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John S. Chapman, MD: neglected pioneer in sarcoidosis

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John S. Chapman (1908-2000) was an academic pulmonary physician in the US state of Texas who made major contributions in the understanding of sarcoidosis and nontuberculous mycobacterial (NTM) disease. In our view, he has not received proper credit for his contributions to the field. Born in the small town of Sweetwater, he graduated from Southern Methodist University (SMU) in Dallas. He then entered the University of Texas Medical Branch in Galveston, the oldest medical school in Texas, where he graduated in 1932. There he met and married Marianne Ryan, a nurse to whom he was happily married until her death in 1992 (1).

Early on, Chapman entered medical practice with his father in his hometown. In 1943, he moved to Dallas and became an associate of two of the early thoracic surgeons in the area, Robert R. Shaw and Donald Paulson. Shaw, Paulson, and Chapman established the first 14-bed ward for tuberculosis at Baylor University Hospital. This was the initial hospital thoracic unit in Dallas. Good diet, bed rest, sunshine (now known to be valuable for its positive effects on vitamin D), were staples of therapy in that era. Therapeutic pneumothorax to collapse cavities and convert sputum to negative also was a major tool used for treatment. There was limited therapy of value beyond that. Effective tuberculosis chemotherapy had not yet become available (2).

Soon after he came to Dallas, Chapman became a consultant to the tuberculosis control program of Dallas County, where there was then an enormous amount of tuberculosis in the white, Hispanic, and African-American populations. He also became affiliated with the University of Texas Southwestern Medical School in Dallas, from its founding in 1943, the same year the Baylor University College of Medicine moved to Houston. Chapman rose to become a Professor of Medicine, and later Associate Dean for Postgraduate Education, and remained active with the school until his retirement in 1984.

Texas research studies

Chapman was active among the clinicians who, in the 1950's and 1960's, essentially described NTM disease (mostly in the lungs, but also involving cervical nodes in young children, and various other parts of the body, especially in immune suppressed subjects). He edited a monograph on this topic published in 1960 (3). In that monograph, it was clearly stated in two articles, one written by Chapman, that, in contrast to tuberculosis, NTM lung disease seemed not to be contagious from person to person but was acquired in some fashion from the environment. In 1977, he wrote a book, *Atypical Mycobacte-*

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ria and Human Mycobacteriosis, published by Plenum Medical Book Company of New York, which was the most up-to-date review of the topic at that time (4).

Furthermore, in the course of his studies of pulmonary mycobacterial disease, Chapman happened to notice an unusual phenomenon. When there was a sarcoid patient in a household being evaluated for mycobacterial disease, the contacts of that household in Dallas County had positive skin test reactions to NTM more than double the rate of those of healthy controls, and the difference was statistically significant (5, 6). This observation meant that these contacts had had significant exposure to environmental mycobacteria. The sarcoidosis patients on the whole tended to have diminished or absent skin test reactions, compared to the household contacts. Later, this phenomenon (dampening of skin test reactions as part of cell-mediated immunity) was appreciated as part of the "peripheral anergy" of patients with sarcoidosis.

In the 1960's, Chapman was among the first to describe antimycobacterial antibodies in the sera of sarcoidosis patients. In a later study, he and colleagues found high titers of antimycobacterial IgM and IgA antibodies in subjects with recent onset of sarcoidosis. These same individuals, when followed up, had lower or unmeasurable titers of these antibodies, suggesting recent exposure to nontuberculous mycobacteria. This work was presented at the 1964 American Thoracic Society annual meeting, and published in the journal now known as the American Journal of Respiratory and Critical Care Medicine (7-11).

The 1960's immunological studies of Chapman have been largely overlooked and forgotten. They may have had criticism by some because of their "lack of sophistication". Chapman's latter studies, however, were done in collaboration with John Baum, MD, of the Rheumatology Division of the U. of Texas Southwestern Medical School, later a Professor at the University Of Rochester School Of Medicine. The Rheumatology Division at Southwestern was headed by Morris Ziff, MD, PhD, who had come there from the New York University School of Medicine, and was a respected figure in the field of rheumatology, having done early work clarifying the nature of rheumatoid factor or factors in patients with rheumatoid arthritis.

Further research on the association of sarcoidosis and mycobacteria since then:

Fast forward about thirty years to the late 1990's. In 1999 Japanese and European investigators, using techniques unavailable to Chapman in his early studies, reported that tissues taken from sarcoidosis patients (mostly mediastinal lymph nodes) had substantially greater amounts of microbial DNA from mycobacteria and propionibacteria than tissue taken from patients who went to surgery for lung cancer. (12) More data from these investigators was published in 2002 and 2005 (13, 14). It should be noted, however, that there may be culturable propionibacteria in lymph node tissue taken from persons having thoracic surgery for treatment of lung cancer, with no clinical evidence of sarcoidosis. Furthermore, people using regular tap water in activities of daily living (eating and drinking, showering) are in all probability exposed to nontuberculous mycobacteria from time to time.(15) Therefore, it seems likely that it must take a genetic predisposition, plus exposure to particular microorganisms, or other environmental trigger(s) to cause the disease.

In 2002, Drake et al at Vanderbilt University in Tennessee reported results on molecular analysis of tissues from 25 sarcoidosis patients, as well as specimens from 25 controls and found Mycobacterium species 16S ribosomal RNA and ribosomal polymerase, beta subunit, in 60% of sarcoidosis specimens. They did not find any evidence of IS6110, a molecular sequence considered specific for the presence of Mycobacterium tuberculosis. The Vanderbilt group has later published data documenting Th-1 type immunologic responses to several important mycobacterial antigens in sarcoidosis subjects, much more than in healthy control subjects who have no evidence of cellular immunity to mycobacteria (16-21).

