REAPPRAISAL OF PREVAILING PREMISES IN SARCOIDOSIS

Jerome M. Reich

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This effort is dedicated to the guidance provided *in absentia* by the penetrating analyses of JG Scadding, and C Munro.

Human experience, which is constantly contradicting theory, is the great test of truth.
—Samuel Johnson

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PREFACE

MY SARCOIDOSIS ODYSSEY

My investigative interest in sarcoidosis was provoked and sustained by three events that acted as inflection points: As a practicing pulmonologist, I naturally shared an interest in this curious disorder. My informal observation of its natural history, which, at the time, reflected 10-years of practice at Kaiser Permanente, NW Region, differed materially from published reports. For example, I could not recall a single instance of fatality (or hospitalization) attributable to sarcoidosis. The contemporary edition of Harrison's, Principles of Internal Medicine and the sectional leader of a 1980's, annual meeting of American Thoracic Society each cited a 10% sarcoidosis mortality. The disparity provoked my curiosity and led me to inquire about a possible investigative interest at the Center for Health Research, Kaiser Permanente, Northwest Region (CHR, KPNW). The Center furnishes community-based health care information based on data compiled from medical records sourced from the serviced health maintenance population. Eager to demonstrate the utility and value of community-based health care research, Mitchel Greenlick, PhD, the CHR director, in response to my inquiry, encouraged me to pursue my interest, and provided funding, staff support and asked Richard Johnson, PhD, an experienced researcher, to furnish guidance. Among 86 persons identified with sarcoidosis in the serviced KPNW population observed long-term, we found no instances of fatality or hospitalizations attributable to sarcoidosis. I coauthored an article with Dr. Johnson's mentoring, Course and Prognosis of Sarcoidosis in a Nonreferral Setting . . . (The title paid homage to Sones' and Israel's seminal1960 article) and submitted it to The American Journal of Medicine, which accepted it within one week.[1] The response was extremely gratifying: we received more than 100 reprint requests. This encouragement constituted the first inflection point. It kindled a previously latent investigative spirit, which led me to reevaluate other aspects of sarcoidosis (and other pulmonary disorders), often with the resources and guidance of CHR.

Professor Izumi's 1994 article, demonstrating the long-term effect on the course of sarcoidosis imposed by elective corticosteroid therapy (CST), furnished the second inflection point. He reported on 185 asymptomatic, largely stage I individuals, one-third of whom received CST for a variety of non-therapeutic indications (e.g., to clear up radiographic abnormalities for employment). Izumi furnished clear evidence that it imposed harm evidenced by an adverse clinical and radiographic outcome long-term in the treated vs. the untreated controls.[2] In our 1985 paper, I had ascribed our favorable experience vs. published series, presumptively, to adverse selection for referral to reporting tertiary care settings. In response to Izumi's disturbing findings, I systematically reviewed the sarcoidosis mortality literature and reported the effect of long-term CST, which corroborated Izumi's conclusion. I added the observation that the harm imposed by CST was confined to persons with recent-onset sarcoidosis.[3]

The third inflection point was generated by a conversation with Dr Colin Munro at the 1986 American Thoracic Society meeting, in which, in response to my queries, he clarified and expanded on his novel investigative findings, which provided an evidence-based reversal of the prevailing sarcoidosis paradigm, from a systemic granulomatous disease of unknown etiology to a fallback granulomatous syndrome due to inefficient cell-mediated immune function.[4] This conceptual framework replaced a granulomatous response to an unidentifiable causal agent with an immunological deficit as the fundamental disorder underlying sarcoidosis. The ramifications of the proposed genesis provided a fruitful and coherent accounting for numerous enigmatic and seemingly paradoxical observations characterizing sarcoidosis.[5]

Like paroxysmal nocturnal hemoglobinuria (of which it is said that more people study it than have it!), sarcoidosis inspires far more published research—30K items returned in a Medline search for "sarcoidosis," 36K for "emphysema," and 300K for "lung cancer"—than appears justified by either its incidence or its morbidity/mortality. This reflects, I believe, its baffling, enigmatic character, which resembles no other disorder. Its fundamental nature—autoimmune disease? hyperimmune response? infection? aberrant immunological response? —remains uncertain. Its etiology remains unknown despite more than a century of the most arduous and varied investigative efforts. Many features remain inscrutable. For example, more than 90% of cases involve the lungs, leading investigators to infer that it is caused by a respired agent. However, in contrast to infectious respiratory diseases which incite a granulomatous response, e.g., tuberculosis and histoplasmosis, its radiographic pattern is

symmetrical and its progressive evolution, typically retrograde, from hilar adenopathy to pulmonary involvement. Its immunological features defy ready explanation. For example, why would sarcoidosis, defined as a multisystem noncaseating granulomatous disorder of unknown etiology, be confined in some instances to the liver, skin or central nervous system? What accounts for the local immune hyperactivation and peripheral anergy, the paradoxical divergence between the intense pulmonary immunological response and the cutaneous anergy manifested by a lack of response to delayed type hypersensitivity agents? Why is the defining response granulomatous? Is sarcoidosis a disease (sui generis) or a syndrome? What criteria are useful in making the distinction? What accounts for the secular increase in sarcoidosis mortality? As there is no evidence of pre-existing hypersensitivity to any component of Kveim suspension in subjects with sarcoidosis, what, precisely, does a positive (granulomatous) response at four-six weeks signify?

To the extent possible, I will endeavor to furnish evidence-based responses to these questions. For those aspects of sarcoidosis in which I cannot help resolve the issues, I offer the sentiments of David Hilbert (1842-1943), head of the Department Of Mathematics, University of Göttingen, widely regarded as the foremost mathematician of his time, who famously enunciated 23 fundamental unsolved problems which he considered the outstanding challenges in the new century at the 1900 annual International Conference of Mathematicians:

> If we do not succeed in solving a . . . problem, the reason frequently consists in our failure to recognize the more general standpoint from which the problem before us appears only as a single link in a chain of related problems. This conviction of the solvability of every . . . problem is a powerful incentive to the worker. We hear within us the perpetual call: There is the problem. Seek its solution." [6] "*Wir müssen wissen, wir werden wissen*.

My views on this subject have been largely shaped by the penetrating insights of Professors JG Scadding and C Munro and by my correspondence with the latter.

Notes

[1] Reich JM, Johnson RE. Course and prognosis of sarcoidosis in a nonreferral setting: analysis of 86 patients observed for ten years. *Am J Med.*1985;78:61-67.
[2] Izumi T. Are corticosteroids harmful to sarcoidosis—a conclusion drawn from a retrospective study on the chest radiographic prognosis of 185 asymptomatic patients with pulmonary sarcoidosis followed up for more than ten years. *Sarcoidosis*.1994;11(Supp 1):119-122.
[3] Reich JM. 2003 Adverse long-term effect of corticosteroid therapy in recent-onset sarcoidosis*. Sarcoidosis Vasc Diffuse Lung Dis*. 20(3):227-234.
[4] Munro CS, Mitchell DN, Poulter LW, Cole PJ. Immunological processes active in developing Kveim responses differ in normal and sarcoidosis subjects. *Amer Rev Respir Dis*. 1986;132(Supp):A244
[5] Reich JM Anomalies in the dominant sarcoidosis paradigm justify its displacement. *Immunobiology.* 2017 222(4):672-675. DOI: 10.1016/j.imbio.2016.12.005
[6] Hilbert D. Mathematische Probleme. *Göttinger Nachrichten.* 1900: 253-297. English translation: Joyce D. http://babbage.clarku.edu/~djoyce/hilbert/problems.html#note1.

CHAPTER ONE

DEFINITION

Sarcoidosis can be defined as a disorder of unknown etiology, characterized histologically by noncaseating epithelioid granulomas involving various organs or tissues, with symptoms dependent on the site and degree of involvement. The most recent, updated definition was provided in the 1999 Joint Statement of the ATS/ERS/WASOG expert panel:

> Sarcoidosis is a multisystem disorder of unknown cause. It commonly affects young and middle-aged adults and frequently presents with bilateral hilar adenopathy; pulmonary infiltration, ocular and skin lesions. The liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscles, bones and other organs may also be involved. The diagnosis is established when clinico-radiograpic findings are supported by histological evidence on non-caseating epithelioid cell granulomas. Granulomas of known causes must be excluded. Frequently observed immunological features are depression of cutaneous delayed type hypersensitivity and a heightened Th1 immune response at sites of disease. Circulating immune complexes along with signs of B-cell hyperreactivity may also be found. The course and prognosis may correlate with the mode of onset, and the extent of the disease. An acute onset with erythema nodosum or asymptomatic bilateral hilar adenopathy usually heralds a self-limiting course., whereas an insidious onset, especially with multiple extra-pulmonary lesions, may be followed by relentless, progressive fibrosis of the lungs and other organs.[1]

The earlier, similar, but less elaborate definition adopted at the Seventh International Conference on Sarcoidosis in 1975—"Sarcoidosis is a multisystem granulomatous disorder of unknown etiology, most commonly affecting young adults and presenting most frequently with bilateral hilar adenopathy . . ."— was rejected by Scadding and Mitchell on the basis that the lengthy ". . . description was intended to stand in

place as a definition;" ". . . that it provided no way in which agreement might be reached in a case in which informed observers disagree; and that it lacked a proviso that changes of a specific type must be widely disseminated." The authors recommended its replacement by a morbid anatomical definition: "Sarcoidosis is a disease characterized by the formation in all of several affected organs or tissues of epithelioid-cell tubercles, without caseation though fibrinoid necrosis may be present at the centres of a few, proceeding either to resolution or to conversion into hyaline fibrous tissue." They added: "Since there is no agreement concerning the etiology of sarcoidosis, nor indeed whether sarcoidosis is an etiologically homogeneous group, no reference to etiology can be made in the definition." This definition eliminates plausible etiological candidates (cancer, histoplasmosis, tuberculosis) from *a priori* exclusion. An additional benefit of excluding the requirement of unknown etiology from the definition, emphasized by the authors, is that: ". . . sarcoidosis may represent an unusual reaction to an agent or agents already known and normally causing a well-recognized disease, but difficult to demonstrate in the unusual manifestation of sarcoidosis."[2] The definition proposed by Scadding and Mitchell eliminates the anomaly of persistent failure, despite the most varied and arduous efforts, to ascertain *the* etiology of sarcoidosis: Like the unsuccessful 19th century searches for *caloric, aether* and *phlogiston*, 20th century efforts to identify "*sarcoidogen*" have been futile because, under the terms of this definition, it does not exist. The traditional descriptive definition of sarcoidosis is inherently unsatisfactory because it fails to characterize its fundamental nature.

Scadding observed that the definition of a disease progresses according to increased knowledge from an initial clinical-descriptive, through pathological, to an etiological basis.[3] I will adopt the operational (*i.e.,* morbid-anatomical, pathological) definition advanced by Scadding and Mitchell. Under this definition, "sarcoid like" vs. sarcoidosis is a distinction without a difference. Following Scadding's usage, where a plausible etiology has been identified, the term can be attached as a modifying adjective or noun e.g., "beryllium sarcoidosis" or "sarcoidosis due to tuberculosis."

Notes

[1] Hunninghake GW, Costabel U, Ando MH, et al. ATS/ERS/WASOG statement on sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 1999;16(2):149-173.

[2] Scadding JG, Mitchell DN Definition. In: *Sarcoidosis*, 2nd ed. I985 University Press, Cambridge, UK:13-35.
[3] Scadding JG. Principles of definition in medicine. *Lancet*.1959;1(7068):323-325.

CHAPTER TWO

FUNDAMENTAL NATURE

Characterization of granuloma immunogenesis, its defining element, is a useful means of comprehending the fundamental nature of sarcoidosis. A T-cell helper type-1 (T_H1) response, sarcoidosis granulomas can be considered a fallback to a primitive immunological alternative that evolves following failure of efficient cell-mediated immunity to completely eliminate an intracellular antigen, e.g., M. tuberculosis. Its principal cellular constituents are CD4+ lymphocytes and macrophages. Grunewald et al.,[1] and Lynch et al.[2] furnish a detailed description of the cellular and cytokine components and their interaction. Chen and Moller[3] provide a critical assessment of causal candidates.

Kveim-induced granulomas resemble those of sarcoidosis microscopically, in cellular composition, and phenotype as assessed by monoclonal antibodies.[4,5,6,7,8,9] The early response to a validated Kveim suspension provides a means of assessing the sequence of immunologic events that result in the production of non-caseating epithelioid granulomas.[10] Biopsy-assessed at 28- to 42-days, a granulomatous response to Kveim reagent furnishes a model of sarcoidosis. Its genesis may therefore be considered representative of the sarcoidosis paradigm in which the cellular and cytokine components recapitulate those of the disease. O'Connor and Fitzgerald clearly framed the fundamental question about the conceptual nature of sarcoidosis:

> Assuming an antigenic inciting agent . . . current evidence suggests that the majority of affected individuals mount an efficient and controlled response, resulting in the elimination of antigen and the effective curtailment of the initial response. The prolonged nature of this response (up to 2 years) most likely reflects an inherent resistance to degradation by the antigen, enabling it to persist within the tissue and granuloma for some time. In a proportion of individuals, effective elimination of the inciting agent(s) and/or curtailment of the initial response do not occur and chronic disease ensues. The lack of an efficient response in the latter individuals may be

> due to: (a) exposure to higher doses of inciting antigens or exposure over a longer period of time than in individuals in whom the response resolves; (b) an inability, as a result of genetic or other factors to mount an adequate T-cell mediated response; (c) a defective regulation of the initial response; or a combination of all three of these factors.[11]

Kveim

Classification of sarcoidosis as a disease *sui generis* vs. a syndrome like erythema nodosum with a well-defined clinical presentation and distinctive pathology of varied etiology rests on the distinctive clinical and histological features, oligoclonality of the CD4+ response[12] and frequent positivity of the Kveim response in sarcoidosis. However, positive Kveim responses wane in persons with longstanding sarcoidosis and are less frequently positive in persons with advanced stages in contrast to what one might expect were it a marker of an immunological response. The origin of the suspension (tissue), evolutionary time scale (four- to six-weeks) and histology of a positive response (granulomatous vs. dense lymphocytic infiltration) distinguish it from that in delayed type hypersensitivity (DTH) tests e.g., Mantoux. The features of the Kveim test closely resemble the Mitsuda lepromin test, which is based on the intradermal injection of a suspension of lepromatous tissue containing (killed) causal acid-fast bacilli. The Mitsuda test does not distinguish between normals and individuals with known leprosy. Instead, it correlates with the clinical pattern of disease: those with the tuberculoid form (granulomatous, paucibacillary) test positive; those with the lepromatous (multibacillary) form test negative. This distinction is reflected in the cytokine response. Employing polymerase chain reaction (PCR) amplification of messenger RNA extracted from lepromatous tissue, Yamamura et al. reported that IL-2 and IFNγ (the principal T_H1 cytokines) were most evident in the resistant (granulomatous) form; and IL-4, 5 and 10 (T_H2 cytokines) predominated in the susceptible (lepromatous) form.[13] By analogy, this suggests the possibility that the Kveim reaction detects a special form of tissue reactivity, not a response to a specific antigen or infectious agent.

A positive response to validated Kveim suspension has been assumed to reflect hypersensitivity to some component of the sarcoidosis-spleen-derived agent. The unexplained features associated with this formulation are:

1) No such component has been identified.[10,14]
2) The reasons for selectivity (*i.e.*, specificity) of a "good" suspension are unknown.[10]
3) Efforts to develop an *in vitro* Kveim test (analogous to the beryllium lymphocyte proliferation test) have been unsuccessful.
4) The frequency of positive responses declines with the duration of sarcoidosis.[10]
5) The prevalence of positive Kveim responses in normal persons--0.7 to 2%--far exceeds the prevalence of sarcoidosis.[10]
6) The observation that a high proportion of healthy, young, British adults who failed to convert their tuberculin test following repeated BCG immunizations proved to be Kveim-positive supports the view that a positive Kveim response is a marker of the inability to develop delayed type hypersensitivity (DTH).[15]

Munro et al. employed the test as a model of sarcoidosis in Kveim-positive sarcoidosis subjects vs. normals in a brilliantly conceived sequence of experiments intended to generate an understanding of the genesis of systemic granulomas by immunohistochemically defining the early cellular immunological events that eventuate in a granulomatous response in persons with sarcoidosis.[16] Initially, they evaluated the 48-hour response to intradermal injections of 10-units of tuberculin (Mantoux) and of validated Kveim suspension. Positive tuberculin responses, signifying intact DTH, are characterized by dense, dermal, lymphocytic infiltration. Kveim suspension at 48-hours failed to elicit this response in either normals or Kveim-positive sarcoidosis patients; their cellular components were indistinguishable. The investigators concluded that: ". . . in comparison with healthy controls there is no evidence of pre-existing hypersensitivity to a component of Kveim suspension in subjects with sarcoidosis; neither is there any other manifestation of changed immunological reactivity unique to them at this stage." They further suggested that ". . . subsequent differences between sarcoid and normal subjects in the development of granulomas in the Kveim response may therefore relate to the different handling of the foreign material by the cells affected, rather than to differences in the early, non-specific recruitment of the cells to the test site."[17]

The authors then compared the 11- and 18-day (*i.e.,* three to four weeks prior to maturation) response in healthy controls, Kveim-negative, and Kveim-positive sarcoidosis subjects. The majority of healthy controls and Kveim-negative sarcoidosis subjects responded with features characteristic of DTH reactions: a dense perivascular infiltrate of mononuclear cells

composed of T-cells ("T" designates lymphocytes that arise and mature in the thymus) of helper and suppresser types, with markers of activation (Tac+; Leu9+), and dendritic (Langerhans) cells (OKT6+; RFD1+) with strong HLA-DR expression. Of 13 Kveim-positive sarcoidosis patients, 1 developed a comparable response. The remaining 12 developed a more gradual response characterized by close associations of phagocytic macrophages and helper T-cells, some of which were also Tac+; notably, dendritic cells were absent. The authors inferred that the systemic granulomas characterizing sarcoidosis represented a default to an immunologically more primitive and less efficient response as a consequence of an undefined deficiency in cell mediated immunity. In this paradigm, the exuberant systemic granulomatous response (SGR) and DTH anergy—the "immune paradox" of sarcoidosis—are dual manifestations of the same inefficiency.[17]

Prevailing View vs. Alternative Hypothesis

The prevailing view of sarcoidosis (PV) is that the SGR reflects a genetically-conditioned response to an unidentified antigen(s). The alternative (Munro) hypothesis (HA) is that the characterizing SGR is a distinctive form of reactivity, an immunological fallback reflecting an inefficient cellular immune response. The PV conceptualizes sarcoidosis as a disease *sui generis;* HA, as a syndrome. The corollaries imposed by these alternative hypotheses generate testable, corroborative, "if-then" observations, referred to as "affirming the consequence." Accepting either paradigm means rejecting the alternative; it supports but does not affirm the unrejected paradigm.

If the PV is true, then one would expect: 1) an identifiable causal agent; 2) greater intensity of the immune response would be a marker of disease severity manifested by an adverse prognosis and a consequent need for treatment; 3) sustained suppression of the response, *e.g.*, with corticosteroid therapy (CST), would have a long-term favorable effect by preventing lethal or disabling pulmonary fibrosis; 4) the occurrence of sarcoidosis would not be materially influenced by cellular immune dysfunction unless profound.

If the HA is true, then one would expect: 1) a multiplicity of plausible causative candidates; 2) greater intensity of the response would be a marker of favorable prognosis and the absence of a requirement for treatment; 3) suppression of the (inefficient) immune response would have an adverse long-term effect by hindering resolution; 4) the propensity to

develop sarcoidosis would be exhibited by individuals with a variety of cellular immune dysfunctions. Additionally, one might hope to find direct evidence of cellular immune dysfunction in otherwise healthy persons with sarcoidosis who lack an apparent cause of immune dysfunction.

The rationale justifying displacement of a PV is worth considering: Kuhn described the conditions required for fundamental changes in natural science in *The Structure of Scientific Revolutions.*[18] His inferences were based on historical observations drawn largely from physics (Newton vs. Einstein), chemistry (Priestly vs. Lavoisier) and astronomy (Ptolemy vs. Copernicus). He found that a PV paradigm crisis arose when data from nature failed to conform with the dominant epistemology and when anomalies and violations of paradigm-induced expectations were experienced. Kuhn noted that, in each instance, cumulative examples subverting the tradition of scientific practice led to the sense that something was fundamentally wrong. He emphasized that the revolution in scientific thought was invariably transformative, not cumulative; the supplanting paradigm did not augment the previous theory; it displaced it. He likened its effect to a gestalt-like transformation e.g., the image-ground reversal in the well-known, rabbit-ears/duck-beak exemplar. He further pointed out that theory choice depended not on demonstrable "truth," a philosophically elusive objective, but on practical, empirical criteria: 1) which theory better fit the facts, *i.e*., explained the available evidence; 2) offered comparative simplicity, *e.g*., Copernicus (*De revolutionibus orbium coelestium*) vs. Ptolemaeus (*Almagest;*< Gk, *al magiste*, the greatest); 3) its promise as a guide to future research (fruitfulness); 4) its ability to resolve some otherwise unresolvable, outstanding problem; and 5) its preservation of a large part of previously accrued problem-solving ability. Additional desirable paradigm values were: accuracy, predictive ability, self-consistency, plausibility, and compatibility with other theories. The dominant criterion for theory-choice was the demonstrated ability to set up and to solve puzzles presented by nature.

