasal colonization of personnel were performed in the BICU and positive persons were treated to eliminate or control carriage but there was

no effect on case rates. The problem in burn patients decreased by constructing a new burn unit at the hospital and then another new unit in the newly constructed New Parkland Hospital (13). A special study was done in 2008 to elucidate the origins of MRSA that were being transmitted in the hospital and clearly indicated that community acquired MRSA was entering the hospital and being transmitted there.

1982. AIDS at Parkland. The AIDS epidemic was recognized nationally in 1981 and the first patient with AIDS was hospitalized at PMH in 1982. A Clinic managing patients with this disease at PMH was set up in 1983 and 1984. Originally manned by Allergy and Immunology and Infectious Diseases, the ID Division took over its practical management of patients with Dr. Silvia Resta, an ID fellow and Dr. Luby first seeing patients there. The population of patients with CDC defined AIDS seen at the clinic or hospitalized at PMH grew from 1 in 1982 to 170 in 1987 to 501 through June 15, 1988. As of July 1, 1988, 270 of the 501 cases had expired, an indication of the lethality of the disease in the early part of the epidemic. Eventually, as many as 7,000 patients with HIV infection were being seen each year at PMH. Problems related to care of these patients during the early part of and throughout the epidemic were recruiting personnel who would care for the increasing number of patients and providing up-to-date therapy, often with treatment regimens that had only limited proof of efficacy, e.g., pentamidine prophylaxis for pneumocystis pneumonia, azidothymidine (AZT) treatment prior to a national randomized control trial showing a time-limited benefit.

Important additional personnel contributing to the care of these patients included Drs. Daniel Barbaro from Infectious Diseases and Drs. Stephen Nightingale, Delores Peterson and Stephen Pounder in General Internal Medicine. Drs. Philip Keiser and Naiel Nasser in ID also would contribute significantly to the care of the patients in the Clinic. Drs. Amneris Luque. Mamta Jain, and Ank Nijhawan are contemporary leaders in the care of HIV infected patients at PMH. Newer physicians seeing patients AIDS at the Clinic and hospital are Drs. Ellen Kitchell, Arti Barnes, Jeremy Chow, Abby Lau, Susana Lazarte and Helen King.

At the Dallas Veterans Administration Medical Center, Drs. James Smith, David Margolis, Roger Bedimo, Henning Drechsler and James (Brad) Cutrell run a clinic for patients with AIDS and did important investigations into its latent persistence (Dr. Margolis) and the relationship between AIDS, age, cardiovascular and bone disease and hepatitis C virus (Drs. Bedimo, Drechsler and Cutrell).

1986. Dr. Munford discovers AOAH, a human and animal enzyme which detoxifies endotoxin in vivo. Dr. Munford radio-labelled endotoxin preparations and showed that in animals and humans that endotoxin was degraded to an inactive molecule. This had never been described before and led to the isolation and purification of the enzyme which accomplished the degradation, Acyloxyacyl Hydrolase (AOAH). The end-product of the reaction reduced the toxicity of lipopolysaccharide and preserved its capacity for beneficial inflammatory and immune stimuli. Its significance and clinical impact is presently under investigation (14). Dr. Munford left UTSW in 2009 to become a Senior Investigator at the Clinical Center of the National Institute of Allergy and Infectious Diseases.

1989. Histoplasmosis at UTSW. Illustrative of the variety of problems encountered by the ID Division in 1989 and extending through 1996 was a campus-wide epidemic of histoplasmosis which involved 29 laboratory documented cases and an estimated 600 infections and that was shown to be related to construction activities centered around one major research building and the connector tying the south campus with the north campus and the University Hospital. With repair of the filtering system for outside air for this and adjacent buildings and control of aerosol creation from construction activities, there have been no new cases of campus-related histoplasmosis since 1996. The epidemic illustrated the vulnerability of persons to infection by fungal spores in modern air-conditioned buildings in urban environments and the necessity for adequate filtration of air entering the buildings (15).

