What is sarcoidosis?

Verum esse ipsum factum

"The true itself is made"

Giambattista Vico, Scienza Nuova

Human illness routinely fails to fit neatly into the constructs we define as "diseases". In fact, the very concept of a "disease" as a discrete nameable entity is useful only insofar as it informs our understanding of the pathophysiologic phenomena affecting a patient, or provides clinical information regarding prognosis and therapy. Nosology, the study of disease classification, is intrinsically based on Cartesian epistemology—meaning that analytic approaches can uncover fundamental truths about the natural universe, including the naming of identifiable entities we are able to observe and measure. However, this Cartesian conception of nosologic certainty can fail to account for the fact that biology is a spectrum. While some individuals' illnesses are dead center within any given construct, there are others who must arbitrarily be labeled as having one or the other disease based on our analytical constructs, not on the individuals' behavior or properties. One has either sarcoidosis OR hypersensitivity pneumonitis—not both. One has either idiopathic pulmonary fibrosis OR non-specific interstitial pneumonia—not both. And so on. Despite our practical need to label, all of us routinely diagnose and treat individuals who fall somewhere in between our simple constructs.

Judson et al. have dived into murky nosologic waters by suggesting in this issue that some patients labeled with sarcoidosis may in fact have granulomatous reactions caused by connective tissue diseases (CTD) like scleroderma [1]. They reviewed carefully-vetted diagnoses from two academic medical centers, and found a statistically unexpected surfeit of patients with co-existence of sarcoidosis and CTD. Their findings may be due to referral bias, ascertainment bias, suboptimal specificity of diagnostic criteria for CTD in the setting of another immune-mediated inflammatory disorder (sarcoidosis) or overlapping pathophysiologic mechanisms. An alternative explanation, one highlighted by the authors, is that some of the patients' granuloma syndromes were actually a reaction to CTD rather than a manifestation of "true" sarcoidosis. As they noted, their data cannot provide definitive answers among the competing explanations. An existential question arises from observations like this one: how important is it to have a "purist" definition of sarcoidosis? Does splitting the construct of "sarcoidosis" into parts improve our ability to prognosticate, treat, or study our patients?

One way to handle the uncertain distinction between immutable universal knowledge (truth) and useful constructs (empirical or practical forms of knowing) is to pass on the question by focusing not on disease entities but on syndromes. In sarcoidosis, this approach has been termed the "sarcoidoses" [2]. Whether it is useful to be "lumpers" or "splitters" of multisystem granuloma syndromes is being debated right now, where the theories of sarcoidosis as a single phenomenon with variable clinical phenotypes [3] versus a spectrum of granulomatous inflammation (sarcoidoses) [4] are competing nosologic hypotheses that will be tested by science and time. Thus, a range of entities are variably labeled as sarcoidosis, including granulomatous disorders associated with World Trade Center dust [5], medications (interferons or tumor necrosis antagonists) [6,7], pediatric granulomatoses [8], necrotizing sarcoid granulomatosis, and single organ granulomatous syndromes affecting the skin, liver, eye or heart [9,10]. Clearly there are some patients with these phenotypes who are better approached as if they fit a purist definition of sarcoidosis, and others who behave much differently. As a result, the clinical approach to each might best be individualized to focus on behavior and manifestations, rather than on a label based on a construct [11].

In illnesses with unknown etiology and no single validated confirmatory test, diagnosis relies on meeting a set of standards agreed to be definitional by implied consensus or expert recommendations. There is no working group definition for a fractured humerus, but there is a shared understanding of what that term implies. In more complex diseases like sarcoidosis and CTD, a set of criteria must be met to label an individual as having the diagnosis. Even when there are criteria for defining the presence of a
broader construct, such as a sarcoidosis syndrome or an overlap CTD syndrome, the interpretation of the proposed diagnostic criteria, the specific testing used to evaluate them, when in the course of a pathophysiologic process they are assessed, and how avidly alternatives are pursued may all lead to substantial diagnostic variation when they are operationalized. Such criterion variance has implications for determining prevalence, studying natural history, performing translational or clinical research, and routine clinical care. One can consider the different results that might be obtained in two parallel studies: one that requires histologic confirmation of sarcoidosis involving at least one organ and evidence of a second involved organ (purist definition) compared with a study that applies looser definitions, such as a compatible clinicoradiologic picture of isolated pulmonary, cardiac or ocular "sarcoidosis".

Until the pathophysiology of the disease we recognize as sarcoidosis can be more fully elucidated, we will be forced to define sarcoidosis phenomenologically. Analogous with gene expression clustering techniques, classification of multisystem granulomatous illness in the current era may involve careful delineation of which syndromes behave more similarly and which are more divergent. As such, there will continue to be clinical and academic tension between more specific (splitters) and more sensitive (lumpers) criteria for sarcoidosis.

The presence of uncertainty does not eliminate the need to follow careful principles when assigning a diagnosis of sarcoidosis. We still must exclude known causes of granulomatous reactions prior to arriving at a diagnosis [12]. A reasonable heuristic for diagnosis is an empiric one, as suggested by Dr. Judson: "the diagnosis of sarcoidosis... is arbitrarily made when the statistical likelihood of alternative diagnoses becomes too small to warrant further investigation" [13]. However, since the cause of sarcoidosis is unknown, over-reliance on exclusion of all diseases associated with granulomatous reactions, as well as overly strict application of diagnostic criteria will necessarily exclude many patients whose pathophysiology or clinical care might be best aligned with that for more typical sarcoidosis. So, while true that patients with contemporaneous CTD and sarcoidosis might instead have variants of either that look alike, the definition may be less important than the individuals' behavior, along with a healthy dose of clinical skepticism.

References


Daniel A. Culver
Department of Pulmonary Medicine, Respiratory Institute, Cleveland Clinic, USA

Department of Pathobiology, Lerner Research Institute, Cleveland Clinic, USA

E-mail address: culverd@ccf.org

25 June 2013