Affirming the Consequence

1. Identification of *the* causal agent:

Despite more than a century of the most arduous and methodologically varied efforts, the etiology of sarcoidosis remains unknown. Its status is well characterized in the concluding paragraph of this recent review in which the authors' conclusion is consistent with the HA:

> The inability to identify a single "cause" of sarcoidosis, as well as the wide variability of disease course and manifestations, suggests that sarcoidosis may represent a heterogeneous spectrum of disorders, caused by a complex interplay of a variety of host factors, infectious processes, and non-infectious environmental exposures that results in a final common pathway to systemic granulomatous inflammation. A plausible hypothesis is that multiple different antigens, when introduced to a host with a susceptible genetic background and appropriate immunologic milieu, may be capable of inducing this aberrant immune response.[19]

A multiplicity of plausible etiological candidates for non-caseating epithelioid SGRs have been advanced, e.g., tuberculosis, neoplasia, histoplasmosis and drugs that suppress the cellular immune response, particularly immune checkpoint inhibitors. Some of these responses have been characterized as "sarcoid-like reactions" by adherents of the view that sarcoidosis is a disease,[20] although their SGRs are indistinguishable from those of sarcoidosis. None of these candidates have proven acceptable as either *an* or *the* etiology.

The provisional classification of sarcoidosis as a disease (vs. a syndrome), rests in part on the response to validated Kveim reagent, which however, lacks an identifiable antigen. Efforts to develop an *in vitro* Kveim test (analogous to the beryllium lymphocyte proliferation test), employing a T-cell response, enabling the identification of the putative antigen, have been unsuccessful thus far.

The PV consequence is not affirmed.

2. Greater intensity of the response would be a marker of disease severity reflected by adverse prognosis and need for treatment:

Individuals exhibiting a brisk granulomatous response have a favorable outcome:

Patients with an acute onset of stage I disease with erythema nodosum, who are known to have a highly favorable prognosis, characteristically exhibit high-intensity lymphocytic alveolitis (assessed with bronchoalveolar lavage--BAL).[21,22] Conversely, persons with high-intensity lymphocytic alveolitis at any stage exhibit more favorable outcomes.[23,24] This observation led Haslam to advance the hypothesis that, "Patients with more efficient inflammatory responses may be better able to eliminate an unknown agent or antigenic stimulus in sarcoidosis."[24]

The PV consequence is not affirmed.

3. Sustained suppression of the SGR would have a long-term favorable effect:

Cyclosporine-A, a fungal metabolite, was considered an ideal therapeutic candidate for sarcoidosis because it specifically suppresses the granulomatous response by inhibiting nuclear factor of activated T cells (NFAT), which leads to a reduction in IL-2, IFNγ, and CD40L, the principal cytokines promoting granuloma genesis. Contrary to expectation, in a controlled, randomized trial limited to persons with progressive pulmonary shadowing, 58% of the subjects who received combined treatment with cyclosporin-A plus prednisone improved vs. 67% of those who received prednisone alone. Among 16 subjects who exhibited a favorable response, 5 of the 7 combined treatment recipients relapsed post-treatment vs. 2 of the 9 prednisone recipients.[25]

Milburn et al.[26] demonstrated that CST in sarcoidosis down-regulates the T_H1 response (granulomatous inflammation followed by resolution) in favor of the T_H2 (pulmonary fibrosis) response. In metanalysis of referral settings (RS), in which CST was provided to 41% of their patients, cumulative sarcoidosis mortality (4.8%) was 10-fold that in population-based (PBS) settings (0.5%), in which CST was provided to 6%. Correction for adverse selection (as indicated by the proportion with stages III, IV) reduced the mortality differential to 6-fold. Stage-normalized mortality was strongly correlated with the proportion treated with CST in the RS.[27] It seems likely that this marked mortality differential has been tacitly ascribed to adverse selection for referral to RS. However, no RS report has documented adverse selection by furnishing a comparison of the pulmonary functional status of their subjects to a reporting PBS. Scadding was the sole author from a RS to furnish information re. disease severity or duration in their reports. He reported that, " . . . many [all stage IV] patients were referred to me after prolonged periods of observation by other physicians because of an unfavorable course."[28] It is noteworthy that the proportion of patients with stage III, IV sarcoidosis in his series (47%) was more than threefold that of the case-weighted mean (15%) of the remaining six tabulated RS series. In an unpublished metanalysis of five competent controlled trials studies of CST in early stage II and III disease,[29,30,31,32,33] long-term adverse outcomes—radiographic deterioration, progressive multisystem sarcoidosis —were consistently higher (range of odds ratios: 2.0, 6.9) in the treated cohorts and deaths due to sarcoidosis were seen only in CST recipients.

The PV consequence is not affirmed.

4. The occurrence of sarcoidosis, widely considered a hyperimmune response, will not be materially influenced by modestly impaired cellular immune function:

4.a Common variable immunodeficiency Disorder(s) (CVID):

Up to 50% of persons with CVID have a deficiency in T lymphocytes in association with their hypogammaglobulinemia. Granulomatous disease in CVID is associated with diminished numbers of myeloid and plasmacytoid dendritic cells.[34,35] Fasano et al. reported the occurrence of sarcoidosis in 8 of 80 patients (10%) with CVID in the combined case registries of Johns Hopkins University and Children's Hospital of Philadelphia. All eight had chronic sarcoidosis, and T-lymphocyte deficiency was identified in the seven in whom subset characterization was reported. This 10% prevalence is 7-fold the estimated lifetime risk of acquiring ascertainable sarcoidosis in a screened Scandinavian population (a high incidence ethnicity).[36] The authors found 22 additional cases of the association in a literature survey.[37] Gathmann[38] and Resnick[39] reported a similar prevalence of SGR in larger CVID populations.

The PV consequence is not affirmed.

4.b Acquired immunodeficiency syndrome (AIDS):

Gomez et al. reported 12 instances in which sarcoidosis developed in individuals with AIDS. In 7, the CD4+ lymphocyte count was only modestly reduced. In the 5 who developed sarcoidosis during immune reconstitution following highly active antiretroviral therapy (HAART), the onset of sarcoidosis coincided with CD4+ repletion to normal or near-normal levels.[40] One might interpret these events as follows: AIDS-induced CD4+ lymphocyte depletion impaired normal cellular immune processing in a fashion similar to that seen in CVID; that, as a consequence, an undefined antigen(s), which, under normal lymphocytic function would have been eliminated, induced a SGR. This scenario became evident in AIDS patients with modest CD4+ depletion and in severely CD4+ depleted individuals only following HAART-induced CD4+ repletion.

The PV consequence is not affirmed.

4.c Drug-induced immune suppression:

Chopra et al. undertook a systematic analysis of drug classes in which numerous instances of SGR have been reported. Tumor necrosis factor alpha (TNFα) is one of the cytokines upgraded in sarcoidosis.[1] TNFα antagonists (etanercept, adalimumab and infliximab) have frequently been cited in the genesis of "sarcoidosis-like reactions."[41,42] Curiously, this drug class has been employed therapeutically for sarcoidosis.

Immune checkpoint inhibitors such as CTLA4-, PD1- and PDL1-blocking antibodies are known to generate "sarcoidosis-like reactions".[1,43] Unlike TNF antagonists, they enhance the immune response to malignant neoplasms by (confusingly) countering the neoplasm-induced, immune blockade. A plausible surmise for the mechanism by which they generate SGR is that, by suppressing the immune-response blocking actions of CTLA4, PD1, and PD1L, they enable cytotoxic lymphocytes to attack malignant cells with the consequent generation and release of abundant tumor antigens.

The PV consequence is not affirmed.

These findings and observations are consistent with HA, and are consonant with clinical observations .The unifying view of sarcoidosis as an etiologically-heterogeneous, immunologically-mediated syndrome as the central abnormality, not a disease (*sui generis*), serves to eliminate the anomalies, paradoxes, puzzles, and violations of expectations associated with PV: It holds that the defining SGR reflects a default to a more primitive and inefficient immunological response attributable to a deficit in efficient cellular immune processing. It thus accounts for its frequent development in persons with CVID and the propensity with which recipients of TNF suppressants and persons with AIDs (during immunological reconstitution) develop sarcoidosis. It elucidates the nature of the "immune paradox." The same deficiency in cellular immune processing that defaults to a granulomatous response (clinically and exemplified in the Kveim response) is manifested by the inability to generate a DTH response to tuberculin. It abolishes definitional shortcomings, eliminating spurious semantic distinctions between "sarcoidosis," pseudo sarcoid," "sarcoid reaction," and "sarcoid-like." It accounts for failure to identify both the etiology of sarcoidosis and the antigenic component of the Kveim suspension as well as the inability to produce an *in vitro* Kveim test. It provides a plausible explanation for the consistent observation that response intensity was positively correlated

with favorable outcomes and that, conversely, its suppression often has an unfavorable long-term effect. Additionally, one might speculate that the unanticipated protective effect of cigarette smoking is attributable to ongoing stimulation and enhancement of cellular immune processing by antigens contained in cigarette-smoke.[44]

Proposed Immunological Mechanisms

1. Influence of HLA II:

Under the assumption that the propensity to acquire sarcoidosis is dependent, in part, on the efficiency with which certain antigen classes are presented to or processed by CD4+ lymphocytes, there would be an expected variance in incidence or course in persons possessing certain HLAII alleles. Berlin et al. found both to be the case. The authors matched the HLA haplotypes of 122 Scandinavian patients with sarcoidosis against a healthy group of 250 control subjects: HLA-DR17 was twice as frequent in the former than the latter; and HLA-DR146 and HLA-DR152 were each associated with chronic disease.[45] On the basis of reports of familial clustering and the varying prevalence of sarcoidosis in different populations, McGrath et al. suggested that genetic predisposing host factors conveyed a susceptibility to develop a SGR to one or more microbes behaving in a non-infectious fashion. Their review of its association with the major histocompatibility complexes illustrated its influence on both the incidence and course of sarcoidosis.[46]

2. Influence of dendritic cells:

Dendritic cells (DC) are characterized by their potent ability to induce T cell proliferation, their high expression of MHC class II peptides, their facility at blood-borne migration in and out of tissue and their migration to lymph nodes. Their principal function is to capture, process and present antigens to and activate naïve T cells located in lymph nodes. They are of three general types: myeloid (“conventional”), plasmacytoid and Langerhans. Myeloid dendritic cells (mDC), the DC most directly involved in sarcoidosis, are derived from hematopoietic precursor cells. They are abundant at barrier sites, i.e., intestines, skin and lungs. They possess a versatile component of receptors for complement, Fc, C-type lectins, and, additionally, the ability to take up nonspecific antigens by means of macropinocytosis. They respond to bacterial stimuli by ligation with Toll-like receptors (TLR) that recognize bacterial cell wall components of peptidoglycan/lipoteichoic acid (TLR2) and

lipopolysaccharide (TLR4). Ligation of TLR2/TLR4 increases the expression of tumor necrosis factor (TNF) and upregulates MHC II and molecules that promote T cell activation. They constitutively produce IL-12, a T_H1 T cell-polarizing cytokine found at high levels in sarcoidosis BAL, which is augmented by co-culture with IFNγ. IL-12 amplifies its own response through induction of more IL-12 release from antigen presenting cells and up-regulation of IL-12b expression on activated T cells ("self-amplifying scenario"), further polarizing them toward the T_H1 lineage. IFNγ , produced by T_H1 T cells is the most highly expressed cytokine in sarcoidosis BAL fluid. T_H2 T cells do not develop in the presence of IFNγ.[47]

Lommatzsch et al. found a unique increase in CD1a-negative mDC employing four-color flow cytometry analysis of BAL cellular constituents. In addition, they observed altered expression of costimulatory molecules (increased CD80 and decreased CD86 expression) on their mDCs.[48] (CD80 and CD86 are costimulatory molecules expressed on antigen-presenting DCs to the receptor, CD28, on the T-cell.)

Mathew et al. hypothesized that diminished DC function might be the source of decreased DTH responses to recall antigens in affected persons. They reasoned that cutaneous anergy could be the consequence of abnormal antigen uptake or presentation or a defect in the effector arm—lymphocytes involved in the DTH response. In a series of immunological assessments, they isolated, phenotyped and assessed the function of ex-vivo blood mDC, plasmacytoid dendritic cells (pDC) and lymphocytes in normals and individuals with active, untreated sarcoidosis and demonstrated that sarcoidosis-derived mDC exhibited an impaired ability to generate T-cell proliferation vs. normals as judged by their diminished ability to incite an allogeneic mixed lymphocyte response (MLR). Moreover, they found evidence of a quantitative clinical counterpart: greater impairment in mDC function correlated with both impaired DTH response to Candida antigen and with advanced radiographic stage, a marker of disease severity. They reported that pDC derived from sarcoidosis subjects incited a normal allogeneic MLR. The number of circulating mDC and pDC were similar to normals. Functional analysis of MLR employing sarcoidosis-derived lymphocytes and control (normal) mDC showed a normal response. Costimulatory and maturation markers in DC of persons with sarcoidosis were up-regulated. T helper-1 (TH1) cytokines—IFNγ , IL-6, TNFα and IL-12—were present in increased amounts. They concluded that the diminished allogeneic immune response was due to isolated mDC functional attenuation and that the function of

sarcoidosis-derived lymphocytes was intact. Reflecting the generally accepted definition of what the presence of a granuloma signifies and thus echoing Munro's interpretation, they stated: “Granuloma formation occurs when the cellular immune response fails to eliminate the antigenic stimuli . . .”[49]

Ten Berge et al. reported the opposite findings: mDCs in BAL from sarcoidosis patients were increased in number when compared with healthy controls; mDCs purified from BAL of sarcoidosis patients induced T cell proliferation and differentiation and did not show diminished immune reactivity. Additionally, immunohistochemical analyses revealed increased numbers of mature CD86+ DCs in granuloma-containing airway mucosal biopsies.[50]

Zaba and coworkers reviewed the role of dendritic cells in the pathogenesis of sarcoidosis. They noted that mDC are twice as rich in sarcoidosis BAL than in BAL of normals, a finding specific for sarcoidosis. These mDCs were phenotypically immature as reflected in their decreased expression of maturation marker CD83 and co-stimulatory CD86 and that sarcoidosis lung DCs were less able to induce T cell proliferation than normal lung DCs. They reported that mDC recovered from peripheral blood of sarcoidosis patients exhibited reduced function compared with those retrieved from peripheral blood in control subjects and suggested that blunted end organ cellular immunity may contribute to sarcoidosis pathogenesis. They further suggested that: “Decreased DC function is a potential mechanism for sarcoidosis-induced anergy, and may suggest that reduced cellular immunity at the end organs is responsible for disease perpetuation rather than resolution.”[47]

Uslu and co-workers demonstrated that dendritic cell vaccination, intended to augment the immunological response to metastatic cutaneous melanoma, had a notable effect: In 4 of 249 treated individuals, the vaccine generated a sarcoidosis response accompanied by a greater than 4-year freedom from metastasis or progression.[51]

3. CD4+ anergy:

Oswald-Richter et al. demonstrated that CD4+ anergic responses to polyclonal T-cell antigen receptor (TCR) stimulation were present peripherally and within the lungs of sarcoid patients. Consistent with prior observations, they found spontaneous release of IL-2 in sarcoidosis bronchoalveolar lavage CD4+ Tcells.

> However, in contrast to spontaneous hyperactive responses reported previously, the cells displayed anergic responses to polyclonal TCR stimulation. The anergic responses correlated with diminished expression of the Src kinase Lck, protein kinase C-u, and NF-kB, key mediators of IL-2 transcription. Although T regulatory (Treg) cells were increased in sarcoid patients, Treg depletion from the CD4+ T-cell population of sarcoidosis patients did not rescue IL-2 and IFN-γ production, whereas restoration of the IL-2 signaling cascade, via protein kinase C-u overexpression, did. Furthermore, sarcoidosis Treg cells displayed poor suppressive capacity indicating that T cell dysfunction was a global CD4+ manifestation. Analyses of patients with spontaneous clinical resolution revealed that restoration of CD4+ T_H1 and Treg cell function was associated with resolution. Conversely, disease progression exhibited decreased T_H1 cytokine secretion and proliferative capacity, and reduced Lck expression.[52]

Summary

The PV is rejected. The cumulative evidence justifies displacing the prevailing paradigm in favor of the parsimonious, unifying, alternative paradigm. The inference that what we designate as "sarcoidosis" is a syndrome attributable to cellular immune dysfunction, not a disease, is supported by the multiplicity of agents reported to infrequently generate an SGR indistinguishable from sarcoidosis. The view that sarcoidosis is etiologically heterogeneous is supported by Thomas and Hunninghake, who wrote, " . . . the disease might be triggered by different agents . . . the factor that would determine the development of the disease we recognize as sarcoidosis would be the host's immune response to the inciting agent" [italics added].[53] and in Cullinan's summary of the epidemiological evidence in which he suggested that sarcoidosis is ". . . an idiosyncratic response to one or more relatively common environmental agents."[54] Under this formulation, it is erroneous to dismiss a causal candidate because it is not uniformly present. The formulation that a SGR is a fallback to a more primitive response attributable to a variety of cellular immune deficiencies is supported by its frequent appearance in individuals with congenital, infectious and drug-induced cellular immune dysfunctions. Inefficient dendritic cell function appears the most likely underlying cause of sarcoidosis in persons lacking an otherwise apparent cause of impaired cellular immunity.

The HA is falsifiable by the identification of a universally present, confirmed-causative agent, which would imply that sarcoidosis is a disease, not a syndrome. It is reciprocally reinforced by the adverse impact of immunosuppression in recent-onset (presumably T_H1) disease.[55] For example, the far more frequent provision of CST in RS vs. PS (cited above), provided to suppress the granulomatous immune response with the expectation of preventing lethal pulmonary fibrosis, appears to account for their far higher sarcoidosis mortality.

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CHAPTER THREE

INCIDENCE

Introduction

While valid assessment of annual sarcoidosis incidence appears straightforward, requiring nothing beyond dividing the annual number of newly identified cases (numerator) per 100,000 in the source population (denominator), the apparent simplicity is illusory, for the numerator is dependent on a number of variables including ascertainment methodology, completeness of reportage, diagnostic criteria, and ethnic composition; and the source population is often implied rather than specified. Sarcoidosis incidence is therefore not a constant; instead, it is a function, in part, of the prevailing imaging frequency and intensity (CT).

Ascertainment Methodology

Ascertainment depends on access to medical care and thoroughness of reportage. Additionally, it reflects acuteness of recognition, which is influenced by the experience and assiduity of the interpreting radiologist. Sensitivity to subtle hilar adenopathy and pulmonary shadowing, easily overlooked in mass population screening, is likely to be enhanced ("ascertainment bias") by awareness of a putative, germane exposure.

Health maintenance organizations (HMO) provide optimal conditions for accurate incidence assessment because they furnish universal accessibility for diagnostic evaluation, uniform radiographic interpretation, a centrally maintained medical record that is available for data acquisition, and a numerically- and demographically-defined source population.

Methodological diversity is a major impediment to obtaining comparable incidence data in observable (*vide infra*) cases. To avoid ambiguity and achieve valid inter-population comparison, the term "incidence" must be preceded by an adjective which defines the operation by which the numerator was acquired. Observable cases are divisible into three

operationally-defined classes, each subsuming the prior class: Cases identified because of symptoms or an incidental chest radiograph are designated "clinically identified." Addition of cases identified by health or employment screening chest radiographs (which will vary systematically between populations) define "clinically recognized." Addition of cases identified by population screening defines "clinically ascertainable." Cases that are identifiable solely at post-mortem examination are designated "lanthanic." This classification scheme can be conceptualized as concentric circles in a Venn diagram in which lanthanic cases are, by far, the largest component.