1997. Dr. Richard (Rick) Koup becomes head of the Division of Infectious Diseases in 1997. He was the first Jay P. Sanford Professor of Infectious Diseases at UTSW. He served as head of the Division from 1997 to 2001 when he left for the National Institutes of Health where he became Chief of the Immunology Laboratory,

Vaccine Research Center. He has been involved in studies of the role of cellular immunity in the control of HIV, and basic immunopathogenic mechanisms in HIV infection (16,17). He attracted a cadre of basic science investigators studying HIV to join him at UTSW that included Drs. Don Sodora, J. Victor Garcia-Martinez, Daniel Douek and David Margolis.

2004. Dr. Beth Levine was recruited to UTSW where she served as the Chief of the Division of Infectious Diseases and second Jay P. Sanford Professor of Infectious Diseases from 2004-2011. Prior to coming to UTSW, she was Director of Virology Research at Columbia University College of Physicians & Surgeons where she originally discovered the first mammalian gene shown to function in autophagy, beclin 1, and its role in antiviral immunity (18). During her tenure as Chief of Infectious Diseases at UTSW, the Division continued to expand its educational, clinical, and research activities. Specifically, the Fellowship Program doubled its number of trainees; a new NIH T32 Fellowship Training Grant was obtained; new Infectious Diseases inpatient clinical services were established at St. Paul University Hospital and in Transplantation Infectious Diseases; new outpatient clinics were established in general infectious diseases at Aston Clinic and in parenteral antimicrobial infectious diseases at PMH; a new antimicrobial stewardship program was created at University Hospital; a new leader of Infection Prevention at PMH was recruited; and several clinician educators, clinical scholars and tenure-track research faculty were recruited. Two of the physician scientists recruited included Dr. David Greenberg, an expert on bacterial pathogenesis, biofilms, and the control of bacterial growth using antisense oligonucleotides, and Dr. Michael Shiloh, an expert on host-pathogen interactions that govern the pathogenesis of M. tuberculosis. Dr. Levine's own research program focuses on the role of autophagy in innate immunity as well as in cancer, developmental biology, aging, and neurodegenerative disorders (19). In 2008, she received the Peter O'Donnell Award from the Texas Academy of Sciences for outstanding research in Medicine and became a Howard Hughes Medical Research Investigator. In 2011, she became the Director of the Center for Autophagy Research at UTSW, and she was elected into the National Academy of Sciences in 2013.

2005. UT Southwestern takes over operation of St. Paul University Hospital. This acquisition will eventually lead to an Infectious Diseases Service caring for patients at the two university hospitals (St. Paul and Zale Lipshy). In actuality, two services are placed into operation. The first seeing patients with general infectious disease problems (General ID) with the second consulting on transplant recipients, including those patients having kidney, liver, lung, heart and bone marrow transplants (Transplant ID). The Infectious Diseases Division of the medical school will also appoint the medical director of the Infection Prevention Unit at the two hospitals. Dr. Julie Trivedi became the director of the Unit in 2017. The acquisition of the two hospitals will increase the clinical load of the Division and necessitate enlargement of an outpatient clinic at the Aston Center seeing patients with continuing problems after an acute hospitalization period. Dr. Bonnie Prokesch was enlisted to supervise running this clinic. In November 2014, St. Paul University Hospital ceases functioning and patients are transferred to a newly built facility, Clements University Hospital.

2005. UTSW Transplant Infectious Diseases Unit established at St. Paul Hospital. Although the first organ transplant performed at St. Paul Hospital involved a heart and occurred in 1988, a full University Transplant Infectious Diseases Unit was established when the University took over the control of St. Paul Hospital. In 2012, Dr. Binh-Minh (Jade) Nguyen Le returned from her ID fellowship and assumed directorship of the Unit. She filled that role until 2017 when she entered private practice. Other physicians joining the Unit included Drs. Pearlie Chong, Ricardo La Hoz, and Reuben Arasaratnam. Dr. Chong is the present chief of the Unit.

