RESEARCH ARTICLE

Perspective on Sarcoidosis History and Clinical Research (featuring local colleagues)

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Abstract

A new organization, Americas Association of Sarcoidosis and Other Granulomatous Disorders (AASOG), had its inaugural meeting recently (April 7-8, 2017) in central Pennsylvania. As the provider of an overview of Sarcoidosis, this was an opportunity to review and feature some of the area's local medical and research interests that have been important in attempting to understand and manage patients with this illness. This introductory commentary features area investigators and clinicians who have been helpful in elucidating the pathophysiology and management of this illness.

Commentary

My last appearance before a Sarcoidosis meeting was the 12th Bronchoalveolar Lavage meeting conjoined with the 10th WASOG meeting (1) in Maastricht, The Netherlands (June 15-18, 2011). Recently, I was pleased to participate in the Americas Association of Sarcoidosis and Other Granulomatous Disorders (AASOG), closer to home, and to give "A Historical Perspective on Sarcoidosis." My biased review will focus on local clinical investigators involved with caring for people with sarcoidosis and on those who have contributed knowledge about this disorder in the greater Pennsylvania-Mid Atlantic area. But as a formal history of this multi-system granulomatous disorder and its major clinical presentations, one might review a chapter in a well-known pulmonologist's text book (2), whom we all have respected and learned from, Dr. Alfred P. Fishman (University of Pennsylvania Medical Center, Philadelphia, PA).

As respiratory involvement, especially bilateral mediastinal lymphadenopathy, is very eye catching on a chest radiograph especially for patients with Löfgren's Syndrome (more about this later), retrieving lympho-

cytes and characterizing their identity and activity in describing cellular immunology was of special interest in the late 1960's – early 1970's, especially at the National Institutes of Health (NIH) in Bethesda, Maryland. For me, a Clinical Associate in the Laboratory of Clinical Investigation (1967-1970) of the National Institute of Allergy and Infectious Diseases (NIAID) and returning to that laboratory as a Senior Investigator (1971-1976), I was captivated with investigating the immune system, especially in the respiratory tract. Interest in 1960-1970's of lymphocytes and their role in immunity was in part attributed to Dr. Baruj Benacerraf, a most famous immunologist (3, 4) and specialist in cellular hypersensivity. He was recruited to the NIH, NIAID to direct the Laboratory of Immunology in 1968. Two colleagues, Drs. William Paul and Ira Green, came also and both contributed to this immunology interest. Further fanning this immunological interest in the summer of 1971, we received a gift of a fiber-optic bronchoscope, designed by Dr. S. Ikeda (5), which permitted us to extend our animal lung lavage studies into human subjects. Dr. Harold Newball and I subsequently presented bronchoalveolar lavage (BAL) cellular and non-cellular findings from non-smoker and smoker normal volunteers (6). Also, we characterized the lymphocytes in BAL of Rhesus monkeys (Macaca mulatta) to prepare an animal model for continuing immunology research (7). This has remained the cornerstone of my clinical research interests for the past 40 years (8, 9).

Further studies of lung inflammation with a primate model focused on initiation of the lung's inflammatory response by alveolar macrophages (10). Clinical research centered on forms of interstitial lung diseases (11), especially pulmonary fibrosis, which were done in collaboration with Dr. Ronald G. Crystal (Division of Lung Diseases, National Heart, Lung and Blood Institute, NIH) and colleagues. While IPF was a main focus, we concentrated on the immunological response to hypersensitivity pneumonitis (12), while others studied the response in sarcoidosis (13). In analyzing BAL cells obtained from sarcoidosis patients, a very interesting immunologic finding was noted – a T-cell Rosette – with T-lymphocytes attached or sticking to the surface of alveolar macrophages. This was reported by Dr. Henry Yeager and colleagues at Georgetown University Hospital (14). What an intriguing sight that for me illustrated "dynamic immunology" occurring. What was happening? Were these lymphocytes being given some antigen or received a microbial entity that was the etiology for subsequent granuloma formation by the host? This was not such a clear or immediate finding, nor one that is pathognomonic for lung tissue affected with sarcoidosis. The definitive etiology is still waiting to be found (15).

With my move to Yale University's College of Medicine in New Haven, Connecticut (1976-1988), I left the field of active sarcoidosis research, except for that being done by Dr. Bernard Gee and others in our Pulmonary Division (16). Returning to Hershey, Pennsylvania in 1988 reintroduced me to sarcoidosis, but with a very different group of investigators and a new emphasis

on multi-organ involvement and systemic disease.