Ethnic Composition

1. White incidence in representative Western populations:

The incidence of clinically identified cases peaks at ages 20-49. It varies widely between ethnic and geographic populations; it is far higher in black people and Northern Europeans. The annual incidence (incidence and prevalence figures are given as cases $\times 10^{-5}$) of clinically identified sarcoidosis in Great Britain (largely Whites) is 3.4,[1] and in the U.S., 2.8.[2] In a more recent U.K. study, Gribben et al. reported an ethnically mixed incidence of 5.1.[3] In a Swedish study, clinically identified cases were more than twice as high as in the U.K.—8—and constituted a minority (42%) of clinically ascertainable cases—19—identified by triennial mass population screening.[4] The latter figure underestimates the clinically ascertainable incidence, for more frequent screening (by identifying cases with a briefer duration) and screening the entire population rather than 64% would have materially increased the numerator. The clinically recognized incidence of 5 in a U.S. population of mixed Northern European ancestry (in which patients frequently received a screening chest radiograph as a routine component of their periodic physical examination) is somewhat higher than the U.K. clinically identified figure.[5] Horwitz and coworkers reported a clinically identified incidence of 5 in a large Danish study; population screening tripled that figure to a clinically ascertainable 15.[6] Sartwell et al. corroborated the tripling effect of periodic chest radiographic (CR) screening on incidence by noting that only 28% of sarcoidosis cases in a US Naval population were identified because of symptoms.[7] Others have reported a higher proportion of symptomatic sarcoidosis in radiographically-surveyed populations.[8]

In summary, among U.S. Whites, 3 is a plausible provisional estimate of clinically identified sarcoidosis incidence; 4 may be considered an upper

bound. The White incidence is slightly higher in the U.K. The clinically identified incidence in Scandinavian populations is 5. The clinically ascertainable incidence is three-fold the clinically identified incidence.

2. Black: White incidence ratio:

The clinically identified sarcoidosis incidence in Blacks in the two reporting, ethnically mixed, U.S. HMOs were 36.4[2] and 35.5.[9] The reported incidence in Whites in the latter (Rybicki) report, 10.9, is an outlier.[9] As noted by the authors, it far exceeds the White US incidence figures in the seven reports they cited. It is more than twice that reported in Scandinavian sources.[3,5] Their cited, clinically identified incidence, exceeds by more than two-fold the clinically recognized incidence in a U.S. population of mixed Northern European ancestry.[5] The Black/White rate ratio we computed, 36.4/2.8 = 13 is within the range of previous reports.[2] It far exceeds that reported by Rybicki and coinvestigators, 35.5/10.9 = 3.3, which is well outside the ratio range (10-17) reported in the articles they cited. The authors offered no explanation for their far higher estimate.[9] Detailed examination of their Figure 2, age-specific sarcoidosis incidence, suggests a possible explanation: The age-incidence in Whites was uniform from age 20 to 69; it lacked the expected, age 20-49 incidence peak, diverging in that respect from the incidence peak seen in Blacks in the same figure. A visual estimate shows the maximum disparity in B: W incidence (in the age-range 20-49) of 4.5:1. The age incidence uniformity in Whites was due to the absence of a decline in incidence in the 50-69 age group. One might speculate (absent a systematic occupational history) that older White workers had been more frequently occupationally-exposed to metal dusts (particularly beryllium), fumes, and organic antigens capable of causing a granulomatous lung disease difficult to distinguish clinically from sarcoidosis than their Black counterparts.[10]

3. Possible influence of Nramp1 on Black sarcoidosis incidence:

There is a marked, unaccounted for, Black vs. White differential incidence in three diseases that share a granulomatous response—sarcoidosis, tuberculosis, and non-tuberculous mycobacterial pulmonary disease (NTMPD): Blacks are constitutionally far more resistant than Whites to NTMPD;[11] their incidence of tuberculosis is eight-fold;[12] and of sarcoidosis, 13-fold that of Whites. Differential allocation of natural resistance-associated macrophage protein 1 (Nramp1) alleles may be responsible for or contribute to this granulomatous response nexus.

Nramp1 is encoded by the SLC11A1 gene. It is an integral membrane protein expressed in the lysosomal compartment of monocytes and macrophages. After phagocytosis, Nramp1 is targeted to the membrane of the microbe-containing phagosome, where it may modify the intraphagosomal milieu to affect microbial replication. It provides monogenic influence on susceptibility to (intracellular) mycobacterial disease, differing in this respect from host control of other intracellular bacterial infections which are ubiquitously influenced by multiple trait loci. Allelic variants differentially affect resistance to mycobacterial species. Koh et al. reported that allelic variants of Nramp1 were associated with susceptibility to NTMPD in a Korean population.[13] Maliarik et al. suggested the existence of a common pathophysiology of sarcoidosis and tuberculosis based on their shared histological and clinical features.[14] In a case/control study of Nramp1 polymorphisms in Blacks with sarcoidosis, they found an allele that exerted a protective effect. Dubaniewicz et al. demonstrated a positive association between allele 3 at the functional (GT)n promoter region repeat polymorphism of SLC11A1 and the risk of sarcoidosis.[15]

Diagnostic Decision

1. Clinical diagnosis:

The requirement for histological verification is often not stipulated in sarcoidosis incidence compendia. Clinical experience has verified the accuracy of clinical diagnosis in stage I; Hillerdal et al., in addition, accepted a clinical diagnosis of stage II.[4]

2. Misclassification:

Individuals exhibiting a local or regional granulomatous (“sarcoid”) response to a neoplasm are not infrequently misclassified as having sarcoidosis because of terminological imprecision. The proportion of unascertained chronic berylliosis in sarcoidosis registries is unknown. A phenocopy of sarcoidosis, it can escape detection unless careful inquiry into industrial exposure, supported by beryllium-lymphocyte proliferation testing, has been undertaken.[16]

3. Lifetime prevalence:

Autopsy prevalence is an imprecise measure of lifetime prevalence because of the lack of a diagnostic gold standard and ignorance of the natural history of histopathological features. Enumeration is contingent, in part, on case definition, *i.e.*, the pathologist's decision re. whether lone pulmonary involvement suffices, whether one or more than one organ demonstrating epithelioid granulomatous changes are required for confirmation, and whether historical or pathologic evidence of potentially confounding, co-existent diseases or exposures are present. In a Swedish autopsy series of 6,706 cases, Hägerstrand and Linell reported a prevalence of "certain" (pulmonary or multi-organ epithelioid granulomas) of 640, and a prevalence of uncertain cases of 210. The 640-figure was 10-fold the point prevalence estimated by mass radiographic screening in a Stockholm population.[17] In an Ohio forensic autopsy series numbering 9,324, in which Blacks constituted one-third, Reid identified 31 "accepted" cases of sarcoidosis. This prevalence of 333 was 10-fold that reported on Cuyahoga death certificates.[18] An additional 11 cases (prevalence, 110) were rejected due to possible confounding, principally by illicit drug exposures. Thus, lanthanic cases exceed observable (clinically ascertainable) cases by more than ten-fold, which implies that the natural history of sarcoidosis is so favorable that the overwhelming proportion of cases do not even reach a clinically diagnosable threshold.

In the year 2000, Blacks constituted 11.5% of the Ohio state population.[19] Reid noted a ratio of Black: White sarcoidosis cases of 4.7:1 in an autopsy population in which Blacks constituted one third. Correcting for their autopsy over-representation, the B: W sarcoidosis prevalence ratio is 1.6:1. This low ratio puts in question whether the reported far higher observable Black incidence might reflect, at least in part, a more exuberant response leading to a far greater likelihood of ascertainment.

It is not known whether histopathological residuals are present in all resolved cases. If not, then post-mortem figures underestimate the lifetime prevalence of sarcoidosis, for most cases resolve. Had we a marker of sarcoidosis similar in its simplicity, persistence, sensitivity and specificity to the tuberculin test, the true incidence and lifetime prevalence of sarcoidosis could be crudely estimated. These figures are currently indeterminable; cited figures constitute lower bound estimates.

Computation

Employing as the denominator the number of persons at risk (rather than the population from which they are drawn) in computing the incidence of sarcoidosis leads to a spuriously elevated figure if the age range of the at-risk population coincides with the peak age sarcoidosis incidence. This consideration is directly applicable to the occupational incidence of sarcoidosis because about 80 percent of cases are identified in the working age group.[3] When comparing occupational incidence with population incidence, correction for mean age is obligatory.

Misapplication

Several investigators have inferred a causal connection between sarcoidosis and occupational exposures based on a marked incidence differential vs. population-based, clinically identified figures.[20,21] This inference is weakened by ascertainment bias, lack of an identified putative antigen, the incidence-tripling effect of radiographic surveillance of the at risk cohort, and the employment of the surveyed, working age cohort as the denominator in the computation.

Reported sarcoidosis mortality may result in an erroneous inference of greater disease severity in Blacks if allowance is not made for ethnic incidence differential.[22] To circumvent this error, interethnic comparisons of sarcoidosis mortality should be replaced by the cumulative case-fatality rate, which is incidence-independent. For example, if one relied solely on mortality data, one might erroneously conclude that sickle cell disease was more severe in AA than in Ashkenazi Jews, and that the reverse obtained for Tay Sachs disease.

Summary

1. Absent a modifying adjective conveying an operational definition, the meaning of the term “sarcoidosis incidence” is ambiguous. Valid inter-population incidence comparison requires methodological comparability.

2. The clinically identified incidence of sarcoidosis in U.S. Whites is 3×10^{-5}; in US Blacks, 36×10^{-5}; in U.K. Whites, 3.4×10^{-5}; in persons of Scandinavian descent, 5×10^{-5}. The clinically ascertainable incidence (obtained by population screening) is three-fold the clinically identified incidence.

3. Sarcoidosis is a common disorder; its apparent rarity reflects the small proportion of (observable) cases that exceed the clinical and radiographic recognition thresholds. The “true incidence” of sarcoidosis is a notional concept: more than 90% of cases are subclinical and unobservable.

4. Occupational causal inference based on incidence differential vs. populations is confounded by differences in case acquisition and incidence computation.

5. Due to incidence disparities, case fatality is preferred to mortality for comparison of disease lethality between ethnicities.

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CHAPTER FOUR

TISSUE CONFIRMATION OF STAGE I SARCOIDOSIS

Absolute certainty in diagnosis is unattainable, no matter how much information we gather, how many observations we make, or how many tests we perform. Our task is not to attain certainty, but rather to reduce the level of diagnostic uncertainty enough to make optimal therapeutic decisions.[1]

> "At present, the diagnosis of sarcoidosis is a statement of belief or knowledge that non-caseating epithelioid tubercles or their hyalinized remnants are present in a number of affected organs or tissues. This belief is justified in the presence of a combination of clinical, radiological and laboratory findings known to be associated with such changes, and supported by a compatible clinical course. In such cases, corroborative histological evidence from biopsy of an accessible tissue or a Kveim test is usually easy to obtain, and is desirable; *but some clinical presentations are so characteristic that for the practical management of the case of a patient presenting them, confirmation by biopsy is not essential, especially if a benign course is probable".* [italics added] [2]

In the 1980's, medical textbooks advocated tissue confirmation of sarcoidosis as a standard of practice. Questioning its necessity in stage I sarcoidosis (isolated bilateral hilar lymphadenopathy—BHL), where the clinical picture is stereotypical, Winterbauer and colleagues undertook the seminal quantitative investigation of this requirement by reviewing medical records of 100 patients with BHL. Sarcoidosis was confirmed in 29 who were asymptomatic and had normal results of a physical examination, and in 13 symptomatic persons with accompanying uveitis or erythema nodosum. The authors advocated forgoing biopsy in favor of continued observation of such patients.[3] To my knowledge, only exceedingly rare exceptions to their observations have been published.

While acknowledging that stage I sarcoidosis (SIS) was the predominant cause of asymptomatic BHL (ABHL), authors of standard references continued to advocate histologic confirmation (by transbronchial needle aspiration, transbronchial lung biopsy or mediastinoscopy, in the absence of more accessible tissue), implying that earlier recognition of an unspecified, treatable, alternative diagnosis mimicking SIS might prove beneficial.[4,5,6] Advocates of continued observation maintained that tissue confirmation was unnecessary because exceptions are so rare that a secure *a priori* diagnosis can be made on clinical grounds.[3,7,8] Quantifying the consequences of both policies provided a means of resolving this dispute. We systematically reviewed the published literature to compare the annual number of cases of SIS vs. annual number of cases of tuberculosis (TB), lymphoma and non-Hodgkin's lymphoma (NHL) presenting with ABHL. We considered that other causes of ABHL simulating S1S—histoplasmosis, coccidioidomycosis, early AIDs, silicosis—could be effectively excluded by a combination of epidemiological, serological and anamnestic criteria, that persons with advanced, metastatic neoplasms would rarely present with ABHL, and that earlier detection of the latter would not materially alter the course of their disease.[9]

Based on a survey of the published literature we estimated the U.S. incidence of each of these four disorders and the proportion that each presented with ABHL in order to compute a numerical estimate of each entity as the product of proportion presenting as ABHL x annual U.S. age-specific disease incidence. We computed the race-normalized, U.S. annual number of cases of sarcoidosis = 9.3×10^3. Employing liberal estimates of the proportion presenting as ABHL we estimated the annual numbers for alternative diagnoses simulating SIS at 9.1×10^{-9} for tuberculosis, 10.4×10^{-9} for Hodgkin's disease, and 11.3×10^{-10} for NHL.

We calculated that, assuming 100% accuracy, *i.e.*, 100% sensitivity and 100% specificity of mediastinoscopy and transbronchial biopsy, if 33,000 persons (*ca.* 3.5-fold the annual number of U.S. SIS cases) underwent either procedure, 32,982 (positive predicted value, PPV >99.95%) would be found to have SIS or, very rarely, a disorder not requiring intervention. Persons with a biopsy demonstrating non-caseating epithelioid granulomas would be comforted by confirmation of the presumptive diagnosis and reassurance that the biopsy excluded malignancy and TB. Eighteen persons (at most) would achieve an earlier diagnosis—eight with TB, nine with Hodgkin's disease and one with NHL. The tangible benefit would be trivial to non-existent (Primary TB most often resolves spontaneously and earlier diagnosis of Hodgkin's disease furnishes a marginal advantage.)

These benefits would be offset by collective procedural charges of hundreds of millions of dollars plus hospitalizations resulting from major complications.[9] Mediastinoscopy has been largely supplanted by ultrasound-guided transbronchial needle aspiration (TBNA) and transbronchial lung biopsy, but the same considerations apply.

Metastatic renal cancer[10,11] is a rare cause of BHL. About half the reported cases had a prior diagnosis of the cancer. I found no reported Western instances of ABHL due to TB or lymphoma. The collective current populations of Europe, US, Canada, Australia, New Zealand and UK ≅ 1.2 billion. Discounting population growth, ≅ 55-billion person-years have passed since the publication, 46-years ago, of Winterbauer's seminal paper.[3] Assuming a mean clinically identified annual sarcoidosis incidence in these populations' of 4×10^{-5}, the collective number of cases in this interval would be 4.4-million. Assuming half are SIS, there would be 2.2-million cases. If as many as five in ten-thousand persons (10,000 – 9,995) with AHBL had one of the alternative diagnoses we considered, their collective numerical occurrence in the past 46-years in Europe, U.S., Canada, Australia, New Zealand and UK would be in the order of 1,100. None have been reported. Our cited PPV of >99.95% for ABHL = sarcoidosis, not TB/lymphoma, may be regarded as an underestimate.

Recently, some investigators have suggested that one can forgo tissue confirmation when ABHL is accompanied by polyarthralgia, uveitis and/or erythema nodosum (Löfgren syndrome).[12] While these features serve to increase the medical provider's confidence in making a clinical diagnosis, the PPV of isolated ABHL is so high as to leave no measurable opportunity for increase.[13] When considering a policy of tissue confirmation to exclude the rare instance of sarcoidosis simulated by an alternative diagnosis, weight should be given to the likelihood that the alternative is both treatable and that earlier diagnosis confers a measurable benefit, and, if so, that the benefit offsets the harm imposed by the very large number of entailed invasive procedures. It is worth emphasizing that biopsy verification of noncaseating granulomas does not constitute apodictic evidence of sarcoidosis: they may be identified in lymph nodes draining malignant neoplasms and in the small volume sampled by transbronchial biopsies in pulmonary tuberculosis.

Patients and referring physicians may have the expectation of tissue confirmation of a rare and difficult-to-explain disorder, possibly more so in tertiary care settings. Conceivably, they may be put off by a seemingly casual dismissal of their concern following a perfunctory medical history

and physical examination and a brief review of their chest radiograph/CT. Excluding cancer is intuitively considered a categorical (*i.e*., unconditional) good. A radiographic interpretation of isolated BHL that incorporates tuberculosis, fungus disease and malignant lymphoma (along with sarcoidosis) in the differential may influence the decision to proceed with tissue confirmation, if only to forestall the possibility of litigation for failure to diagnose. Institutions that have invested heavily in costly equipment may encourage its utilization. Complications following invasive procedures for tissue confirmation are likely to be under-reported.[14]

In summary, the disproportion between the risks and costs of tissue confirmation of SIS vs. its infrequent necessity and lack of tangible benefit put in question the categorical justification for its requirement. A provisional diagnosis, followed by continued observation (which is indicated in either case), is sufficient. Lack of familiarity or agreement with the published data cannot justify its ongoing advocacy: collectively, the quantitative analyses[3,9] have been cited more than 400-times, and their data, interpretations and conclusions remain unchallenged in the published literature.

Notes

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CHAPTER FIVE

TREATMENT

Unfortunately, to this date, sarcoidosis remains a poorly understood entity of uncertain etiology, based on nonspecific pathology, which pursues a variable course and has unclear indications for treatment with a variety of unproven therapies.[1]

The necessity for treatment of CNS, ophthalmic, cardiac and hypercalcaemic manifestations of sarcoidosis is undisputed. This critical analysis will be confined to intrathoracic sarcoidosis where indications for treatment vary between individuals and institutions.

Justification for treatment of pulmonary sarcoidosis is intuitively highly persuasive: A small percent die of the disease, most often due to a combination of pulmonary fibrosis and cor pulmonale. A favourable short-term response to glucocorticosteroid therapy (CST), manifested in clinical, physiological and radiographic improvement is nearly universal. (The exception is individuals with residual pulmonary fibrosis *i.e.*, no disease activity.) No unfailing predictive marker that identifies individuals destined to spontaneously resolve exists, although Stage I, particularly when it presents acutely, almost invariably resolves within a short time. The sole validated predictive variable is Scadding stage, which is imprecise. Individuals who express reservations about treatment emphasize that the majority of cases resolve spontaneously, that spontaneous resolution cannot be predicted, that it may take place years after onset, and that CST suppression has failed thus far to demonstrate a long-term benefit in trials. To which they add the well-known side effects of long-term CST.[2,3] Additionally, although it is not widely acknowledged, there is persuasive evidence that suppression of the immune response hinders resolution, resulting, in some instances, in long-term harm. Recent therapeutic investigations have centred on drugs known to suppress the cytokines involved in generating granulomatous responses with the hope and expectation that this specific suppression might prove to

be both more effective than CST and simultaneously circumvent its well-known side effects.

Wells and his co-authors furnish a thoughtful, practical and succinct discussion of treatment guidelines:

> The long list of indications for active intervention, specified in many texts, can be subdivided into two broad *reasons to treat:*
>
> - Danger from disease
> - Unacceptable loss of quality of life
>
> [Absent these indications] *the correct management approach is therapeutic inaction, coupled with meticulous observation.*
>
> . . . The distinction between dangerous disease and active symptomatic disease, without significant involvement of major organs, lies at the heart of accurate management.[4]

The authors' indication for CST for pulmonary sarcoidosis can be summarized as evident progression manifested clinically by increasing breathlessness, worsening radiographic or pulmonary functional abnormalities.

Prognostic Markers

Management of individuals with pulmonary shadowing and trivial symptoms not compelling intervention, who exhibit no clear evidence of progression or regression after an adequate period of monitoring, is the vexing issue. The concern is that, left untreated, ongoing active granulomatous inflammation may evolve into (irreversible) pulmonary fibrosis. Advocates of intervention hope that some biomarker of progression—as distinguished from markers of activity—will be identified or devised. A difficulty with this formulation is that available markers of activity (ongoing inflammation) and its magnitude—gallium lung scanning, serum angiotensin converting enzyme (SACE) and BAL lymphocytic alveolitis—which, intuitively, might have been expected to function as prognostic markers, have proven unrelated to prognosis;[5] that the latter, a measure of the intensity of alveolitis, has a seemingly-paradoxical, counter-intuitive relationship to outcome—persons with an acute onset of stage I disease with erythema nodosum, who are known to have a highly favorable prognosis, characteristically exhibit high-intensity lymphocytic alveolitis;[6,7] and persons with high-intensity lymphocytic alveolitis at any stage exhibit more favorable outcomes.[8,9] These markers

of disease activity as a prognostic guide for the need for intervention were investigated and discredited by Turner-Warwick and colleagues who measured them in the course of a CST trial in persons with persistent pulmonary sarcoidosis in which the investigators applied a predetermined, standard clinical protocol. Periodic measures of each proposed prognostic variable were obtained but were not used in management decisions:

> "There was no predictive value in the initial lavage lymphocyte counts or the SACE or gallium measurements." "The interrelationship between these variables and clinical indices—chest radiograph (CR), vital capacity and transfer factor—were fairly poor. They were therefore not viewed as useful additions because the relationship of each to the course of sarcoidosis was highly variable."5

The countervailing concerns expressed by those unwilling to treat in the absence of robust evidence of benefit are the well-known, long-term side effects of CST and the possibility that this intervention may interfere with spontaneous resolution. Thus far, no reliable marker of future progression has emerged. In theory, a transition from a T_H1 to T_H2, BAL-assessed cytokine display might prove useful.