In recent years, investigators at Johns Hopkins University have uncovered impressive changes seemingly unique to sarcoidosis. Early on, they found the protein *Mycobacterium tuberculosis* catalase-peroxidase as a tissue antigen in the lungs of sarcoidosis patients (22-23). They also showed evidence of antibody formation to this antigen in the blood of patients whose lung biopsies they had examined. Later on, Swedish investigators, collaborating with the Hopkins group documented that there was T-cell responsiveness of a similar degree to mycobacterial

antigens in sarcoidosis patients, both from Stockholm and Baltimore. These recent studies, deriving from more sophisticated techniques than available to Chapman, are true testimonials to his foresightedness in recognizing the connection of mycobacteria and sarcoidosis.

Chapman had diverse interests beside pulmonary medicine, in history, literature and the arts. He wrote a book about the history of the U. of Texas Southwestern Medical School, and, on a totally different note, another about Lord Byron, and Byron's relationship with his half-sister, Augusta Leigh. Most importantly, he made notable contributions to medicine that deserve to be recognized more than they have been in the past.

References

1. Dallas Morning News. Obituary, John S. Chapman, MD. - August 4, 2000.
2. Urschel HC Jr. History of the cardiothoracic surgery service at Baylor University Medical Center (BUMC). BUMC Proceedings 2003; 16: 422-9.
3. Chapman JS, editor. Anonymous mycobacteria in human disease. Charles C. Thomas, Publisher, Springfield, IL, 1960.
4. Chapman JS. The Atypical Mycobacteria and Human Mycobacteriosis. Plenum Medical Book Company, New York and London, 1977.
5. Chapman JS, Potts WE, Speight M, Dyerly M. Cutaneous reactions of household contacts of patients with established diagnosis of sarcoidosis. Am Rev Resp Dis 1963; 88: 95-6.
6. John S. Chapman, W.E.Potts, B.G.Black, et al. Cutaneous reactions of household contacts of sarcoidosis patients. Acta Medica Scandinavica 1964; 176 (S425): 198-202.
7. Chapman JS. Mycobacterial and mycotic antibodies in sera of patients with sarcoidosis. Ann Int Med 1961; 55: 918-24.
8. Chapman JS. A serological reaction associated with sarcoidosis. Proc Soc Exp Biol Med 1961; 107: 321-4.
9. Chapman JS, Speight M. Further studies of mycobacterial antibodies in the sera of patients with sarcoidosis. Acta Med Scand Suppl 1964; 425: 146-8.
10. Chapman JS. Epidemiology of sarcoidosis in the United States of America. Acta Med Scand 1964; 425: 146-8.
11. Chapman JS, Baum J, Clark J, Speight M. Mycobacterial antibodies in immunoglobulins IgA and IgM of patients with sarcoidosis. Amer Rev Resp Dis 1967; 95: 612-7.
12. Ishige I, Usui Y, Takemura T, et al. Quantitative PCR of mycobacterial and propionibacterial DNA in lymph nodes of Japanese patients with sarcoidosis. Lancet 1999; 354: 120-3.
13. Eishi Y, Suga M, Ishige I, et al. Quantitative analysis of mycobacterial and propionibacterial DNA in lymph nodes of Japanese and European patients with sarcoidosis. J Clin Micro 2002; 40 (1): 198-204.
14. Ishige I, Eishi Y, Takemura T, et al. *Propionibacterium acnes* is the most common bacterium commensal in peripheral lung tissue and mediastinal lymph nodes from subjects without sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2005; 22: 33-42.
15. Falkinham JO 3rd. Surrounded by mycobacteria: nontuberculous mycobacteria in the human environment. J Appl Microbiol 2009; 107 (2): 356-67.
16. Drake WP, Pei Z, Pride DT, et al. Molecular analysis of sarcoidosis tissues for mycobacterium species DNA. Emerg Infect Dis 2002; 8 (11): 1334-41.
17. Carlisle J, Evans W, Hajizadeh R, et al. Multiple mycobacterium antigens induce interferon-gamma production from sarcoidosis peripheral blood mononuclear cells. Clin Exp Immunol 2007; 150 (3): 460-8.
18. Allen SS, Evans W, Carlisle J, et al. Superoxide dismutase antigens derived from molecular analysis of sarcoidosis granulomas elicit systemic Th-1 immune responses. Respiratory Research 2008; 9: 36.
19. Oswald-Richter K, Sato H, Hajizadeh R, et al. Mycobacterial ESAT-6 and katG are recognized by sarcoidosis CD4+ T cells when presented by the American sarcoidosis susceptibility allele, DRB1*1101. J Clin Immunol 2010; 30 (1): 157-66.
20. Oswald-Richter K, Culver DA, Hawkins C, et al. Cellular responses to mycobacterial antigens are present in bronchoalveolar lavage fluid used in the diagnosis of sarcoidosis. Infect Immun 2009; 77 (9): 3740-8.
21. Oswald-Richter KA, Beachboard DC, Zhan Z, et al. Multiple mycobacterial antigens are targets of the adaptive immune responses in pulmonary sarcoidosis. Respir Res 2010; 11: 161.
22. Song Z, Marzilli L, Greenlee BM, et al. Mycobacterial catalase-peroxidase is a tissue antigen and target of the adaptive immune response in systemic sarcoidosis. J Exp Med 2005; 201 (5): 755-67. Erratum in: J Exp Med 2005; 202 (5): 721.
23. Chen ES, Wahlström J, Song Z, et al. T cell responses to mycobacterial catalase-peroxidase profile: a pathogenic antigen in systemic sarcoidosis. J Immunol 2008; 181 (12): 8784-96.