For me, election to the American Clinical and Climatological Association (1978) introduced me to a wide range of academic clinicians including a pulmonologist Dr. Carol Johnson Johns of the Johns Hopkins University School of Medicine in Baltimore, Maryland (17). Dr. Johns was a great leader in academic medicine and a renowned expert on lung diseases; sarcoidosis was her special interest (18) and she founded a sarcoidosis clinic in the early 1960's. One of her trainees in the Pulmonary Fellowship Program was Dr. Rebecca Bascom who co-authored with Dr. Johns an important paper on the natural history and management of sarcoidosis (19).

Three spin offs that relate to Dr. Johns have had importance for the Penn State - Hershey Medical Center. First was the clinical interest in sarcoidosis affecting multiple organs in patients that prompted our comparison of presentation and management of multi-organ disease (20) with other clinical series. Our findings were similar to other clinical series, including those from Johns Hopkins reflecting an experience of 50 years (18). Second, we were very pleased to recruit Dr. Bascom to be Chief of the Pulmonary, Asthma and Critical Care Division at Penn State Hershey Medical Center in 1997. She was then nearby at the University of Maryland in Baltimore but still had a joint appointment at Johns Hopkins. Her special clinical interests are in interstitial and occupational lung diseases. I asked Dr. Bascom to prepare some comments about Dr. Johns and her manner of helping other medical trainees and colleagues. Some of these written by Dr. Bascom follow:

> "I began my fellowship in Pulmonary/Critical Care Medicine 1979, and Carol Johnson Johns was "Dr. Sarcoid" at the Johns Hopkins Hospital. She organized a weekly sarcoidosis clinic – recognizing the value of themed clinics well before they were commonplace. She allowed me and other interested residents to have a panel of patients, and provided wonderful tutoring on the approach to this fascinating disease. She further accepted the task of coaching me on my first try at composing a review article, patiently pointing out the usual pitfalls into which my early drafts stumbled. At the American Thoracic Society, she accepted my invitation to attend an informal Sunday evening supper with senior women faculty who introduced "newbies" on the pulmonary scene. The warmth of those valuable suppers provided "you can do it" encouragement at critical junctures in our careers. It also incubated the current Women's and Minority Luncheons that are sell-out fixtures of the annual American Thoracic Society International Conference. Carol was an early mentor for me and I salute her smarts, her grace, and her caring."

Third, the fourth Dean of our Medical College was Dr. Harold Paz[1]. He is a pulmonologist and had completed fellowship training at Johns Hopkins and he had a special interest in sarcoidosis; he was here from 2006-2014. Dr. Paz often joined us in the pulmonary outpatient clinic to help with teaching pulmonary trainees; we made certain he got to precept all the sarcoidosis patients.

Refocusing our attention on sarcoidosis again was from the generous referral of these patients to us in Hershey by Dr. Harold Louis Israel. Dr. Israel was a prominent pulmonologist who saw patients throughout the Philadelphia area for more than 40 years. He was a graduate of Amherst College and earned his medical degree from Jefferson Medical College; he had training in the care of those with tuberculosis but then became more involved with enigmatic afflictions affecting the lungs and multiple organs – i.e. sarcoidosis. He was Chief of Pulmonary Medicine at Philadelphia General Hospital and then at Thomas Jefferson University (21). His presentation of sarcoid patients (22) was helpful for comparing multi-organ involvement in our clinical series (20). Again, we appreciate the inclusion of some of his patients in our practice when he retired from active practice in 1996.

Finally, much closer to "home" was local research being done on a possible genetic predisposition for developing the disease in the lungs from an environmental trigger that might determine the lymphocytic reaction in patients' lungs, or the ratio of Th_1 and Th_2 lymphocytes and if this ratio was affected by IL-4, an immunomodulator. This research involved micro array analysis of 23 sarcoidosis patients from the group in our study (20). As medical students are required at this College of Medicine to participate in a research project, as an academic requirement for completing a medical degree, William Stuart Reynolds was involved with Dr. Michael J. Chorney (23) in this basic research. The conclusion was that allelic polymorphisms of Il-4R did not contribute to genetic susceptibility to sarcoidosis in patients; this work was not accepted for publication (23). But, maybe such genetic factors or stimuli will be found (24)? Although Dr. W. Stuart Reynolds, now a urologist on the faculty of Vanderbilt University Medical Center, Nashville, Tennessee, is now not doing clinical research in sarcoidosis, he is in contact with Dr. Wonder Drake, an Associate Professor of Medicine and Pathology, Microbiology and Immunology at VUMC. Dr. Drake is active in WASOG and has evaluated antimycobacterial therapy for patients with chronic pulmonary sarcoidosis (25). Dr. Drake will direct a newly established Sarcoidosis Center of Excellence which will offer patient care and bring together collaborators doing related research (26).