Non-Indications

There are generally agreed upon therapeutic non-indications: Treatment of stage I is not indicated, for, in the absence of pulmonary shadowing (potentially prefibrotic lung changes), non-trivial pulmonary fibrosis will not develop. Moreover, persons with stage I almost invariably resolve spontaneously or leave no more than residual hyalinized hilar lymph nodes. Clinical follow-up is all that is required. The majority of patients with inactive disease and residual pulmonary fibrosis have it to a degree that is anatomically limited and not clinically disabling. The pathogenesis of fatigue and lassitude associated with sarcoidosis is unclear. These distressing symptoms are not in themselves indications for CST.

CST Trials

Scadding and Mitchell reviewed and summarized 13 long-term uncontrolled and 8 long-term controlled CST trials. Each demonstrated a short-term benefit, and none, a long-term benefit. Based on the lack of clear-cut evidence of long-term benefit, their indication for CST resolved to:

> ". . . relief of symptoms severe enough to interfere with the patient's normal conduct of life. The assumptions underlying this policy are: a) In many patients with pulmonary sarcoidosis, the active stage comes spontaneously to an end, leaving no evident or only trivial changes. There is no evidence that corticosteroid treatment in such cases either reduces the duration of the active stage or diminishes the amount of residual fibrosis; b) in those with symptoms restricting their activities, the relief of these is sufficient justification for the use of corticosteroids., provided that the required dose is tolerable for long-term administration."[10]

The Cochrane meta-analysis of CST trials, in which the authors reported no clear-cut benefit or harm, was methodologically flawed because it conflated trials in which subjects had sarcoidosis of various duration, persons with stage I disease (for whom it is not indicated), and trials of inhaled CST, which, due to its limited efficacy, is not recommended for treatment of persons with pulmonary shadowing. These design limitations render this analysis inapplicable to persons with non-progressive pulmonary shadowing, the issue at hand.[11]

The seminal case/control trial of elective CST, in which neither compelling symptoms nor clinical findings dictated treatment, demonstrated an adverse long-term outcome: Izumi,[12] reported on the long-term follow-up of 185 asymptomatic, predominantly young (mean age, 25.5) patients, largely detected by health examinations before 1982, and followed for more than 10-years at Kyoto University Sarcoidosis Clinic. Eighty-four percent were stage I. None had abnormal pulmonary function at diagnosis. Sixty-three (34%) received prednisolone, ≥20mg for > three-months with one of three justifications:

a) the attending physician's belief that it would avert the development of pulmonary fibrosis; b) the subject's participation in a nationwide double-blind study of its efficacy; or c) the subject's hope that it would eliminate radiographic shadows deemed unfavorable for employment or for their marriage.

Izumi observed an important age-dependent differential: the outcome was more unfavorable in persons diagnosed at an older age. Because the inception of sarcoidosis is insidious in asymptomatic individuals, it seems reasonable to infer greater chronicity in persons in whom it is identified later in life. If this inference is correct, the age-related outcome is confounded by disease duration, *i.e.*, their adverse prognosis may reflect

selection of individuals characterized by a prior failure to spontaneously resolve rather than an inherently worse prognosis associated with advanced age. Among the 101 patients diagnosed in their twenties, in whom disease duration was a less pervasive, potential prognostic confounder, 30 had received CST and 71 were untreated. After 10-years, CR abnormalities persisted in 2 of the untreated 71 (2.8%) and in 8 of the treated 30 (23%) patients ($p<0.01$). The 2 untreated persons with persistent changes had isolated BHL (presumably, hyalinized). Among the 8 treated with persistent changes, 2 had isolated BHL, 2 of 5 showed progressive pulmonary shadowing without functional deterioration; and the remaining 3 developed dyspnea and deterioration in pulmonary function detected >10-years after diagnosis. In one, who presented with stage I, bullae appeared 11-years after detection; her functional loss required ongoing CST and oxygen therapy. The most compelling aspects of this analysis reside first in its unbiased allocation of treatment, for none of the individuals selected for treatment had either pretreatment findings or therapeutic indications known to influence outcome, and, second, in the lengthy period before adverse consequences of CST appeared.

The sole trial that reported a long-term CST benefit was that undertaken by The British Thoracic Society (BTS). The design differed fundamentally from other trials by providing a six-month period of untreated observation (absent compelling symptoms) to allow those with improving or resolved abnormalities to self-select for exclusion. The investigators recruited from consultant members of the BTS 149 *newly presenting* [italics added] patients with pulmonary shadowing. Immediate CST for compelling indications was required by 33; 58 were classified as observed and treated only if needed. The comparison arms were: 27 allocated to receive long-term CST sufficient to maximize their radiographic resolution (L) vs. 27 treated selectively (S) for either symptoms or functional deterioration*, i.e.,* not with the intent of maximizing their radiographic appearance. These 54 patients were alternately assigned to the L or S cohort. At five-year follow-up, a multidimensional assessment showed that the L cohort experienced a small, statistically significant improvement in FEV_1 and VC vs. the S cohort.[13]

Critical analysis: a) Alternating allocation to the L and S cohorts failed to achieve matching of critical baseline characteristics: The L cohort had a higher mean diffusing capacity and half the number with stage IV disease vs. the S cohort. b) Three features suggest that many of the subjects in the L and S cohorts had chronic disease: their mean age was 40, a decade beyond the estimated mean age of onset (31) in England;[14] they were eight

years older than the observed group (that improved spontaneously); and 13 of 58 (22%) exhibited pulmonary fibrosis at allocation, indicative of chronicity. Thus, the small favorable results are open to question; and they may not extend to young patients with trivial or no symptoms who fail to improve spontaneously within six months or to those with known recent onset. c) Additionally, one would like to know whether the benefit was confined to those exhibiting progressive pulmonary disease (the treatment indication advanced in joint statements by the BTS, Australian and New Zealand TS, and Irish TS,[15] and by the joint American TS, European Respiratory Society and The World Association of Sarcoidosis and Other Granulomatous Diseases.[16]) This information was not furnished. As noted by the BTS authors, it is exceedingly difficult to assemble an adequate number of suitable cases in a timely fashion to conduct a therapeutic trial.

Advocates of intervention emphasize that the reported CST trials demonstrating no mean benefit failed to judiciously select candidates for intervention for, by example, including in the treatment arms persons with trivial symptoms, persons with stage I disease and persons with inactive stage IV disease. They add that some treated individuals do experience long-term benefit. Granting this, a mean, null treatment benefit in a setting in which some achieve a long-term benefit mathematically entails the existence in others of an offsetting, commensurate harm.

Mortality in Tertiary Care vs. Population-based Settings

While less rigorous than a case/control trial, the effect of treatment can be assessed by a metanalysis of outcomes in tertiary care settings (TCS), which provide CST with a far higher frequency vs. the more conservatively managed experience in population-based settings (PBS). Under the assumption that suppression of the systemic granulomatous response is effective in preventing death from pulmonary fibrosis and cor pulmonale, one would expect to find a reduction in mortality in settings where it was more liberally applied. Instead, the reverse obtains. Mortality rate (which may be age-adjusted) is defined as the annual number of deaths (from specific disease) $\times 10^{-5}$ person-years. As employed in sarcoidosis trials and case series, “mortality” is operationally defined as a percent: cumulative case fatalities in the studied population during a specified period-range of observation divided by the number of cases under surveillance. It is an imprecise measure of mortality.

I tabulated nine reports identified in a MEDLINE search of publications in the English language since 1960 (and separately summarized one outlier)

that evaluated the long term course and prognosis of sarcoidosis originating in large, outpatient, adult practices in Western countries, unsorted by chronicity, and that furnished Scadding stage data.[17] I employed the proportion of patients with Stage I disease as a marker of non-adverse selection because this stage almost invariably has a favorable outcome and infrequently requires CST. Similarly, I employed the proportion of patients identified by means of population screening radiographs, who are typically asymptomatic stage I, as a similar marker. Conversely, I employed the proportion of patients with advanced (stages III, IV) disease, whose prognosis is known to be the least favorable, as a marker of adverse selection. Because not all reports distinguished between stage III (pulmonary shadowing without hilar adenopathy) and stage IV (radiographic evidence of pulmonary fibrosis); I pooled these categories under the rubric "stage III/IV." I excluded series based on hospitalized patients to minimize the effect of a disparity in outcome attributable to patient source. Similarly, I excluded compendia based solely on newly-diagnosed patients to ensure an adequate duration of follow-up.

TABLE 5.1 SARCOIDOSIS MORTALITY TERTIARY-CARE SETTINGS (TCS)

First author	Number	Stage I%	Stage III/IV%	CST%	Mortality
Smellie[1]	125	38	12	N/A	7.2
Sones[2]	199	36	28	44*	7.6
Neville[3]	700	65	13	49	6.1
Siltzbach[4]	1454	47	15	50	5.0
Scadding[14]	136	24	47	40**	6.6
Case-weighted mean		**49**	**17**	**49**	**5.7**

* Some patients in this series were stage 0 and received CST for non-pulmonary indications.

** Long term CST was provided in 21%; the remainder received two to eight weeks of therapy.

TABLE 5.2 SARCOIDOSIS MORTALITY POPULATION-BASED SETTINGS (PBS)

First author	Number	Stage I%	Stage III/IV%	CST%	Mortality
Henke[5]	70	N/A	N/A	N/A	1.4
Hillerdal[6]	490	61	11	*	0.8
Romer[7]	243	56	5	3	0
Reich[8]	79	53	16	2.4	0
Case-weighted mean		**59**	**10**	**2.4**	**0.56**

* "small number"

The assumption appears plausible that adverse selection for referral to TCS accounts for the latter's higher reported mortality vs. PBS. This assumption however, implies the systematic existence of an ability on the part of referring physicians to accurately discern adverse prognosis independent of stage. The trials summarized in tables 5.1. and 5.2 provided, in general, little detailed information about patient source, disease severity, pulmonary function, or other indications of adverse selection, for example, the proportion of cases referred vs. the proportion assembled from the institutional clinic populations, or the proportion that were screen-identified. The Hillerdal series reported the highest percentage of persons identified by population screening radiographs, 57%;[23] it was 34% in the Siltzbach compendium,[21] and 46% in the Smellie series.[18] The seven remaining series lacked this information. The sole TCS that reported on chronicity and severity was authored by Scadding: ". . . many (all were stage IV) were referred to me after prolonged periods of observation by other physicians because of an unfavorable course." The proportion of patients with stage III/IV disease in this series (47%) was three-fold that of the case-weighted mean of the remaining four TCS series (15.3%), clearly validating advanced stage as a marker of adverse selection. Fifty-four of 136 patients (40%) in this series were treated; however, because the author observed no sustained benefit in asymptomatic patients, 25 of the 54 treated cases received CST for only two to eight weeks. Long-term CST was thus provided in 21% of the cases, the lowest percentage in the TCS series.[14] Despite strong evidence of adverse selection, indicated by patient source, characterization, and stage, the mortality rate (6.6%) in Scadding's conservatively managed series did not differ materially from 5.7% case-weighted mean in the other TCS (Table 5.1.) As expected from referral bias, the proportion of patients with the prognostically least favorable

stage (III, IV) is higher in TCS (17%) than in PBS (10%). Our PBS report is an outlier in this respect with 16% stage III, IV patients.[25] This distribution may reflect the absence of a policy of providing screening CRs in this health maintenance organization, which predominantly identify asymptomatic stage I persons. Sarcoidosis mortality is remarkably homogeneous within each setting: in TCS, the case-weighted mean is 5.7% (range: 5, 7.6, Table 5.1); in PBS,[6-9] it is 0.56% (range: 0, 1.4, Table 5.2). Notably, there is no intergradation. The relative risk of dying of sarcoidosis in a TCS/PBS is therefore 10. Correcting for the inequality of advanced cases in the two settings under the assumption that sarcoidosis mortality occurs exclusively in those with stage III/IV reduces the relative risk to 7.

I separately summarized Johnston's TCS experience with 159 cases followed for 10 to 20 years in the University Chest Clinic in Dundee because his therapeutic indications and outcomes differed greatly from the other TCS. He reported that 30% of his patients were screen-identified. The stage percentages were nearly identical with the case-weighted mean of the TCS experience: 81 (51%) were stage I, and 27 (17%) stage III/IV. He treated his patients far more conservatively than those cited in table 1: four (3%) received it (for progressive pulmonary shadowing). No deaths were attributed to sarcoidosis.[26]

Applying mean values for missing (N/A) data in the two tables, correcting for III/IV stage, and adding Johnston's data, the Spearman's rank correlation coefficient (ρ_s), between the provision of CST and mortality in these 10 trials =.79; the CST-attributable risk = 62%.

Additional Outcome Experience

I excluded two case series from tabulation because they lacked staging information. Both demonstrated that mortality from sarcoidosis is infrequent/rare in PBS: In an epidemiological survey of nearly 1,500 persons with sarcoidosis in 24 regional centres in Moravia and Silesia, Kolek reported that "The course of the disease was benign with only sporadic extrapulmonary complications or pulmonary fibrosis." ". . . advanced cases causing death were extremely rare."[27] Bunn reported a zero percent sarcoidosis mortality rate in 71 patients, 44% of whom had been identified by screening radiographs.[28]

I excluded the Hannuksela report from tabulation because it was confined to individuals with documented recent onset (≤ 6-months), untreated, tissue-confirmed sarcoidosis and because it furnished only moderate ("up to nine-years") follow-up. The mean age of their 135 patients was 31 (males) and 39 (females). In this analysis of the natural history of recent onset sarcoidosis, none received treatment during follow-up. Of 119 patients with intrathoracic sarcoidosis, 113 were available for follow-up >24-months since onset; 79 (70%) were stage I and 34 (30%), stage II, III. "Seventy-six percent of the cases healed completely within two years." The authors reported no deaths in patients with intrathoracic sarcoidosis.[29]

In contrast, Kirkil et al. reported a sarcoidosis mortality of 8.4% in 452 patients with complete pulmonary function testing and chest imaging assessed in two university settings.[30] Their mortality exceeded by nearly 50% the pooled, 5.7% TCS figure (Table 5.1), and it was 15-fold that in PBS (0.56). The authors ascribed the adverse outcome to CST-unresponsive pulmonary fibrosis and pulmonary hypertension. It was not possible to determine from the report whether these features were initially present or became evident in the course of their follow-up. The authors did not furnish either treatment selection criteria or treatment details. An additional, striking finding was reversal of the cumulative mortality graphic: The typical survival graphic is characterized by an initial rapid decline as the severest cases rapidly succumb followed by a gradual diminution in the rate of the decline reflecting improved survival of successively milder cases. The graphics in Kirkil's paper showed an initial slow decline followed, after *ca*. 5-years, by a rapidly accelerating decline. This pattern implies that an intervening occurrence, presumably treatment, produced the delayed, precipitous decline in survival. If this inference is correct, irreversible pulmonary fibrosis and pulmonary hypertension were the consequences of treatment.

Disease Duration

Disease duration critically influences long-term treatment response. In published trials of persons with recent onset stage II/III, those allocated for CST were more than twice as likely as untreated subjects to exhibit radiographic or clinical progression or death; in cases of intermediate duration, the effect of universal vs. selective provision of CST varied from neutral to slightly beneficial. Patients with progressive chronic sarcoidosis either improved or stabilized, intermediate term, in response to CST.[31,32,33,34,35] This differential effect most likely reflects the

immunological character of the disease, which presumably differs according to duration. Because those with recent onset have the greatest propensity to spontaneously resolve, they correspondingly have the greatest likelihood that CST will interdict an otherwise favorable course.

Relapse Rates

Relapse rates constitute an additional metric of CST benefit/harm. In a TCS population of 337 persons with sarcoidosis, Gottlieb[36] observed relapse requiring retreatment in 76 of 103 (74%) persons initially treated for compelling symptoms who achieved induced remission of at least 1-month following ≥12-months of CST. In comparison, among 118 persons whose symptoms were initially insufficient to require CST, new onset of compelling symptoms required CST in 10 (8%). The authors observed:

> "The striking difference in relapse rate between treated and untreated patients suggests that patients with disease that would later be severe and protracted were almost unerringly identified early in their course. One explanation is that severe presenting symptoms portend a protracted and recurrent course; an alternative explanation is that corticosteroids contributed to the prolongation of the disease by delaying resolution." In distinguishing between these two explanations for the 9-fold difference in "relapse" the authors commented: "If selection bias were the explanation for the high relapse rate in treated patients, we would have had to have been almost unerring in treating only those patients destined to have chronic relapsing pulmonary or extrapulmonary disease. In effect, our clinical assessment would have succeeded where other tests of 'activity' such as BAL, ACE activity, or gallium scanning have failed. Therefore, either our determination of symptom activity (and need for treatment) stands out as a unique and highly accurate predictor of tendency to suffer relapse, or some other factor explains the relationship between treatment and relapse. We suggest that an alternative explanation cannot be excluded: that corticosteroid treatment itself, rather than the need for treatment, contributed to the propensity for relapse."

In support of the latter view, the authors cited the experience of three other institutions whose reported findings provided a similar interpretation: a) Eule et al.[35] randomized 182, screen-identified persons with asymptomatic sarcoidosis to receive 6- or 12-months of CST or no treatment. Similar to the trial summary furnished by Scadding and Mitchell,[10] they reported no

differences in lung function at a mean 8.9-year follow-up. However 22% of the treated required retreatment for post-treatment recurrence vs. 13% in the untreated who required treatment post randomization for either relapse or progression; b) Izumi reported at ten-years post treatment follow-up of the 101-persons subgroup that 27% of persons in the treated cohort had persistent radiographic abnormalities vs. 3% in the untreated cohort;[12] c) the BTS trial reported that 20 of 58 (34%) initially treated persons were still receiving CST at final assessment vs. 5 of 89 (6%) initially untreated.[13]

Drugs Directed at Specific Immunological Targets

Several trials of drugs specifically designed to block granulomatous response have been undertaken. Each was based on the premise that the granulomatous response is harmful and that the response to the broad spectrum of corticosteroid immune suppression could be improved by selective inhibition of specific immunological T_H1 targets. All either failed or had the (seemingly paradoxical) opposite effect from that intended, placing the underlying premise in question:

Cyclosporin-A inhibits nuclear factor of activated T-cells (NFAT), which leads to a reduction in IL-2, a T_H1 cytokine that favors granulomatous inflammation. It therefore appeared to be an ideal therapeutic candidate to suppress or resolve the systemic granulomatous response. A randomized trial in persons with progressive pulmonary shadowing showed that 58% of those treated with prednisone plus cyclosporin-A demonstrated improvement vs. 67% of recipients of prednisone alone. After termination of treatment in 16 subjects who responded favorably, 2 of 9 prednisone recipients experienced relapse vs. 5 of 7 prednisone plus cyclosporin recipients.[37] Metzger and Peterson demonstrated earlier that Cyclosporin-A markedly intensifies the (T_H2, fibrotic) response to injected Schistosoma mansoni eggs in mice,[38] which suggests a possible mechanism for the adverse effect of this agent on the T_H1 response of the therapeutic candidates.