2009. Dr. Pranavi Sreeramoju becomes head of Infection Prevention at PMH. After receiving her MPH at Tulane and an ID fellowship and further training at the University of Chicago, Dr. Sreeramoju assumes directorship of Infection Prevention at PMH. Dr. Luby had held that position from 1975 through 2009. A former ID fellow at UTSW, Dr. Carolee Estelle, joins Infection Prevention to assist Dr. Sreeramoju in 2017.

2010. Dr. Kavita Bhavan becomes the Medical Director of the Outpatient Parenteral Antimicrobial Clinic/Infectious Diseases Clinic at PMH. With an enlarging population of patients seen at PMH needing parenteral antibiotic therapy for prolonged periods, Dr. Bhavan begins a program of self-administered outpatient antibiotic therapy (S-OPAT) in which patients are educated in the technique of delivering antibiotic solutions by gravity, hand hygiene technique, aseptic technique connecting solutions to the IV catheter and then tested for mastery of the procedures. S-OPAT patients were compared to Healthcare administered OPAT (H-OPAT) usually accomplished while the patient was hospitalized with there being no difference in one year mortality and with S-OPAT treated patients actually faring better in terms of 30 day readmission rates. These findings have far-reaching consequences in terms of furnishing long-term antibiotic treatment of infections in indigent populations (20). In 2016, she wins the 2016 Gage Award for innovation and excellence and in 2017 the Innovation in Clinical Practice Award presented by the Infectious Diseases Society of America. Dr. Aurelia Schmalstieg and other physicians become involved in seeing patients at the ID OPAT Clinic.

2012. One of the largest West Nile Virus (WNV) epidemics occurs in Dallas County and the adjacent three counties (Tarrant, Collin, Denton) causing over 900 laboratory documented cases in the four county area with Dallas having the largest number of cases (400 including 20 deaths) (21). WNV has apparently displaced St. Louis encephalitis as the major cause of urban epidemics causing CNS infection in the United States. Aerial spray of insecticide was needed in Dallas for its control. The Vector Index (a measure of the concentration of infected and transmitting mosquitoes) is shown to have promise in predicting the course of urban epidemics of WNV and perhaps in predicting when aerial spraying may be best applied.

2016. Dr. Trish M. Perl becomes the sixth head of the Infectious Diseases Division and the third Jay P. Sanford Professor of Infectious Diseases. She attended medical school at the University of North Carolina at Chapel Hill and did a fellowship in Infectious Diseases with Dr. Richard Wenzel at the University of Iowa. She became the hospital epidemiologist at Johns Hopkins Hospital and later

Senior Epidemiologist at the Johns Hopkins Health System. Her investigative interests have revolved around infection control and prevention, health-care associated infections, surgical site infections, antimicrobial resistance and infections due to Staphylococcus aureus and Clostridium difficile.

Kudos to past mentors and friends not members of the UTSW ID faculty. Dr. Ralph Tompsett was the former Chief of Infectious Diseases and Internal Medicine at the Baylor University Medical Center from 1957 through 1979. While at Cornell University, he with others successfully treated patients with Enterococcal endocarditis for the first time. He made clinical rounds with fellows and residents every Thursday at Parkland and enormously contributed to the intellectual excitement and standards of patient diagnosis and treatment at the hospital. Also included in this category are members of the practicing ID community in Dallas who consistently attend and participate in conferences and are available for consultation and advice and include Drs. Edward Goodman, Steven Seidenfeld and Leigh Hunter. Dr. Robert Haley, Chief of the Epidemiology Division at UTSW contributed with his experience and counsel.

The Future. The Infectious Diseases Unit is now seeing patients at Parkland with two Services seeing the patients (General ID and ID seeing mostly HIV antibody patients and patients with bone and joint infections). At CUH and ZLUH, patients are being seen by General ID or the Transplant ID Service. At DVAMC, patients are seen by just one General ID Service.

Essential to the functioning of the ID Unit is the fellowship program. Since Dr. Sanford left the medical school there have been an additional 75 fellows trained at UTSW to make a total of 115 fellows. Three-four fellows per year are being recruited and the fellowship program is under the supervision of Drs. Brad Cutrell and Paul Southern. The expanded program is thought to be essential in view of the enlarging number of patients seen at three hospitals and an expanding Clinic system.

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