A special presentation of an acute form of sarcoidosis has been of great interest – Löfgren's Syndrome (27, 28) characterized by acute onset, mild symptoms, erythema nodosum, polyarthralgia, often involving the

[1] Harold L. Paz, M.D., M.S.
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ankles, and bilateral hilar lymphadenopathy. This illness is usually of limited duration. There is an association with patients having a human leukocyte antigen, DRBA*03, and an acute disease that resolves within 2 years (29, 30); whereas, patients who are negative for this antigen have a non-resolving disease. This has clinically separated two forms of sarcoidosis, or given it "two faces" (31), as Löfgren's Syndrome is a self-limiting form, suggesting a different etiology and/or host response; whereas, the chronic persistent form is more usual. Susceptibility variations linked with phenotypes are unlocking the form of disease a person might have (32). The acute form, Löfgren's Syndrome (27) was of particular interest in our group of patients presented (20), accounting for 6 of 67. These patients had careers of nursing, respiratory therapy, dental hygiene and grade school teaching suggesting that proximity perhaps to coughing people and from respiratory care encountered in their working environment may have exposed them to an aerosolized microbial agent.

With identification of multi-organ involvement and its management, recent interest in heart-related illness has been reported (33-35). In this context, we have known several people who have experienced cardiac arrhythmias with consequences that have been profound, including death. At autopsy, cardiac involvement involving the conducting system has been found with granuloma disrupting it. This occurred in the young adult son of one of our distinguished medical families in Hershey. This family has been diligent in raising research monies for cardiac research (36).

Finally, clinical interest in evaluating and managing sarcoidosis has been foremost for Dr. Richard C. Bernstein, a faculty member in this Division; he has evaluated approximately 450 patients in the past several years. Through his contact with Dr. Robert Baughman and others, he has organized this meeting of the AASOG that we are participating in.

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References

1. Reynolds, H.Y. Review and Perspective of the 12th Bronchoalveolar Lavage Conference within the Second Joint WASOG-BAL International Conference. Sarcoidosis Vasc Diffuse Lung Dis. 28:156-160, 2011.

2. Moeller, D.R. Systemic Sarcoidosis (Chapter 69) in Fishman's Pulmonary Diseases and Disorders, 3rd Edition (1998), Volume 1: 1055-1068, McGraw- Hill Companies, New York.

3. Baruj Benacerraf, from Wikipedia Encyclopedia https://en.wikipedia.org/wiki/Baruj_Benacerraf in November 2016, and from Les Prix Nobel, 1980, Wilhelm Odelberg, Editor; Nobel Foundation, Stockholm, Sweden, 1981.

4. Willerson, J.T. Baruj Benacerraf: In Memorian (editorial) Texas Heart Institute Journal, 39(#3): 315-316, 2012.

5. Ikeda S, Yanai N, Ishikawa S. Flexible Bronchofiberscope. Keio J Med 17: 1-16, 1968.

6. Reynolds, HY and Newball, HH: Analysis of proteins and respiratory cells obtained from human lungs by bronchial lavage. J. Lab. Clin. Med. 84:559-573, 1974.

7. Kazmierowski, JA, Fauci, AS and Reynolds, HY: Characterization of lymphocytes in bronchial lavage fluid from monkeys. J. Immunol. 116:615-618, 1976.

8. Reynolds, HY: Sampling local respiratory tract sites for inflammation. Sarcoidosis Vasc Diffuse Lung Dis 18:138-148, 2001.

9. Reynolds, H.Y. Bronchoalveolar Lavage and other Methods to Define the Human Respiratory Tract Milieu in Health and Disease. Lung 189:87-99, 2011.

10. Kazmierowski, JA, Gallin, JI and Reynolds, HY: Mechanism for the inflammatory response in primate lungs: demonstration and partial characterization of an alveolar macrophage-derived chemotactic factor with preferential activity for polymorphonuclear leukocytes. J. Clin. Invest. 59:273-281, 1977.

11. Weinberger, SE, Kelman, JA, Elson, NA, Young RC,Jr, Reynolds, HY, Fulmer, JD and Crystal, RG: Bronchoalevolar lavage in interstitial lung disease. Ann. Int. Med. 89:459-466, 1978.

12. Reynolds, HY, Fulmer, JD, Kazmierowski, JA, Roberts, WC, Frank MM and Crystal, RG: Analysis of cellular and protein content of bronchoalveolar lavage fluid from patients with idiopathic pulmonary fibrosis and chronic hypersensitivity pneumonitis. J. Clin. Invest. 59:165-175, 1977.