Etanercept inhibits TNFα, a T_H1 cytokine active in the induction and maintenance of the granulomatous response. A trial of etanercept was protocol-terminated because of a high proportion of unfavorable responses: Among 16 persons with progressive stage II or III disease who completed therapy, 11 showed radiographic or pulmonary function deterioration or both; only 5 showed any improvement.[39]

A trial of Infliximab, another anti-TNFα antibody, achieved a mean increase of 2.5% in percent predicted FVC, compared with no change in placebo-treated patients ($p = 0.038$).[40] The response was deemed too small to justify widespread application or insurance coverage. Jamilloux et al. reported a clinical response rate of 64% among persons with prednisone-refractory sarcoidosis following the addition of anti-TNFα (largely, infliximab) therapy in a multicenter study of 132 patients. More than half the subjects experienced adverse side effects requiring termination in 31 (23%); and 13 relapsed following discontinuation of anti-TNFα treatment.[41]

A multicenter trial of patients with cutaneous and/or pulmonary sarcoidosis that employed ustekinumab and golimumab, monoclonal antibodies that specifically inhibit IL-12/IL-23 and TNF-α, respectively, showed no benefit.[42]

Conversely, thalidomide, a drug that enhances granuloma genesis by augmenting dendritic cell activation and T-cell infiltration of granulomas, had a favorable effect on cutaneous sarcoidosis. Oliver treated eight persons with cutaneous sarcoidosis for 16-weeks and reported that all skin biopsies showed decreases in granuloma size and reduction in epidermal thickness. Microscopically there was:

> . . . extensive T cell recruitment into the granulomas, the appearance of multinucleated giant cells, and increased numbers of dermal Langerhans cells (CD1a (+)) and mature dendritic cells (CD83(+) or DC-LAMP (+)). Plasma IL-12 levels increased and remained elevated during the treatment period. We noted increased HLA-DR expression on peripheral blood lymphocytes and a corresponding drop in the naive T cell marker CD45RA. Our data suggest that thalidomide treatment of sarcoidosis results in granuloma differentiation to a T_H1-type cellular immune response usually associated with protective immunity to tuberculosis and tuberculoid leprosy.[43]

Several reports indicate a favorable response of pulmonary sarcoidosis to thalidomide. For example, Fazzi[44] treated 19 patients with cutaneous and pulmonary sarcoidosis with thalidomide and reported significant improvement in radiographic appearance and in DLCO. Lenalidomide, a thalidomide congener, has proven effective as well.[45] Thalidomide stimulates the T_H1 response. It inhibits TNFα, IL-1β, 6 and 12; it induces proliferation of T lymphocytes and their cytokine production, increases IL-2 production with a concomitant increase in IFNγ production.[46] Judson,[47] however, in a trial in subjects with steroid-dependent pulmonary

sarcoidosis, reported failure of thalidomide (in conjunction with ongoing CST) to improve quality of life or pulmonary function. A possible explanation for the failure to reproduce the favorable response seen in cutaneous sarcoidosis is that thalidomide lacks the ability to reverse the transition from a T_H1 to a T_H2 response induced by CST. (See Chapter 12. Questions; Section 4, Immunology: T_H1 vs. T_H2.)

The employment of other, largely experimental second-line agents with limited efficacy—azathioprine. methotrexate, pentoxifylline—are beyond the scope of this book. Moller, among others, summarized their immunological mechanisms and clinical effects.[48]

Treatment addressed to specific immunological targets shows that drugs that suppress the T_H1 response have an adverse effect on the course of the disease, and that thalidomide, which enhances this response, has a markedly favorable effect on cutaneous and a possible benefit in pulmonary sarcoidosis. Adverse outcomes in response to T_H1 suppression and favorable responses to T_H1 augmentation reinforce the formulation advanced by Munro that the systemic granulomatous response characterizing sarcoidosis is a default to a more primitive and inefficient response that comes into play when more efficient, cell-mediated, adaptive immunity fails to deal effectively with an unspecified antigen(s). A therapeutic trial of thalidomide in untreated persons with non-progressive, persistent, stage III sarcoidosis is warranted, providing that intercurrent pregnancy can be assiduously avoided.

Secular Increase in Sarcoidosis Mortality

The belief that persons with stable sarcoidosis are at great risk for the development of lethal or disabling pulmonary fibrosis may generate a self-fulfilling prophecy if it leads to indiscriminate provision of CST. Swigris et al., drawing on U.S. National Center for Health Statistics data for years 1988–2007 reported that age-adjusted, sarcoidosis-related mortality rate increased 50.5% in women and 30.1% in men in this 20-year interval.[49] Absent evidence of more liberal provision of CST, attribution of the secular increase to more liberal provision of CST, possibly influenced by published TCS treatment policies, is purely speculative. Gideon and Mannino reported an increase of age-adjusted sarcoidosis mortality of 23% in males and 32% in females between 1979 and 1991.[50] A concurrent, French national study demonstrated a similar, secular increase in sarcoidosis standardized mortality between 2002 and 2011. Employing their age-adjusted sarcoidosis mortality rate data from Table 1., I

calculated a least-squares linear regression slope indicative of a 7% annual increase. However, the probability of a difference from horizontal (no increase) did not achieve a significant level ($p = 0.11$). The French investigators hypothesized that the observed increase possibly reflected a higher likelihood of diagnosis due to increased CT imaging.[51] This explanation seems implausible because sarcoidosis of sufficient severity to prove lethal does not require sophisticated imaging for its recognition.

Summary

The natural course of sarcoidosis is highly favorable, with an expected mortality, under conservative management, of less than 1%. Because the majority of patients with pulmonary sarcoidosis resolve spontaneously, it is essential to provide a run-in period of observation among potential treatment candidates (in whom symptom severity does not mandate immediate intervention) to observe for this effect. Adherence to this policy will reduce treatment-induced harm. The evidence that unselective administration of CST leads to increased mortality is compelling. The presumptive mechanism is a drug-induced conversion from a T_H1 (inflammation succeeded by resolution) to a T_H2 (fibrogenic) profile mediated by IL13 and TGF-β,[52] which effectively suppresses spontaneous resolution. Strict adherence to the sole categorical pulmonary therapeutic indication promulgated in the two, joint, thoracic society guidelines,[53,54] (progressive disease evidenced by increased radiographic shadowing, increased dyspnea and worsening pulmonary function), would be expected to improve long-term outcomes.

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CHAPTER SIX

NEOPLASIA IN THE ETIOLOGY OF SARCOIDOSIS

Introduction

In the syndromic conceptual framework advanced in Chapter 2, a causal candidate for sarcoidosis cannot be dismissed on grounds that it is not universally present. This and the two following chapters advance evidence supporting three plausible causal candidates which collectively account for, at most, a small minority of cases. The numerical prevalence and preponderance of occult sarcoidosis (lanthanic, autopsy-identified) combined with their unknown mean duration (from which its true lifetime prevalence might be estimated) indicate that the lifetime incidence of sarcoidosis is quite high. However, computation of lifetime incidence requires an estimate of its (unknown) mean duration (i.e., natural history). Autopsy Prevalence (P) = incidence (I) × duration (D); I = P/D. Based on the magnitude of its lanthanic incidence, it appears reasonable to conjecture that the usual causal antigens are both diverse and commonplace.

A 2019 Medline search for "sarcoidosis AND neoplasia" returned more than 4,000 citations. The granulomatous component has been variably characterized as "sarcoid-like," "sarcoid reaction," "sarcoidosis," and, more recently as "paraneoplastic sarcoidosis."[1] The nature of the association was variably regarded by the authors as non-existent, causal, casual (fortuitous), or uncertain. When authors inferred causation, malignancy was most often ascribed to sarcoidosis. The adjectival choice depended on the author's nomenclatural proclivity and whether he conceptualized sarcoidosis as a disease *sui generis* or an etiologically-nonspecific-response to unassimilable tumour antigens ("nondegradable remnants."[2])

The origin of this terminological ambiguity and differing causal attribution resides in the combined effects of a definition of sarcoidosis that

categorically excludes the diagnosis in instances in which a plausible causal agent is identified and the difficulty in assigning temporal precedence to two disorders—neoplasia and sarcoidosis—when both occur in the same individual, for the inception of each is typically insidious and therefore indefinable. The relationship remains a vexed issue: whether the association is fortuitous or causal has been disputed. Some advocates of a causal relationship have advanced the hypothesis that sarcoidosis predisposes to neoplasia; others have suggested that sarcoidosis is an infrequent response to neoplasia, or that there is a common cause e.g., infection. These hypotheses are not mutually exclusive.

Limitations of Epidemiological Analysis

Epidemiological studies of the association are hindered by systemic impediments: Preexistent sarcoidosis in unscreened populations is underascertained because a large proportion of such individuals are asymptomatic. More than 90% of cases are clinically and radiographically inevident (lanthanic), ascertainable only at autopsy.[3] The medical history of individuals with malignancy is unlikely to routinely include the presence/absence of a past history of sarcoidosis, and patients may not volunteer this information. Sarcoidosis is uncommon, and few cases co-occur with neoplasia. Thus, very large populations plus assured 100% reportage are required to demonstrate a significant increase in incidence of malignant neoplastic disorders in sarcoidosis and to identify with which specific types it is associated. Exclusion of cases in which identification of the neoplasm preceded the appearance of sarcoidosis based on the *a priori* assumption that sarcoidosis is a risk factor for neoplasia, serves to weaken epidemiological evidence of an association. While epidemiological evidence links sarcoidosis with malignant myeloproliferative disorders, lymphomas, (uterine) cervical, lung, breast and testicular cancer, it has been reported with a variety of solid malignancies. Thus, evidence of causation is less convincing than in instances where one or two types of neoplasms are associated with the putative cause e.g., lung cancer and malignant mesothelioma in persons with asbestosis. Furthermore, testing the incidence of all neoplastic entities in the sarcoidosis population against the incidence of all neoplastic entities in the source population weakens the statistical power of any identified specific associations because, in effect, it is a test of multiple hypotheses. Excess ascertainment, due to the employment of chest radiographic staging of malignancy, is likely to result in spurious associations by identifying subclinical (ascertainable) instances of sarcoidosis. Misattribution of hilar adenopathy to metastatic disease will

have the reverse effect. Misclassification as "sarcoidosis" of intratumoral, local lymphatic and regional granulomatous reactions is not infrequent. For example, in compiling our experience with the association, we identified 16 positive instances in a cross-match of 243 sarcoidosis cases with 30×10^3 cancer cases in our Kaiser Permanente, NW Region Tumor Registry. Of 10 who met our proposed linkage criteria (see below), only 6 (2.5% of the 243 sarcoidosis cases) were confirmed on review of medical records; 4 had been were misclassified, most frequently by designating as sarcoidosis a local granulomatous response. Misclassification is likely to occur more often in lung cancer because of the frequent employment of staging mediastinoscopy, which may demonstrate non-caseating epithelioid granulomas (NCG) in the sampled lymph nodes. In contradistinction to epidemiologic studies in which antecedent event is clear and the variety of consequent neoplasms narrowly delimited e.g., cigarette consumption and lung cancer, or asbestos exposure and mesothelioma, and in which the reverse causal effect is biologically implausible (*e.g.*, the propensity to smoke cigarettes simultaneously confers susceptibility to lung cancer), the opposite obtains in sarcoidosis and malignancy, where the sequence of events is often unverifiable and the variety of neoplasms, unlimited. Compilers of sarcoidosis registries do not invariably require tissue verification. Moreover, it is intuitively tenuous to credit the provisional assignment of sarcoidosis as a causative agent when (employing cancer and sarcoidosis registries) the co-occurrences are temporally remote e.g., sarcoidosis at age 25 succeeded by lung cancer at age 65.

Validity and Causal Assignment in Population Studies

Several investigators, intrigued by the association in case reports, endeavoured to inductively confirm and quantify a non-fortuitous coexistence, identify the at-risk malignancies, and understand its mechanism(s). Brincker and Wilbek,[4] in 1972, proposed a causal relationship, basing their conclusion on an excess of cancer coinciding with or following a diagnosis of sarcoidosis—48 cases vs. 34 predicted—in a crossmatch of the National Sarcoidosis Registry comprising 2,561 subjects against the National Malignancy Registry compiled by the Danish government. The excess cases were confined to two varieties: lung (9), and lymphoma (6). The authors hypothesized that sarcoidosis predisposed to the development of malignancy due to (putative) impaired immunologic surveillance, or, in the case of lymphomas, that (putative) sarcoidosis-augmented-lymphocytic-mitosis increased the likelihood of malignant lymphocytic transformation ("mitogenesis begets mutagenesis.") Brincker went on to

update and summarize his understanding of the relationship between sarcoidosis, sarcoid reactions to cancer, and sarcoidosis in the genesis of cancer in a 1986 review:

Abstract

Tumor-related tissue reactions resulting in the formation of epithelioid-cell granulomas have been known for almost 70 years. Such sarcoid reactions may occur in lymph-nodes draining an area housing a malignant tumor, in the tumor itself, and even in non-regional tissues. Overall, sarcoid reactions occur in 4.4% of carcinomas, in 13.8% of patients with Hodgkin's disease, and in 7.3% of cases of non-Hodgkin lymphomas. Similar histologic changes in sarcoma appear to be extremely rare. Most probably, sarcoid reactions are caused by antigenic factors derived from the tumor cells, eliciting an immunological hypersensitivity reaction leading to the formation of epithelioid-cell granulomas. Sarcoid reactions may be a marker of an immunologically mediated antitumor response of macrophages activated by T-lymphocytes, and in Hodgkin's disease there is evidence that patients with sarcoid reactions have a better prognosis. On occasion sarcoid reactions may be so extensive that they complicate the diagnosis of an underlying malignant disease. Problems may also arise of distinguishing between tumor-related sarcoid reactions and true systemic sarcoidosis.[5]

Hagerstrand and Linell observed an excess number of malignancies in persons with sarcoidosis furnishing support of Brincker and Wilbek's views in their report of 6,706 autopsies performed in Malmo, Sweden. They found definite evidence of sarcoidosis in 43 autopsies (incidence, 6 $\times 10^{-3}$) and sarcoid reactions in an additional14; 22 of the 43 (51%) with sarcoidosis died of malignancy (90% CI, 38.5-63.5) vs. "slightly less than 40%" malignancy-caused deaths" in the autopsied population.3

Epidemiological assessments based on *sarcoidosis registries,* however*,* have uniformly failed to demonstrate persuasive evidence of an association. Brincker's conclusions were challenged by Battesti et al.[6], who found only 7 (1.2%) instances of malignancy in a population of 580 sarcoidosis patients, a number they judged too small for valid statistical comparison with the predicted population incidence. They reported no plausible temporal latency between the occurrences that would have been required were sarcoidosis to generate a dimensionally-ascertainable malignancy, for the malignancy in each instance was either present

simultaneously or became apparent within just a few years following the diagnosis of sarcoidosis. Additionally, the advanced mean age (51) of the subjects rendered implausible, in the judgement of the investigators, attribution of causation to sarcoidosis. Rømer et al.,[7] reported on the follow-up of 555 Danish sarcoidosis patients observed for 9- to 30-years. Linkage with the nationwide Danish Cancer Registry showed no excess of observed cancer over the expected number (O/E ratio), and no increase in the occurrence of malignant lymphomas. Rømer reviewed the cases cited by Brincker and concluded that some of the excess was attributable to misclassification. In rebuttal, Brincker, in an effort to refute these negative assessments, reviewed 131 published case reports of the association. He concluded that sarcoidosis was associated with lung cancer and malignant lymphoma more often than expected by chance.[8] In a more recent Danish National Registry report, Søgaard et al. compared the incidence of cancer in 12,890 patients, identified over 31-years, with a first-time sarcoidosis diagnosis in the Danish National Registry of Patients vs. the Danish National Cancer Registry. Patients diagnosed with cancer before the date of sarcoidosis diagnosis were excluded. They found 1303 incident cancers, standardized incidence ratio (SIR) = 1.3, over a median 10-year follow-up. "The majority of cancers occurred in patients aged 50- to 69-years." The median age at diagnosis of sarcoidosis in the cancer subjects was 40. The cancer risk was particularly high within the first 3 months following a diagnosis of sarcoidosis. The excess was confined to lung, tonsil, Hodgkin's and non-Hodgkin's lymphoma; the association with the last was noted to be "persistent and strong." The investigators concluded that: ". . . the increased short-term risk of cancer most likely reflects the presence of occult cancer, and that reverse causality, misclassification and increased early surveillance may explain the association for at least the first 3 years after diagnosis."[9]

In summary, evaluations of the proposed relationship, based on cross-registry evaluation, have demonstrated a modest association: Two epidemiological analyses reported from Scandinavian countries employed linkage of sarcoidosis registries with national cancer registries. Both tested the hypothesis that sarcoidosis was a risk factor for the development of neoplasia. On the basis of this premise, each analysis excluded, *a priori,* cases in which the diagnosis of cancer preceded, coincided with, or occurred within one year following the diagnosis of sarcoidosis:

Seerholm et al.[10] reported 33 cancers vs. 23 expected in 254 patients with previous sarcoidosis followed for a median period of 25 years, a standardized incidence ratio (SIR) of 1.4 (95% CI, 0.99, 2.0.) They found

one case of non-lymphocytic leukemia and no cases of lymphoma. The authors concluded that their findings did not confirm an association between sarcoidosis and malignancy. They attributed the reported association in other studies to selection bias and misclassification.

Askling et al.,[11] in a larger study of similar design, employing two sarcoidosis registries comprising 9,015 persons matched against a national cancer registry, reported 703 cancers. Fifty developed in the smaller (Uppsala) cohort of 474 persons, an SIR of 1.2 (95% CI, 0.9-1.6); and 653 developed in the larger (Inpatient) cohort of 8,541 persons, an SIR of 1.3 (95% CI, 1.2-1.4). The excess originated in the lung, stomach, small intestine, liver, and skin. There was an excess of non-Hodgkin's lymphoma and leukemia, principally non-lymphocytic leukemia (12 cases, $p = .01$). The authors postulated that the increased frequency of neoplasia was mediated by chronic inflammation due to sarcoidosis and suggested that the agent responsible for sarcoidosis might increase the risk of development of malignant myeloproliferative and lymphoproliferative disorders. The authors reported that 6 of 474 persons in the Uppsala cohort and 538 of 8,541persons in the Inpatient cohort had cancer prior to entry and that 2 of 6 and 146 of 538, respectively, developed cancer during the first year of sarcoidosis follow-up. These cases were excluded to circumvent the possibility of misclassification of sarcoid reactions as sarcoidosis. Consequently, they did not furnish SIR figures.

Bonifazi et al., in a metanalysis of 16 studies reporting on cancer and sarcoidosis and involving >25,000 patients, reported relative risks (RR) for invasive cancer of 1.19 (95% CI, 1.07,1.32), and RR = 1.92 for hematopoietic malignancies. They excluded cases in which the diagnosis of cancer preceded that of sarcoidosis. The investigators concluded that there was a moderate association.[12]

Some investigators have challenged the *a priori* exclusion of pre- or coexistent- sarcoidosis: Israel,[13] in a critical analysis of the 1972 Brincker study, pointed out that the investigators excluded 17 cases in which the diagnosis of the neoplasm preceded the diagnosis of sarcoidosis; that 7 of the 15 cases of lung and lymphomatous neoplasms were diagnosed within one year of the diagnosis of sarcoidosis (which implies that the sarcoidosis might have been a response to the neoplasm); and that the excess malignancies occurred only during the first four-years of follow-up. Israel emphasized that, were the excess malignancies due to impaired immune surveillance, they should not have been confined to two types and should not have been concentrated in the first few years of follow-up. His critical

observations were seconded by Askling's cross-registry analysis, in which the SIR of lung cancer was highest in the 1-4-year sarcoidosis follow-up (2.5), less in the 5-9-year period (1.6), and thereafter was lower than predicted (0.5). Similarly, the SIR of myeloid leukemia (3.0) was highest during the 1-4-year follow-up.[11]

A singular case report puts in question the then prevailing epidemiological rationale in which sarcoidosis is hypothesized *a priori* to be the causal agent. Rubin et al.[14] reported a patient who presented with headache and was found to have hypercalcemia and bitemporal hemianopsia. Transsphenoidal resection of a pituitary adenoma demonstrated intratumoral granulomas consistent with sarcoidosis. The serum angiotensin converting enzyme (ACE) was elevated at 133 U/L, and transbronchial biopsy showed non-caseating granulomas. In this instance, one's causation choice depends on his assessment of which interpretation is more plausible: the patient had (systemic) sarcoidosis which fortuitously localized within the pituitary adenoma, or, an intratumoral granulomatous response to a pituitary adenoma evolved into a systemic one.

The conflicting data (and interpretations) can be resolved by distinguishing as conditional incidences those derived from the two inductive methodologies. In inferring causation, it is essential to distinguish between the incidence (I) of cancer (C) in sarcoidosis (S) registries vs. the incidence of sarcoidosis in cancer registries. The former is a conditional estimate of the incidence of cancer given sarcoidosis. Borrowing from statistical notation, it is designated as I(C/S). The latter is designated I(S/C). The former uniformly showed no excess incidence; the latter uniformly showed somewhat less than twice the expected incidence. $I(C/S) \neq I(S/C)$. The association is valid, but it applies solely to the incidence of sarcoidosis in the presence of cancer, which implies that cancer is the causal agent. If sarcoidosis contributed to the development of cancer, it should have been evident (and was not) during long-term follow-up among 1,135 cases of sarcoidosis reported by Battesti[6] and Rømer.[7]

Sarcoidosis as a Response to Malignancy

Herron et al.[1] recently reported on 289 patients with histologically confirmed sarcoidosis observed over a 6-year period in one center. Fifty (17%) had a prior or concomitant diagnosis of hematological malignancies and of cancers originating in various organs. Furthermore, 66% of sarcoidosis diagnoses, which typically simulated metastatic disease, were established within the first year of their malignancy diagnosis.

Grados et al.[15] reported on 12 cases of sarcoidosis succeeding a diagnosis (and treatment) of solid (predominantly breast) cancers in three French departments of internal medicine and one French oncology department between 2009 and 2014. The median interval for the appearance of succeeding sarcoidosis was 35-months; range, 7 to 82-months. The median age at cancer diagnosis was 54. Eight of the 12 received chemotherapy/radiotherapy; sarcoidosis appeared within the three years. Within a median follow-up of 73-months, none of the 12 with sarcoidosis experienced a cancer relapse. The authors reviewed the literature and found 110 reported cases with a similar sequence. They concluded that sarcoidosis conferred protection against relapse.