13. Crystal, RG, Roberts WC, Hunninghake GW, Gadek JE, Fulmer JD, Line BR. Pulmonary sarcoidosis: a disease characterized and perpetuated by activated lung T-lymphocytes. Ann Intern Med 94:73-94, 1981.

14. Yeager H, Williams MC, Beekman JF, Bayly TC, Beamon BL, Hawley RJ. Sarcoidosis: analysis of cells obtained by bronchial lavage. Am Rev Respir Dis 116:951-955, 1977.

15. Reynolds, HY: The importance of lymphocytes in pulmonary health and disease. Lung 155:225-242, 1978.

16. Gee, JBL, Bodel, PT, Hinman, LM, Stevens, CA, Matthay, RA, Reynolds, HY: Mononuclear phagocytes in Sarcoidosis: Lysozyme and angiotensin I converting enzyme, Sarcoidosis and other Granulomatous Diseases (eds. WJ. Williams and BH. Davies) Alpha Omega Publ. Ltd. Cardiff, U.K., pp. 417-425, 1980.

17. Mellinkoff SM. Memorial: Carol Johnson Jones (1923-2000), Trans Am Clin Climatol Assoc 112:65-66, 2001.

18. Johns CJ and Michele TM. The Clinical Management of Sarcoidosis. A 50-year experience at the Johns Hopkins Hospital; Medicine, 78:65-111, 1999.

19. Bascom R. and Johns C.J. The Natural History and Management of Sarcoidosis. Adv Intern Med. 31:213-241,1986.

20. Reynolds, HY: Sarcoidosis - impact of other illnesses on the presentation and management of multi-organ disease. Lung, 180:281-299, 2002.

21. Saxon, W. Harold Israel, 87, Specialist Focusing on Chest Diseases. *NY Times*, November 26, 1996: http://www.nytimes.com/1996/11/26/us/harold-israel-87-specialist-focusing-on-chest-diseases.html.

22. Israel H (1979) Sarcoidosis. In: Simmons DH (ed) Current Pulmonology, vol. 1, Houghton Mifflin (Boston): 163-182.

23. Reynolds, WS and Chorney, MJ. Research topic: Interleukin 4 Receptor Alpha Genetic Variation and Susceptibility to Sarcoidosis, not published (2003).

24. Reynolds, HY: Pulmonary Sarcoidosis: Do Cellular and Immunochemical Lung Parameters Exist That Would Separate Subgroups of Patients for Prognosis? Sarcoidosis, 6: l-4, 1989.

25. Celada, L.J., Hawkins, C., Drake, W.P. The Etiologic Role of Infectious Antigens in Sarcoidosis. Clin Chest Med 36:561-568, 2015.

26. Wood W. Sarcoidosis Research and Patient Care Focus of Newly Created Center. Vanderbilt University Medical Center Reporter (https://news.vanderbilt.edu/2016/11/17/sarcoidosis-research-patient-care-focus-of-newly-created-center/), November 17, 2016.

27. Löfgren, S. Primary Pulmonary Sacoidosis. Acta Med Scand 145:424-431, 1953.

28. James, D.G. In Memorial: Sven Löfgren (1910-1978). Sarcoidosis 5:77-78, 1988.

29. Grunewald, J. and Eklund, A. Löfgren's Syndrome: Human Leukoeyte Antigen Strongly Influences the Disease Course. Am J Repir Crit Care Med, 179:307-312, 2008.

30. Levin, A.M., Datta, A. Iannuzzi, M.C., et al. Association of HLA-DRB one with Sarcoidosis Suspectibility and Progression in African Americans. Am J Respir Cell Mol Bil 53:206-216, 2015.

31. Millar, A. Two Faces of Sarcoidosis – A Genetic Insight? Am J Respir Crit Care Med 193:942-943, 2016.

32. Rivera N.V., Ronninger M., Shchetynsky K., et al. Higher Density

Genetic Mapping Identifies New Susceptibility Variants in Sarcoidosis Phenotypes and Shows Genomic-driven Phenotypic Differences. Am J Respir Crit Care Med 193:1008-1022, 2016.

33. Sharma S. Cardiac Imaging in Myocardial Sarcoidosis and other Cardiomypathies. Curr Opin Pulm Med 15:507-512, 2009.

34. Ayyala US, Nair AP, Padilla ML. Cardiac Sarcoidosis. Clin Chest Med 29(3):493-508, 2008.

35. Martusewicz-Boros, MM, Boros, PW, Wiatne, et al. Cardiac Sarcoidosis: Is It More Common in Men? Lung. 194:61-66, 2016.

36. Robert Hamilton Memorial for Sarcoidosis Research, Penn State. http://www.pennstatehershey.org/web/heartandvascular/community/robhamilton