Hunt et al. [16] reported from Swedish Medical Center and Swedish Cancer Institute, Seattle, WA that 41 (of 565 performed) mediastinoscopies confirmed sarcoidosis of which 21 were undertaken to exclude metastasis following a diagnosis of cancer. No primary cancer type was predominant. Butt et al.17 reported from Karmanos Cancer Center and Wayne State University School of Medicine on 30 patients with confirmatory non-caseating granulomas, predominantly intrathoracic, obtained subsequent to the diagnosis of cancer with a mean interval of 27.6 months (range 3 to 245 months). Inoue et al.,[18] identified 4 of 376 oncologic cases in which non-caseating granuloma were found on hilar or mediastinal nodes at a post-antineoplastic treatment interval of 9-to 72-months. Suen et al. reported sarcoidosis shortly succeeding treatment of three cases of malignant lymphoproliferative disorders and one case of breast cancer. The investigators concluded that these reflected a “malignancy-sarcoidosis syndrome.”[19] Arish et al., reported a marked increase sarcoidosis succeeding breast cancer and lymphoma. The authors’ decision to exclude cases in which the diagnosis of sarcoidosis coincided with the diagnosis of a malignant neoplasm doubtlessly led to an underestimate of the connection.[20] Conversely, Laverby identified only a single instance of sarcoidosis in a retrospective study of 7,344 patients with pulmonary neoplasms.[21]

An association with testicular cancer (whose peak age occurrence coincides with the peak age incidence of sarcoidosis) has been far more frequently reported than would be expected by chance. One plausible explanation is that the subjects’ ages impose a higher likelihood that they will develop a systemic granulomatous response (SGR) to the cancer. Sarcoidosis succeeded or coincided with malignancy in almost all reported cases. Rayson et al. reported on testicular cancer associated with sarcoidosis in the Mayo Clinic between 1950 and 1996. In 12 of 14

instances, cancer (median age, 31.5) preceded sarcoidosis by ≤5-years. The authors estimated a cumulative incidence of the co-occurrence of sarcoidosis in patients with testicular cancer of 617×10^{-5}, "an approximate 100-fold increase compared with the general population of young White men." They suggested that testicular carcinoma vs. other solid tumors has the strongest association with sarcoidosis.[22] Paparel et al. in a literature review found 64 cases of testicular cancer associated with sarcoidosis. In 35, the diagnosis of cancer was prior in time; and in 20, concomitant.[23] One might postulate that the high incidence of co-occurrence of sarcoidosis with testicular carcinoma reflects the concordance of the peak age incidence propensity to develop sarcoidosis with the peak age incidence of testicular carcinoma.

The concept that sarcoidosis can generate malignancy rests on unproven assumptions: that its associated immunological dysregulation confers this propensity; that increased mitotic rate will lead to neoplastic hematological evolution; and that its inflammatory feature will engender neoplastic transformation. Four considerations strongly suggest that when neoplasia and sarcoidosis co-occur, the granulomas are a systemic response to the neoplasm:

1. If the "sarcoidosis engenders neoplasia" sequence were correct, one would expect malignant transformation predominantly in the most frequently involved organ, the lung. It does not. Conversely, where the succession is identifiable, sarcoidosis evolves principally following cancer in organs that are infrequently affected by sarcoidosis: breast, uterine cervix and testicles. Conversely, were sarcoidosis a response to neoplasia, it would be expected to co-occur with the most frequent types of neoplasms: lung, breast, and uterine cervix.

2. If sarcoidosis engendered the development of neoplasia, one would expect the latter to appear in the peak age incidence range of the former. Instead, the median age at which the association is reported exceeds the former by more than two decades.

3. Intratumoral, local and regional granulomatous responses to cancers originating in a variety of organs are widely acknowledged. To infer that a systemic granulomatous response (SGR) has a fundamentally different source or pathogenesis doubly violates Occam's razor (*entia non sunt multiplicanda praeter necessitatem*) by invoking two, additional, untenable postulates: a) the existence of a transdiaphragmatic barrier, impermeable to lymphocytes, dendritic cells, and cytokines, an entity

which prevents local and regional responses from becoming systemic; b) that, when a SGR (vs. a local or regional GR) co-occurs with a malignant neoplasm, the cause-effect relationship is reversed.

4. Based on what we know of the natural history of malignant neoplasms and sarcoidosis, were the latter causal, one would expect a latency of decades before the neoplasm crossed the dimensional threshold required for its ascertainment. Judging from the temporal pace of acute onset sarcoidosis and of a positive Kveim test, a SGR can be mounted within weeks. Conversely, an interval of decades elapses between exposure to the known carcinogens of lung cancer and mesothelioma and the recognition of the malignancies they induce. Assuming: a) three-year latency for chronic sarcoidosis exposure (the association has been observed exclusively among individuals with chronic sarcoidosis) to generate a malignant neoplastic clone; b) exponential tumor growth; and c) tumor volume doubling time of 180-days, 20-years would be required to produce a clinically evident, 2.5-cm tumor. (The number of tumor volume doublings, X, needed to attain a diameter D (in cm) is: $X = \log 1000D \div \log 1.26$.)[24]

Specific Neoplasms in the Genesis of Sarcoidosis

Evidence for an excess of certain malignancies in sarcoidosis has been most convincing for lung cancer,[9,25] lymphoma (particularly Hodgkin's disease),[4,9,20,26,,27] testicular, [23,28,29] and uterine cancer.[28,30] Numerous case reports support a disproportionate association with acute myeloblastic leukemia,[31,32,33,,34,35,26,36,37,] and other myeloproliferative disorders.[38,39,40,41,42,43,44, 45] Three reports of breast cancer associated with sarcoidosis [19,22,46] are noteworthy both because of the close temporal proximity of the association and the observation that, as in other treated malignancies,[46,47,48] sarcoidosis succeeded therapy expected to induce tumor necrosis, implying that it might represent a systemic response to dispersal of tumor antigens.

If one views the genesis of the SGR characterizing sarcoidosis as a systemic response to inefficiently or incompletely processed antigens, one would expect it be most frequent in systemic malignancies whose antigens are widely dispersed at outset, *i.e.*, malignant lymphocytic and myeloproliferative disorders.[49]

Linkage Analysis of Malignancy-associated Sarcoidosis

Because of the limitations of conventional, inductive means of confirming causality, we adopted a different methodology, one that employed convincing particulars of the individual associations suggesting, largely by means of deduction, that the association was not fortuitous. We hoped to furnish convincing evidence of causation by employing the cumulative weight of seven criteria supporting the view that the two were linked. We crossmatched the Kaiser Permanente Northwest Region (KPNW) Tumor Registry comprising 30×10^3 cases observed over a 32 years period against a sarcoidosis registry of 243 cases observed over 24 years. We reviewed the medical records of 241 persons identified by the Tumor Registry as having Hodgkin's disease to detect an association with sarcoidosis.

The proposed linkage criteria supporting an etiological relationship were:

1. Multiple precedent reports of the associated malignancy—uterine cervix, testicle, lung, breast and lymphohematogenous.
2. Low-probability estimates of a chance association, particularly when supported by multiple case reports.
3. Close temporal proximity of sarcoidosis and malignancy.
4. Late age of onset of sarcoidosis.
5. Atypical evolution of malignancy in the presence of sarcoidosis/ atypical evolution of sarcoidosis in the presence of malignancy.
6. Preferential sparing of granuloma-containing lymph nodes from malignant encroachment.
7. Local sarcoid reactions which later become systemic. Individuals whose systemic granuloma predominate in the lymphatic drainage of their solid tumors were judged to have fulfilled this criterion. [50]

We found reported malignancies in 16 individuals with sarcoidosis in cross-matching the two registries: uterine cervix, 4; colon, 3; breast, 3; acute myeloblastic leukemia, 1; ovary, 1; brain, 1; bile duct, 1; lung, 1. Review of their medical records showed that the diagnosis of sarcoidosis was erroneous in 4 due to misclassification in 2, and lack of histologic verification in 2. The Tumor Registry inclusion of a histologically benign meningioma was considered a misclassification. In total, 5 of 16 individuals (31 percent) were misclassified. Of 11 individuals with this co-

occurrence, 9 were female, reflecting the preponderance of gender-specific neoplasms encountered in 7. We found evidence of linkage, which is the most practical means of judging the likelihood of causality, in 6 (2.5%) of the 243 cases of sarcoidosis.

The justification of criteria 1 through 3 is self-evident. We inferred linkage when one or more criterion was satisfied. Two or more linkage criteria were met by 12 of the 16 cases. I included the one person with a necrotizing granulomatous response to an ultimately fatal lymphoproliferative disorder because necrosis may be considered an indicator of intensity rather than a specie of response. When the temporal interval rendered association unlikely, we classified linkage as "uncertain." Each person exhibiting linkage had either close temporal proximity or simultaneity of both diagnoses, and 12 of 16 (75%) were types of malignancy associated with sarcoidosis in published reports. Details of the statistical assumptions and methodology for the analysis are provided in the reference.[50]

In total, 11 of 243 (4.5 percent) patients with systemic non-caseating granuloma (NCG) classified as sarcoidosis had an associated malignancy. All 3 of the 11 individuals who presented with stage 0 exhibited linkage (each presented as an undifferentiated febrile illness); and each of the 8 remaining persons with intra-thoracic sarcoidosis presented with stage I ($p = .14$). None exhibited pulmonary shadowing.

I reviewed the medical records in a separate analysis of 241 persons classified as having Hodgkin's disease (HD). This number included 18 (7.5%) with non-Hodgkin's lymphoma misclassified due to a software error. None had associated sarcoidosis.

Criterion 1. Multiple precedent reports of the associated malignancy:

Gorton et al.,[35] in an analysis of sarcoid reactions to malignancy in regional lymph nodes, reported that: a) those accompanying cancer of the cervix were seen with more than three times the aggregate frequency of malignancy originating in all other sites when one excepted breast cancer, the second most common cause; b) sarcoid reactions were present in 24 (8%) of persons with carcinoma of the cervix. (All had undergone prior radiation therapy, which would be expected to generate and disseminate tumor antigens.) None had a SGR. Among 8 cases in the cross-registry data in which malignancy preceded sarcoidosis, Brincker found that 6 (75 percent) had cervical carcinoma.[3] In our cross-match, 3 individuals who

met multiple linkage criteria of sarcoidosis and malignancy had squamous carcinoma of the uterine cervix.[50]

Criterion 2. Low probability estimates of a chance occurrence:

Two individuals had myeloproliferative diseases in association with sarcoidosis, a previously reported association. The number of associated cases expected if the conditions were independent = 0.11. The observed-to-expected (O/E) ratio, 2/0.11 = 18.1 (95% CI 12.2, 24.0).[50]

Criterion 3. Close temporal proximity:

Statistical inference: the chance occurrence of two unrelated events in one individual is computed by multiplying the product of the annual incidence of each event by the square of years at risk for each. Thus, for example, the presence of two events separated by five years is 25 times more likely to be due to chance than if both occur within one year. We based our decision to specify clinical manifestation of neoplasia (e.g., evaluated and unexplained anemia) rather than date of histological verification in ascertaining the sarcoidosis-malignancy interval on the consideration that malignancy might be immunogenic for some duration before its aggregate dimension exceeded the diagnostic threshold. In each of the linked cases, both diagnoses were established in close temporal proximity; and in 3 of 7 (43%), their appearance was simultaneous.[50]

Criterion 4. Late age onset of sarcoidosis:

The age at diagnosis of sarcoidosis in cancer subjects was 40 (95% CI, 18-62), almost a decade higher than the mean age at diagnosis of sarcoidosis (31) in the population from which this sample was drawn.[51] Brincker reported that, among the 48 cases in the published literature of lymphoproliferative disorders associated with sarcoidosis, the mean age of onset of sarcoidosis was 46;[30] and Reich noted, among 12 reported individuals with myeloproliferative disorders, the mean age of onset of sarcoidosis was 45.[27,52] If sarcoidosis entered into the genesis of cancer, one would expect the mean age at which it was diagnosed to correspond to its mean age at diagnosis in the population. Conversely, were sarcoidosis (among the cases exhibiting linkage) a response to malignancy, one would expect the mean age at diagnosis of sarcoidosis to be higher than that of the sarcoidosis population, reflecting the advanced age at diagnosis in subjects with most malignancies.

Criterion 5. Atypical evolution of malignancy in the presence of sarcoidosis:

Evidence that sarcoidosis modifies the course of coexistent malignancy constitutes the most persuasive evidence that sarcoidosis is a response to the malignancy. Favorable alteration of the predicted natural history of a malignant neoplasm is the best evidence of this effect:

Hodgkin's disease (HD): O'Connell et al.[53] and Sacks et al.[54] independently observed that the presence of NCG among individuals with Hodgkin's disease was associated with a more favorable outcome. Sacks reported (in surgically staged patients) higher five-year and five-year relapse-free survival in the cohort with NCG in organs usually unassociated with the primary disease (most commonly, spleen and liver) than in those lacking this finding.

Chronic myelogenous leukemia (CML): Cheng et al.[42] reported a striking case of disease course modification. A patient with a strong family history of sarcoidosis presented with chronic myelogenous leukemia. A chest radiograph, obtained at diagnosis, was normal. Histologically confirmed, stage II sarcoidosis developed four months after a course of busulfan. Following this single course, he remained in in remission when last seen, six years later.[55]

Acute myelogenous leukemia (AML): A young woman presented with two weeks of unexplained fever, mild anemia and leukopenia. A chest radiograph showed diffuse pulmonary shadowing; one taken in the previous year demonstrated bilateral hilar adenopathy. A bone marrow biopsy showed no diagnostic changes; the consulting hematologist concluded that she had impaired erythrocyte and leukocyte release of unknown cause. A transbronchial lung biopsy demonstrated NCG. Four years later, progressive anemia led to a bone marrow aspiration and bone marrow biopsy, which, respectively, demonstrated numerous myeloblasts and NCGs. She died of acute myeloblastic leukemia (AML) one year later, 6-years after the onset of sarcoidosis. Neither the hematopoietic disturbance evident at the diagnosis of sarcoidosis nor the smoldering progression of her AML are characteristic of the disease, and their combination suggests an interaction in which sarcoidosis suppressed advance of the leukemia.[56] Murphy et al. reported a case with virtually identical features and an interval of 10-years between the onset of sarcoidosis accompanied by an unexplained normochromic, normocytic

anemia and fatality due to AML.[57] Hermann et al., reported a similar case with a 4½-year interval between the two disorders.[58]

Lung cancer: Lynch et al.[43] reported a case of a 66-year-old man with pulmonary shadowing associated with a steroid-refractory, undifferentiated febrile illness. Open lung biopsy demonstrated NCG. His fever promptly remitted following chemotherapy for small cell cancer of the lung diagnosed one year after the onset of the febrile illness.[59] He remained recurrence-free when last evaluated two years after this single course of chemotherapy, an atypically favorable response.

Criterion 5. Atypical evolution of sarcoidosis in the presence of malignancy:

Recurrence of sarcoidosis years after spontaneous remission is a rare event: Romer reported a single instance of relapse (0.4%)--which took place within one year of complete resolution--among 243 persons with intrathoracic sarcoidosis followed for one to 10 years.[60] Recurrence in the setting of neoplasia implies that the affected individual, who previously demonstrated a constitutional propensity to produce a NCG in response to an unidentified antigen, has responded in the same way to antigens of a malignant source. Recurrence (or re-activation) of sarcoidosis years after its spontaneous remission, was exhibited by Whittington's second case,[61] in two of the seven cases cited by Battesti et al.,[6] in the two AML cases reported by Nordenson,[36] and in a patient with primary renal cell cancer reported by Campbell and Douglas-Jones.[41,62]

Criterion 6. Preferential sparing of granuloma-containing lymph nodes from malignant encroachment:

Brincker noted that in six series of patients with local lymphatic sarcoid reactions to solid malignant neoplasms, malignancy was four times more likely to be absent than present, suggesting that these lymph nodes are preferentially spared. He reported that in patients with Hodgkin's disease, hepatic lymphomatous involvement occurred in only 3 of 55 individuals with hepatic NCG.[63]

Criterion 7. Local sarcoid reactions which later become systemic:

This evolution suggests that the granulomatosis is a systemic reaction to the neoplasm. Brincker reported two patients with HD in whom NCG, evident initially only in regional lymph nodes and interpreted as sarcoid reactions, developed systemic granulomas 5 and 17 years later.[8] Case 1, an

individual with SGR and invasive cervical cancer, exhibited extensive granulomatous change in her parametrial lymph nodes.[50]

Experimental support of causation could, hypothetically, be provided by demonstrating a granulomatous response to intradermal injection of autologous, modified, tumor cells (with suitable controls) among individuals with both sarcoidosis and malignancy or by a lymphocytic transformation test using the same source. A Bayesian approach to establishing evidence of causation would employ the likelihood ratios: (probability of the cited evidence that sarcoidosis generates a malignancy) ÷ (probability of the cited evidence if there were no relation). Lacking numerical data, one can only intuit an estimate.

Summary

1. Malignant neoplasia is an infrequent cause of sarcoidosis

2.. Granulomatous responses to neoplasia comprise a continuum: intratumoral, draining lymphatic, regional organ and systemic. The last is indistinguishable from sarcoidosis.

3. Recognition that sarcoidosis may be associated with malignant neoplasms will prevent confusion when they co-exist.

4. Patients with malignant neoplasms exhibiting a clinical and radiographic pattern consistent with sarcoidosis should have that diagnosis excluded to forestall inappropriate therapy for metastatic malignancy.

5.. This immunological response often confers a favorable prognosis

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CHAPTER SEVEN

TUBERCULOSIS IN THE ETIOLOGY OF SARCOIDOSIS

In his 1960 presentation to the Royal College of Physicians of London, basing his remarks on his extensive consultation experience, Scadding addressed the vexed subject of the etiology and nature of sarcoidosis and its relationship to tuberculosis. He emphasized that:

> a definition incorporating . . . a disease of unknown aetiology is self-stultifying . . . [it leads to the] exclusion from the category any case in which a causative agent can be identified. An investigator that adheres to such a definition must exclude from the category 'sarcoidosis' any case in which a causative agent can be identified, and thus this definition closes his mind to some tenable views concerning aetiology." Scadding advanced the view that ". . . sarcoidosis may be a reaction to an agent or agents already known, but difficult to demonstrate in this particular manifestation." He advocated replacing the current definition with a purely histological one that lacked *a priori* requirements: "Sarcoidosis is a disease characterized by the presence in all affected organs of epithelioid-cell tubercles without caseation, the older lesions tending to become converted into hyalinized fibrous tissue." He suggested that in instances with a known etiology, that the term should be added, e.g., "beryllium sarcoidosis.[1]

The balance of his presentation dealt with the findings in 29 cases of sarcoidosis (of 230 referred for consultation) in which tubercle bacilli were isolated at some stage in their evolution. In 5 they were first isolated at the time of a change from the clinical picture of sarcoidosis to caseating tuberculosis. In 6 they were isolated before the appearance of manifestations of sarcoidosis, at a time when the clinical picture was tuberculosis; *i.e.*, they represented examples of sarcoidosis following overt tuberculosis. In 5 additional cases, there was a history of past tuberculosis but no confirmation of tubercle bacilli isolation. In the remaining 18, tubercle bacilli were isolated in very small numbers, unaccompanied by

any change in the clinical (sarcoidosis) picture. Scadding justified classification of these cases as "sarcoidosis in which tubercle bacilli were found" rather than tuberculosis succeeding sarcoidosis on these distinguishing criteria: their clinical course, tuberculin insensitivity, radiographic pattern, lack of response to antituberculous treatment, response to corticosteroids, prognosis, and absence of other evidence of caseating tuberculosis did not differ in any way from the remaining 201 persons in the consultation series.

He concluded:

> 1. that ". . . no clear line of demarcation can be drawn between sarcoidosis and certain cases which would be accepted as indolent tuberculosis with low tuberculin sensitivity. . .. no reason why the categories 'tuberculosis' and 'sarcoidosis' should be mutually exclusive."
>
> 3. that ". . . low sensitivity of patients with sarcoidosis to agents producing tuberculosis type [DTH] reactions . . . is one aspect . . . of the tissue reactivity of these patients which determines that they develop sarcoidosis in response to an agent or agents more commonly associated with changes of another type."
>
> 3. that "The cause of sarcoidosis must be sought as much in the altered reactivity of the host as in external causative agents."
>
> 4. that ". . . the proportion of cases associated with each [agent] may vary."

Several research institutions have reported PCR detection of mycobacterial DNA from bronchoalveolar lavage (BAL) of individuals with confirmed sarcoidosis. For example, Saboor et al. reported that M tuberculosis DNA was PCR-identified in half, and non-tuberculosis mycobacterial DNA in a further 20% of 20 persons referred to University College and Middlesex School of Medicine for confirmation of sarcoidosis. The investigators qualified their findings by noting a false-positive institutional PCR rate of 9% for M tuberculosis. They concluded, "The findings that a significant proportion of the sarcoidosis patients in this study have mycobacteria in their lungs and that most of these mycobacteria belong to M tuberculosis complex suggest an etiological role for mycobacteria in sarcoidosis."[2]

To ensure that the identified mycobacterial remnants are engaged in the pathogenesis of sarcoidosis and not merely bystanders, *i.e.*, residuals of a

resolved tuberculous infection, it is necessary to show that they generate an ongoing immunological response. Song et al. demonstrated serum immune reactions to Mycobacterium tuberculosis catalase-peroxidase (mKatG) in proteinase-K digested sarcoidosis tissue in 9 of 12 patients with sarcoidosis and in 3 of 22 controls. They reported circulating anti-mKatG IgG in the sera of 12 of 25 (48%) sarcoidosis patients compared with 0 of 11 PPD-negative, healthy controls.[3]

With the same objective, Oswald-Richter et al., evaluated 31 sarcoidosis patients, 9 non-tuberculous mycobacterial infection controls and 14 PPD-negative controls. They employed flow cytometry to assess the T_H1 immune response to multiple mycobacterial antigens, ESAT-6, mKatG, Ag85A, sodA, and HSP. They reported that BAL-derived alveolar T-cells in 22 of the 31 sarcoidosis patients produced a CD4+ response, and 18 a CD8+ response to at least one of the mycobacterial antigens. “The detection of proliferation upon stimulation with the mycobacterial virulence factors demonstrates that these responses are initiated by antigen specific recognition.” They concluded: “Together these results reveal that antigen-specific CD4+ and CD8+ T cells responses to multiple mycobacterial epitopes are present within sites of active sarcoidosis involvement, and that these antigen-specific responses are present at the time of diagnosis.”[4]

Wong et al. reported a 35-year-old Chinese woman who experienced coexistent, culture and biopsy-confirmed, tuberculosis and sarcoidosis. She presented with cervical adenopathy and non-cavitary pulmonary infiltrates compatible with tuberculosis. Aspirated material from the cervical lymph node showed caseating necrosis and abundant acid-fast bacilli; culture was positive for M tuberculosis. She was found to have mild thrombocytopenia and elevated alkaline phosphatase, which the authors initially ascribed to systemic spread of tuberculosis. She was treated with INH, PZA and RMP, later changed to INH, SM, EMB, PZA and ofloxacin. The cervical lymphadenopathy improved, but the reduced platelet count and elevated alkaline phosphatase persisted. She was discharged after 8-weeks and readmitted 13-months later because of progressive pulmonary infiltration accompanied by bilateral hilar lymphadenopathy. Her cervical adenopathy had resolved; her platelet count had declined and she had persistent elevation of her alkaline phosphatase. Lung and bone marrow biopsies both showed non-caseating epithelioid granulomas (NCG) compatible with sarcoidosis. Lung tissue and bronchial washings were culture-negative for fungus and acid-fast bacilli. Lung tissue was strongly positive by PCR for the IS6110 target

indicating the presence of M. tuberculosis DNA. She was judged to have sarcoidosis (which is far less common in Asians than Caucasians[5]) and was given corticosteroid therapy (covered by INH) for one year. Her radiographic changes stabilized and her platelet count and alkaline phosphatase normalized. The authors cited many instances of concomitant tuberculosis and sarcoidosis, and posited that some component of the mycobacteria induced the sarcoidosis immune response,[6] a view seconded in the accompanying editorial.[7] Fortuitous occurrence of tuberculosis in a region of high endemicity (Hong Kong) during the course of sarcoidosis is a possible alternative explanation of events. However, progression of her sarcoidosis simultaneous with successful treatment of her tuberculosis supports the view that the NCG were a response to tuberculous antigens. Furthermore, it appears reasonable to surmise that mycobacterial antigen dispersion, in response to their treatment-induced dissolution, would intensify the immunological response.

A vivid recent example of this relationship is supplied in the case report authored by Maalioune and coworkers. Their 38-year-old non-smoking subject presented with a persistent, cough productive of purulent sputum. Chest CT demonstrated a small cavity in the left upper lobe. Tuberculosis was confirmed bacteriologically, and she was treated successfully with standard drug therapy. She returned two years later with [unspecified] respiratory symptoms and joint pain. A chest CT showed bilateral hilar lymphadenopathy and profuse pulmonary nodularity. Ziehl-Neelson staining of BAL was negative; PCR for all mycobacteria (162bp) was positive, but PCR for M tuberculosis (123bp) was negative. Biopsy of a hilar lymph node via mediastinoscopy demonstrated NCG and no evidence of tuberculosis. She was treated successfully with corticosteroid therapy. The authors concluded that the etiology of sarcoidosis is probably multifactorial and that there was

> ". . . a possible role of Mycobacterium tuberculosis in the pathogenesis of sarcoidosis." [8]

Summary

Antigens derived from M tuberculosis may be added to antigens derived from neoplasia and histoplasmosis as potential causal agents of sarcoidosis.

Notes

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CHAPTER EIGHT

HISTOPLASMOSIS AND COCCIDIOIDOMYCOSIS IN THE ETIOLOGY OF SARCOIDOSIS

The evidence supporting a causal relation between systemic histoplasmosis and sarcoidosis parallels that supporting the relationship of sarcoidosis to neoplasia and tuberculosis. Reflecting the relative infrequency of systemic histoplasmosis, it is quantitatively far smaller, and the evidence of causation consists largely in the cumulative weight of persuasive case reports augmented by its resemblance to the other putative causes. Illustrative examples:

A young woman developed fever following a 1997 visit from her northeastern residency to the Mississippi Valley. Her chest radiograph showed profuse pulmonary shadowing. Her liver function tests were abnormal. Open lung biopsy revealed non-caseating epithelioid granulomata (NCG) consistent with sarcoidosis; her histoplasmosis complement fixation titer was 512, and H. capsulatum organisms were recovered from a lung biopsy. She received a short course of amphotericin B, followed by months of itraconazole therapy and achieved complete resolution. She returned in 2001 with the complaint of severe, progressive shortness of breath. A chest CT demonstrated profuse pulmonary shadowing, diminished lung volumes and linear scarring consistent with advanced, stage IV sarcoidosis. Pulmonary function tests revealed a severe restrictive defect accompanied by a marked reduction in diffusing capacity. No stainable pathogens were identified in her BAL, and culture for H capsulatum was negative. Her histoplasma complement fixation titer was zero. Her alkaline phosphatase was markedly elevated; an abdominal CT demonstrated numerous hepatic microlucencies indicative of either micronodules or microabscesses. A percutaneous liver biopsy demonstrated NCG; no organisms were visible and none were cultured. She improved modestly in response to prednisone; itraconazole was added to prevent relapse of histoplasmosis. The physicians participating in her care concluded that, whereas previously she had progressive disseminated histoplasmosis (PDH), she now had stage IV sarcoidosis.[1]

The descriptive definition provided in the American Thoracic Society statement: "Sarcoidosis is a multisystem disorder of unknown cause(s) . . .. The diagnosis is established when clinicoradiological findings are supported by histological evidence of noncaseating epithelioid cell granulomas. *Granulomas of known causes . . . must be excluded* [italics added]"[2]—leading in the patient described above to a self-contradiction, for it is illogical to conclude that temporally contiguous NCG in the same organs of the same individual denote different, causally unrelated diseases. It seems more plausible that some non-degradable remnant of histoplasmosis generated a systemic granulomatous response in a fashion pathogenetically analogous to the generation of a positive response to Kveim reagent.

Numerous case reports exist of histoplasmosis exhibiting a clinical picture and histological features indistinguishable from sarcoidosis: Wheat et al. reported 11 serologically-confirmed cases in Indianapolis, an endemic area, and suggested that H capsulatum may have triggered a chronic inflammatory disease recognized as sarcoidosis. In about half the subjects in this case series the diagnosis of sarcoidosis preceded by many years an acute exacerbation ascribed to histoplasmosis. These relapses may be viewed as exacerbations of preexistent sarcoidosis induced by the infection. In the remainder, the acute episode of histoplasmosis coincided with the initial diagnosis of sarcoidosis. A notable feature shared by all of these cases was the striking paucity of recoverable organisms: One of the 11 cases had organisms recovered from sputum and one had antigenuria; no organisms were recovered from the remaining 9, implying that the infectious component of the disease (vs. its immunological component) had been largely controlled. This paucibacterial granulomatous response resembles that typified by the granulomatous form of leprosy among those who react positively to the Mitsuda lepromin test. Two of the subjects reported by Wheat, treated with Amphotericin B, failed to respond; eight provided with corticosteroid therapy (CST) responded satisfactorily. [3]

Wynbrandt and Crouser reported a similar instance of transformation of PDH into sarcoidosis. They suggested that infections promote sarcoidosis in predisposed hosts.[4] Gupta reported a similar case history and drew the same conclusion.[5]

Abarquez and Sharma reported a case of stage II sarcoidosis for which the subject received CST for one-year. In the course of tapering the dose, he developed a pulmonary nodule which proved to be a histoplasmoma. The advanced age of onset of sarcoidosis (73) in this Iranian subject was the

other unusual feature in this instance.[6] One plausible interpretation of this sequence is that he generated a systemic granulomatous response to exposure to histoplasmosis, which he held in check until he received immune suppression.

Tebib et al. reported a 49-year-old African immigrant of Caucasian ancestry who presented with subacute, stage II sarcoidosis attended by low-grade fever, anorexia with 10-pound weight loss and weakness. Biopsy of tonsillar ulceration and of a peribronchial lymph node showed NCG; no organisms were recovered. His tuberculin test was negative (it had been positive three-years earlier); his pulmonary shadowing spontaneously resolved over three months. He declined treatment for sarcoidosis and continued to lose weight. Increasing liver enlargement prompted a biopsy which demonstrated NCG. Three months after his initial presentation, he developed a skin ulcer in which yeasts were visualized. He presented in shock due to adrenal insufficiency, and failed to respond to aggressive therapy. Post-mortem tissue examination confirmed PDH. Serologies reported postmortem were confirmative.[7]

Yaseen et al. reported a 61-year-old patient with untreated sarcoidosis who developed PDH 20-years after the initial diagnosis. [8] One plausible interpretation of this event sequence is that his sarcoidosis was a response to latent histoplasmosis infection; that with age-related diminution of his immunological competence, an incompletely suppressed infection with H capsulatum emerged as PDH.

Alternative explanations of these event sequences are: a) sarcoidosis predisposes to PDH; b) PDH was kept in check by a sustained granulomatous response (mimicking sarcoidosis) that ultimately failed. The absence of evidence that sarcoidosis predisposes to systemic infection such as tuberculosis and invasive fungal disease favors the latter interpretation: Winterbauer and Kraemer reported their experience with 122 patients with sarcoidosis: None had invasive fungal disease; three had aspergillus mycetomas; there was a single instance of complicating tuberculosis.[9] Baughman and Lower reported on 753 patients with sarcoidosis among whom 7 developed invasive fungal disease. All were previously immunosuppressed with CST for worsening radiographic or clinical status. The authors concluded that fungal infection occurs rarely in treated patients with sarcoidosis.[10] 2) the striking paucibacillary features in these cases indicate that the proliferation of histoplasmosis was suppressed. The case report of Mathur et al. of PDH in a 51-year-old man with sarcoidosis of 20-years duration for which he received prednisone,

20-mg daily for the preceding 10-years accords with either hypothesis.[11] His chest CT showed a few pulmonary nodules and calcified mediastinal and hilar lymph nodes consistent with either healed histoplasmosis or old sarcoidosis. If the calcifications were due to histoplasmosis, one might speculate that chronic CST immune suppression permitted fungal proliferation that ended in PDH. Alternatively, it seems possible that the preceding sarcoidosis was a sustained and successful response to histoplasmosis which was ultimately overcome by chronic CST-imposed immune suppression. Absence of reports of PDH developing in immune-suppressed individuals with calcified hilar lymph nodes (most often due to healed histoplasmosis) favors the latter explanation.

Kuberski and Yourison reported a case series, culled from the literature, of six instances of sarcoidosis seemingly engendered by coccidioidomycosis.[12] Like the reported cases of tuberculosis and histoplasmosis in association with sarcoidosis, paucity of the causal agents was a striking, uniform feature.

The means by which a disease caused by fungi is transformed into an entity indistinguishable from sarcoidosis is not known. One might surmise that, in individuals with cellular immune dysfunction, processing of the causal agent leaves an undegradable residual which generates a systemic epithelioid granulomatous response (as distinguished from progressive disseminated histoplasmosis/coccidioidomycosis). In this formulation, inefficient cell-mediated immune processing, reflected in both the Kveim response and dendritic cell dysfunction (See Chapter 2, fundamental nature), renders the individual susceptible to the initiating fungal infection to which he develops a systemic NCG response. The asymmetry exhibited by the co-occurrence of histoplasmosis with sarcoidosis—expressible as the conditional probability of histoplasmosis given sarcoidosis P(H/S) vs. the probability of sarcoidosis given histoplasmosis P(S/H)—is similar to the conditional relationship of sarcoidosis and cancer (C): $P(C/S) \neq P(S/C)$, treated in chapter 6. Under this formulation, co-occurrence of both arises when the immune response of the immunologically susceptible individual fails to contain the infection; the appearance of histoplasmosis is delayed in persons with sarcoidosis when the granulomatous response fails to completely eliminate/contain the causative organism. If this inference is correct, it follows that undetectable fungal infections initiate sarcoidosis in some larger portion of the population whose sustained immune response fails to eliminate or indefinitely contain these agents.

Thomas and Hunninghake conjectured that "If [poorly degradable] immune complexes were the cause of granuloma formation in sarcoidosis, it would not be necessary for the disease to be caused by a single initiating agent. In fact, the disease might be triggered by different agents . . . the factor that would determine the development of the disease we recognize as sarcoidosis would be the host's immune response to the inciting agent." [13] Histoplasmosis (and possibly other fungi) may be added to the list of validated causal agents of sarcoidosis—neoplasia and tuberculosis—and to beryllium, an agent that can simulate sarcoidosis clinically and radiographically.[14]

Notes

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CHAPTER NINE

OCCUPATIONAL/ENVIRONMENTAL EXPOSURES IN THE ETIOLOGY OF SARCOIDOSIS

Without adequate attention to the incidence and prevalence of surveillance with diagnostic technology, and without suitable consideration of the technologic effects on what becomes detected or left unidentified, the rates of reported diseases simply represent the rates of diagnostic detection and cannot be accepted as scientific enumeration of the true incidence and prevalence of those diseases.[1]

Numerous epidemiological efforts to identify the etiology(ies) of sarcoidosis by associating its incidence with occupational and environmental exposures have had limited success judged by both their failure to specify a biologically plausible causal antigen(s) and the infrequency with which putative causal exposures have been confirmed by their reproduction in other settings. Newman furnished a thoroughgoing survey and critical analysis of these investigations.[2] The single most comprehensive, systematic and rigorous effort was provided in the ACCESS (A Case Control Etiologic Study of Sarcoidosis) study.[3] Investigators from 10 university centers matched 706 individuals with tissue-confirmed sarcoidosis vs. 706 age, gender and race-matched controls. The latter were recruited by random dialing employing the cases' telephone exchange; a mean of 216-calls were required to recruit each control. The authors compared the responses of cases vs controls to a questionnaire containing a large array of occupational and environmental exposures hypothesized *a priori* as potential causal sources based on medical literature review of occupational and hobby exposures. They then computed the odds ratio (OR) for each exposure.

The OR is a measure of risk of disease given exposure, conventionally computed from a two by two table. For sarcoidosis it is P(**S**/**E**)/P(S/**E**) ÷ P(**S**/E)/P(S/E), where P = probability, / = given, **S** = sarcoidosis, S =

sarcoidosis absent, **E** = exposed, and E = not exposed. Equivalently (Table 1.), a/c ÷ b/d = ad/bc). As, by design, all cases and no controls had sarcoidosis, the numerators in column 2 (a,c) = 1, and in column 3 (b,d) = 0. These lead to incomputable equations. Instead, the designers reversed the association with a retrospective case/control design, for example, replacing P(**S**/**E**) with P(**E**/**S**), i.e., testing the relative risk of an exposure given sarcoidosis (Table 2.). This investigative strategy is the same as that employed by Doll and Hill who elucidated the relationship between tobacco smoking and lung cancer in the 1950's.

Table 9.1 Probability of sarcoidosis given exposure

Exposure	Sarcoidosis	No sarcoidosis
Exposed	a	b
Unexposed	c	d

Table 9.2 Probability of exposure given sarcoidosis

Condition	Exposure	No Exposure
Sarcoidosis	a	b
No sarcoidosis	c	d

The ACCESS investigators reported elevated ORs of ca. 1.5 for exposures to agricultural employment, insecticides, and work environments with mold/mildew exposure. They reported a low (protective) OR (.56) for smoking, confirming previous reports.

The authors added that multiple exposure comparisons might generate statistically significant results by chance, and that recall bias, for example recollection of working in a moldy or mildew setting, could be influenced by increased retrospection in affected individuals. "ACCESS did not identify a single predominant environmental or occupational 'cause' of sarcoidosis."[3] The authors went on to point out that the multiplicity of slightly elevated ORs imply either: a) there are numerous, independent risk factors, or b) the envisaged, plausible exposures failed to include those most relevant. Taylor and Cullinan, in an accompanying editorial, emphasized that the ACCESS investigators experienced great difficulty in

assembling a suitable referent population as a basis for comparison, thereby reducing the likelihood that the controls had a distribution of exposures (other than hypothesized potential causal agents) representative of the source populations from which the cases were drawn.[4] Despite the intuitive plausibility of some of the exposures, for example, exposure to microbiological aerosols as causative agents (most fungi exude volatile organic compounds during active growth), these caveats weaken the conclusions one can draw from the ORs.

Streiner and Norman suggested, as a rule of thumb, and irrespective of confidence intervals, that "ORs <0.50 or >2.0 are seen as clinically important."[5] For example, Doll and Hill reported an OR of 9 for cigarette smoking and lung cancer.[6] A plausible explanation for its causal elusiveness despite the multiplicity of elevated ORs is that individuals with sarcoidosis, lacking some component of efficient cellular immunity, respond with systemic noncaseating epithelioid granulomas (NCG) to a variety of ubiquitous, typically unidentifiable, environmental antigens. Caution is required in judging the significance of large percent computed incidence differentials when inferring causation in a disease as rare as sarcoidosis. For example, in a population of 10,000 with a mean annual sarcoidosis incidence of 3×10^{-5}, identification of five additional cases in five-years would change the computed incidence to 13×10^{-5}, a 433% increase above the base rate. The incidence of putative occupationally/environmentally-caused sarcoidosis (2×10^{-4}) is two orders of magnitude less than the systemic NCG (2×10^{-2}) plausibly ascribed to specific etiologies—tuberculosis,[7] histoplasmosis,[8] neoplasia,[9] and berylliosis[10]--based on the cumulative weight of numerous persuasive reports linking these etiological candidates with sarcoidosis.

Whether sarcoidosis is a clinically and histologically distinctive syndrome with diverse etiologies (like erythema nodosum) or a *sui generis* disease is disputed. It is not generally considered an occupational disease. However, numerous investigations have linked occupational exposures to the development of systemic or intrathoracic NCG, assigning various descriptive titles to the latter.[2] These investigations posit, based on incidence differential, that exposure, for example to unspecified agents encountered in firefighting and aerosolized dust from the World Trade Center Disaster, can generate a systemic NCG response indistinguishable from sarcoidosis. I will confine my specific comments to these two settings in which the investigations have been systematic. To avoid confounding by the far higher incidence of sarcoidosis in Blacks than Whites, I confined the analysis, where possible, to sarcoidosis in Whites.

Incidence Computation

Valid comparisons between the incidences in populations requires methodologically comparable assessment of both the numerator (the number of new cases identified and reported/year) and the denominator (the population from which the cases are drawn). The computed numerators are variably influenced and potentially confounded by: a) equality of access to and comparable utilization of medical care; b) thoroughness of reportage; c) potential confounding by the interpreting radiologists' threshold for recognition of subtle abnormalities in populations receiving chest radiographs (CRs) taken for surveillance because of known or suspected exposure vs. the threshold in the control population; and d) CR-screening triples the clinically-identified incidence.[11,12] Impediments that hinder denominator comparability are: a) some population compendia include in the incidence clinically diagnosed sarcoidosis, counting as cases persons with distinctive presentations e.g., asymptomatic bilateral hilar lymphadenopathy and Löfgren's syndrome; b) reflecting the age-dependent incidence of sarcoidosis, age differential between the exposed and the reference population can spuriously elevate incidence differential; c) differing ethnic composition of the exposed and control populations can have the same effect. For example, individuals of Irish ethnicity have an elevated incidence of sarcoidosis, and they are overrepresented in some municipal occupations such as policework.

Freedonia

An example of the potential for specious etiological inferences is provided in the sarcoidosis incidence report of the Freedonia baseball team, The Notionalists: The Freedonia township ("Land of the Brave, and Free") has a stable White population of 30,000. Their clinically-identified, population incidence (due to symptom investigation or resulting from an incidental CR) of sarcoidosis is 3×10^{-5}. In a 10-year period, the expected number of cases is 9. In this time interval, the middle third, comprising 10,000 Freedonians, age 20-45-years (the peak age incidence range), are required, by statute, to play baseball for the township team. Sarcoidosis in players will constitute 7.2 (80%) of the 9 expected cases. The mandated annual CR for Notionalists triples the number of identified cases to 21.6. Division by 10^5-person-years gives the *clinically-ascertained* annual player incidence of 21.6×10^{-5} (95% CI: 10, 30), 7.2-fold the *clinically-identified*, annual incidence of the Freedonian population. Apprised of this finding, the team physician, recollecting the moldy/mildew aroma in the

communal showers, signifying aerosolization of volatile fungal components, queries the affected players and ascertains that each has a distinct recollection of this aroma. He suggests that respired microbial bioaerosols may be causative, positing exposure to insects in pulverized organic fertilizer on the ball field as a plausible alternative causal agent.

Occupational Reports

Firefighters

The New York City fire department (FDNY) firefighters undergo triennial health examinations, which include CR-surveillance. To determine whether firefighting was a possible cause of sarcoidosis, Prezant et al. reported on its incidence, prevalence and severity in ca. 12,000 firefighters observed from 1985 to 1998 (14-years, 165,000 person-years). Ninety-four percent were White, and 39% of Irish ancestry. The report did not furnish their age distribution. The investigators identified 21 new, biopsy-confirmed cases, age range: 26–41-years.[13] Employing the number surveyed as the denominator, they computed a mean annual *clinically-ascertained* incidence of 12.9×10^{-5}. The number of new cases/year ranged from zero to five. The investigators lacked New York City population sarcoidosis incidence data with which to compare the incidence in firefighters. We estimated the White incidence of clinically-identified sarcoidosis at 2.8×10^{-5} in our Portland, Oregon metropolitan population.[14]

Assuming that the sarcoidosis incidence and age distribution in our population is equivalent to that in New York City, that persons in the 26-41 age range constitute one-third of this population, that the incidence in this age cohort is 2.24 (80% of 2.8), and that CR-screening of this age group triples their ascertainment, the expected number of age-matched, non-firefighters with new, biopsy-confirmed sarcoidosis, clinically ascertained in a sample of 12,000 White persons in Portland, Oregon, subjected to triennial CR-screening for 14-years is $2.24 \times 10^{-5} \times 3 \times 14 \times 12 \times 10^{3} = 11$.

No new cases were identified in the FDNY report control group, *ca.* 2,800 emergency medical services (EMS) workers, who received a similar evaluation that included triannual CR-screening for 4-years. Assuming the EMS workers are similar in age and ethnicity (they were not) to the firefighters, their expected number of new sarcoidosis cases in 4-years is $(2{,}800 \times 4)/ (165{,}000) \times 21 = 1$.

In summary, in a 14-year period, the FDNY firefighters had 0.7 ((21 – 11)/14) more-than-expected, new, sarcoidosis case/year/12,000 persons at risk vs. than that predicted in an age-matched, ethnically unmatched (nearly half of FDNY firefighters were of Irish ethnicity, a highly susceptible cohort), White, Portland, U.S., non-firefighter control group.

World Trade Center Disaster Exposure

Izbicki studied 15,000 FDNY workforce, present at any time between September 11, 2001, and July 1, 2002 during the World Trade Center (WTC) rescue, recovery, and cleanup operation.[15] All 26 clinically-ascertained persons with biopsy confirmed ‘‘sarcoid-like granulomatous pulmonary disease” (SLGPD), diagnosed between 9-2001 and 9-2006, identified either because of symptoms or a screening CR, were present within the first 72-hr of the disaster and thus intensely exposed to airborne WTC dust. The incidence was 86×10^{-5} in the first year and a mean of 22×10^{-5} afterward vs. a mean of 15×10^{-5} preceding the WTC exposure. The first-year incidence demonstrated a striking peak: 13 biopsy-confirmed cases were identified between September, 2001 and September 2002; there was 1-case the year following, and 4 each for the succeeding 3-years vs. a WTC range of 0-4 (mean, 2) in the preceding 16-years.

Crowley screened 20,000 WTC disaster responders who took part in the rescue, recovery and cleanup efforts and contacted the WTC Medical Monitoring and Treatment Program (WTCMMTP).[16] The authors estimated that between 60- and 70-thousand individuals were eligible among those responders. On the basis of interviews, medical record reviews and medical monitoring examinations, the investigators identified 38 clinically-ascertained cases of biopsy-confirmed SLGPD, newly diagnosed post 9/11/2001. Seventy-four percent of the screenees were between the ages of 30- and 49-years, and 34 (89%) of the cases were in this age range. Employing the examined cohort as the denominator, the clinically-ascertained 6-year cumulative incidence in Whites was 35×10^{-5} (mean annual = 6×10^{-5}.) Under the assumption that SLGPD was caused by WTC dust exposure, there are a number of unexplained, anomalous findings:

a) There was no statistical association between SLGPD and the level of dust exposure.

b) Assuming that CR-screening triples the clinically identified incidence of sarcoidosis, their computed, mean-annual, clinically-ascertained

incidence (6×10^{-5}) is not materially different than the estimated, clinically-ascertained incidence in Portland, Oregon assuming that only adults visited the site, and that 90% of cases occurred in adults, who constituted 67% of the denominator population ($2.8 \times .90 \times .67 \times 3 \times 10^{-5} = 5.1 \times 10^{-5}$.)[14] Inspection of their Figure 1 demonstrates the imprecision of the incidence estimate (and its magnification by conversion to cases $\times 10^{-5}$) imparted by trivial variation in the small annual number of cases.

c) The lowest reported incidence (10×10^{-5}) occurred in the first year, ending September, 2002. The incidence was far higher and unvarying in the succeeding three years ending September, 2003, 2004, and 2005, respectively: 54, 55, and 57×10^{-5}. This temporal incidence sequence is precisely the reverse of that reported by Izbicki.[15]

d) The 2- to 4-year interval between putative exposure and the appearance of CR abnormalities in 2003-2005 implies a latency in immunological response which is not consistent with what is known of the time course from exposure to the genesis of a CR-evident, granulomatous response in tuberculosis and histoplasmosis. It is inconsistent with time course for maturation of the Kveim response (4-6-weeks) and with the generation of acute onset sarcoidosis (in which, fortuitously, a recent, normal CR is available for comparison). However, it is well-recognized that the time course from exposure to CR-evident, insidious-onset sarcoidosis need not be the same as in the acute disease: for example, a systemic granulomatous response indistinguishable from sarcoidosis may evolve years following infection with H capsulatum.[17]

Jordan et al. reported on a self-identified registry of 46,000-persons exposed to the WTC disaster on September 11, 2001.[18] In response to questionnaires inquiring into evidence of post–exposure sarcoidosis, the authors, based on review of medical records and contact with physician providers, identified 43 biopsy-confirmed cases (out of 430 who reported a diagnosis of sarcoidosis and gave permission for a medical record review) in persons who met that definition. The authors selected from the registry 4 controls with no history of sarcoidosis for each case, matched by age, ethnicity and gender. Thirty-nine of the 43 cases (91%) were diagnosed in the years 2002 through 2006: 8, 6, 8, 8, 9 cases, respectively. However, because Registry participants were not screened annually, it was not possible to distinguish incident from prevalent cases. In a case-control analysis of 28 persons whose diagnosis was obtained after they were enrolled in the Registry, the OR for work on the debris pile was 9.1 (95% CI, 1.1, 74), and for dust cloud exposure, 1 (95% CI, 0.4, 2.8). Case

identification may have been influenced in favor of those working on the debris pile by their medical coverage, reflected by a greater likelihood that they would utilize surveillance either for reassurance, at the urging from their union, and for the possibility of future workers' compensation. Were WTC airborne dust exposure the causative agent, one would have expected a higher OR for exposure.

In his review of etiologies of sarcoidosis,[2] Newman cited nine criteria advanced by Hill for establishing causation vs association seven of which are applicable: strength of the association, consistency (repeated observation of the association between exposure and disease), specificity of the exposure and the disease, temporal relationship, biological gradient (dose-response), biological plausibility, and analogy (the posited exposure is similar to other agents known to cause granulomatous disease).

In summary, the reported associations of sarcoidosis and occupational/environmental exposures are not entirely convincing: some are weak; others appear to be spurious. None of the industrial and other exposures cited in these epidemiological analyses as causal have been corroborated by widespread reproduction in other settings. Reports of case clusters in farmers who employ insecticides would serve to clinically validate the latter exposure as causal; to my knowledge, none exist. Neither have these exposures received comment in large sarcoidosis case series. Likewise, no reports of case clusters exist, to my knowledge, of sarcoidosis in occupations which entail intense or frequent mold/mildew exposure such as operating a bath house, laundry, swimming facility, or janitorial employment. The evidence of causation provided by a differential incidence of sarcoidosis (or SLGPD) in firefighters and WTC workers is open to question due to methodological dissimilarity in case identification and incidence computation vs. the populations to which they are compared. Time of inception following exposure and lack of a relationship between magnitude of the exposure (dose) and development of sarcoidosis (response) are further impediments to inferring a convincing causal relationship. Other large-city firefighter organizations have either not reported or not experienced a notable increase in sarcoidosis. Reports of sarcoidosis case clusters among industrial demolition workers have not appeared. Neither England or Germany experienced, recognized nor reported an increase in sarcoidosis (or SLGPD) in cities in which workers were exposed to repeated, devastating, firebombing during World War II. Finally, no specific, plausible, causal candidate emerged from any of these investigations.

It seems reasonable to follow the lead advanced by Thomas and Hunninghake who proposed that ‘‘. . . the disease might be triggered by different agents. . . the factor that would determine the development of the disease we recognize as sarcoidosis would be the host’s response to the inciting agents.” [19] A search for causes of inefficient cell mediated immunity in persons with sarcoidosis and the search for identifiable biological markers of susceptibility in cases of a systemic granulomatous response are likely to be more productive avenues of investigation than further epidemiologic assessments, which are potentially misleading, and which are unlikely, moreover, to prove useful in identifying a causal agent.

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CHAPTER TEN

CUTANEOUS SARCOIDOSIS

Cutaneous manifestations of two types appear in approximately 25% of sarcoidosis patients. Erythema nodosum is the principal, etiologically nonspecific, nongranulomatous response. It is an acute immune hypersensitivity reaction, a neutrophilic, septal, subcutaneous panniculitis, principally located (inexplicably) on the anterior tibial surfaces, and thought to result from deposition of immune complexes. Other etiologically nonspecific cutaneous manifestations are quite rare.

Three distinctive, etiologically specific (*i.e.,* granulomatous) patterns of cutaneous involvement occur in sarcoidosis: diffuse cutaneous as part of systemic disease, diffuse cutaneous unassociated with systemic disease, and focal cutaneous disease.[1] The explanatory challenges lie in accounting for both the variety of cutaneous patterns and for the absence of cutaneous involvement in the majority of patients with sarcoidosis in whom the putative antigen, like the viruses of childhood exanthems, is presumably systemic. Why, in most instance, is it selectively spared?

Cutaneous immunity far exceeds systemic immunity in its complexity:

> Although the epidermis is not directly connected with blood and lymph circulation, dermal blood and lymph capillaries allow this interconnection. In particular, lymphatics play a key role in removing foreign antigens and draining activated Langerhans cells from skin sites. The crucial role played by lymph drainage in regulating skin immunity is attested to by the fact that lymph stasis, whatever the cause, may give birth to skin regions with a dysregulation of the immune control . . . skin immunity cannot be maintained. In such a complex system, a sectorial default in immune control may occur in immunocompetent subjects. This regional immune defect can appear and remain confined to differently damaged skin areas, lately labeled immunocompromised districts (ICDs).[2]

Local failure to mount an effective cell-mediated immune response due to a variety of local effects impairing cellular motility accords with the pathogenetic viewpoint advanced for the genesis of systemic sarcoidosis in chapter 2, fundamental nature. Focal cutaneous sarcoidosis in the setting of systemic sarcoidosis is the easiest manifestation for which one can apply evidence-based accounting. Scarred or injured areas of the skin, resulting, for example, from trauma and tattooing, can create regions of *locus minoris resistencia* (ICDs) that can pave the way for focal sarcoidosis. Impaired blood and lymph circulation may be a contributing factor by hindering the transport of immunocompetent cells, hampering local immune control. Damage to sensory nerve fibers that release immunity-related peptides is an additional possible mechanism.[3,4] .

I found no information in a literature search that either identified or suggested a mechanism that would account for cutaneous sparing in systemic sarcoidosis or of its converse, absence of systemic involvement in cutaneous sarcoidosis. If one subscribes to the view that susceptibility to systemic sarcoidosis is most frequently caused by myeloid dendritic cell dysfunction (of unknown cause), one might hypothesize (by analogy) that differing cutaneous dendritic cell function could account for both forms: isolated Langerhans cell dysfunction would confer susceptibility limited to the skin; conversely, normal Langerhans cell function in the setting of myeloid dendritic cell dysfunction in systemic sarcoidosis would serve to prevent cutaneous involvement. I do not know whether assessment of Langerhans function is feasible.

The multifarious manifestations of cutaneous sarcoidosis—papular, nodular, plaque, lupus pernio etc.—remain unexplained. Ruocco et al. provides a comprehensive guide to its management.[1]

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CHAPTER ELEVEN

SARCOIDOSIS AND THE AFRICAN-AMERICAN GRANULOMATOUS NEXUS (AAGN)

The curious dissociation between the marked susceptibility of African–Americans (AA) to the granulomatous diseases sarcoidosis and tuberculosis, and their resistance to non-tuberculous mycobacterial disease (NTM) has received little notice. This disease-specific- disparity in the efficacy of their granulomatous response suggests a nexus, a mediating, cognate, immunological mechanism. Its existence is, perhaps, evidenced in the puzzling response of 5 of 50 healthy AA to the intradermal injection of first-strength purified protein derivative (PPD) who developed minute cutaneous papules at 4-weeks, which, on histological examination, revealed epithelioid granulomas indistinguishable from positive Kveim tests.[1]

AA Susceptibility to Sarcoidosis

The U.S. incidence of clinically identified sarcoidosis in AA, assessed in health maintenance organizations, is $35.5–36.4 \times 10^{-5}$.[2,3] It exceeds the White, U.S incidence (2.8) by 13-fold[3] and the UK incidence (3.4) by 11-fold.[4] The AA: White prevalence ratios for lanthanic sarcoidosis, defined as ascertainable solely at autopsy, are far lower. Reid reported a ratio of AA: White cases of 4.7:1 in a Cuyahoga County, Ohio forensic autopsies in which AA constituted one third of the autopsy population.[5] In the year 2000, AA constituted 11.5% of the state population.[6] Correcting for the proportion of AA in the forensic autopsy population vs. the state populations reduces the ratio to 1.6: 1, which suggests that the far higher, clinically identified incidence in AA, reflects, at least in part, a more intense response, serving to increase its clinical identification.

AA Susceptibility to Tuberculosis

African-Americans are known to be more susceptible to tuberculosis than non-Hispanic Whites; their rates exceed that for the latter by more than 8-fold.[7]

AA Resistance to Nontuberculous Mycobacterial (NTM) Disease

Yeager abstracted a doctoral thesis which reported on a large epidemiological study of HIV-negative females ≥50 years of age with ≥1 positive M. avium culture of pulmonary source. The White: Black odds ratio (OR) was 4.6: 1 (95% CI 2.3–9.2).[8] Fordham et al. reported that disseminated M. avium in patients with AIDS was far less common in undeveloped countries (chiefly Africa) than in developed countries.[9] Morrisey et al. reported that, despite the organisms' high prevalence in soil and water samples in Uganda, M. avium bacteremia in AIDS patients was absent.[10] Bronchiectasis furnishes a setting (presumably, retained secretions) that strongly predisposes to NTM disease.[11] The authors of a multicenter study of 2088 persons with non-cystic-fibrosis-bronchiectasis reported that 1285 (62%) had complicating NTM. There was a marked underrepresentation of the AA in the NTM group: only 8 of 44 (18%) AA in the Bronchiectasis Registry had complicating NTM vs 1279 of 2044 (63%) of Whites.[12]

The relative resistance of Europeans vs. Native Americans and AA to tuberculosis presumably reflects centuries of evolutionary sorting of the former in dense urban populations, effecting relative elimination of those most susceptible. By analogy, one might attribute the inherent resistance to NTM in the AA population to similar sorting in Sub-Saharan Africa, which served to largely eliminate susceptible individuals where these agents are environmentally abundant.[12] To account for this resistance, one might posit the existence of a greater propensity to generate a vigorous granulomatous response, which, if shared with the propensity to develop a granulomatous response to undefined, possibly related immunogens, would account for the far higher incidence and intensity sarcoidosis among AA. However, this mechanistic explanation is inconsistent with the observed, increased susceptibility of AA to M tuberculosis. Some other, better explanatory mechanism is needed.

NRAMP1 in Host Control of Intracellular Bacteria

Monogenic influence on susceptibility to mycobacterial disease differs sharply from host control of other intracellular bacterial infections, which are, for the greater part, influenced by multiple trait loci. Natural resistance-associated macrophage protein 1 (Nramp1), encoded by the SLC11A1 gene, is an integral membrane protein expressed in the lysosomal compartment of monocytes and macrophages in humans. Following phagocytosis, Nramp1 is targeted to the membrane of the microbe-containing phagosome, where it may modify the intraphagosomal milieu to affect microbial replication. Allelic variants differentially affect resistance to mycobacterial species. Koh et al. reported that these were associated with susceptibility to NTM.[13] Kondratieva et al. demonstrated a close to monogenic differential susceptibility to M avium vs. M tuberculosis in a mouse model according to S1C11A1 allele.[14] Maliarik et al. suggested the existence of a common pathophysiology of sarcoidosis and tuberculosis based on their shared histological and clinical features. In a case–control study of Nramp1 polymorphisms in African-Americans with sarcoidosis, they found an allele that exerted a protective effect.[15] Dubaniewicz et al. demonstrated a positive association between allele 3 at the functional (GT)n promoter region repeat polymorphism of SLC11A1 and the risk of sarcoidosis.[16]

Conclusion

The AA nexus of susceptibility to the granulomatous diseases sarcoidosis and tuberculosis and their resistance to NTM disease (AAGN), may be attributable, in part, to evolutionary-conditioned, ethnically-shared, S1C11A1 alleles.

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CHAPTER TWELVE

UNSOLVED PROBLEMS

The chasm between our knowledge (in the descriptive sense) and our understanding —*ein beschreibende Verständnis ohne Kentniss der zu Grunde liegenden Zusammenhänge*—of sarcoidosis is perhaps greater than in any other well-studied disease. In his famous 1900 address at the Second International Congress of Mathematics, David Hilbert, head of the department at the University of Göttingen, and widely regarded as the foremost mathematician of his time, enunciated 23 fundamental unsolved problems as a challenge to mathematicians, for example, determination of the solvability of a Diophantine equation. (By 2019, all but four had been solved or resolved.)

> Sarcoidosis remains a multifaceted and seemingly intractable enigma whose fundamental unsolved problems represent outstanding challenges to investigators in this new century. Its aetiology, fundamental nature, pathogenesis, incidence, ethnic predilections, relationship to the Kveim test and prognostic determinants are largely either unknown or unexplained, and treatment indications, absent compelling findings, remain undefined. Identification of its elusive aetiology—*That Obscure Object of Desire*—would immeasurably enhance our ability to resolve most of these questions.[1]

In the same spirit, I herewith offer a list of 20 fundamental unsolved problems in sarcoidosis worthy of investigation plus suggestions for 2 trials.

A. Fundamental nature

Thomas and Hunninghake conjectured that:

> "If [poorly degradable] immune complexes were the cause of granuloma formation in sarcoidosis, it would not be necessary for the disease to be caused by a single initiating agent. In fact, the disease might be triggered by different agents . . . the factor

> that would determine the development of the disease we recognize as sarcoidosis would be the host's immune response to the inciting agent."[2]

Under the terms of a definition which requires the exclusion of instances with a putative etiology, we have no means of testing this hypothesis.

The development of systemic granulomatous responses in some recipients of allografts from donors with sarcoidosis suggest a causal, transmissible (*i.e.*, infectious) agent.[3] This phenomenon is perhaps equally consistent with a "systemic Kveim response" to the large-scale emplacement of tissue containing the active principle of the Kveim suspension, potentiated by the requisite, post-transplant, immunosuppressive regimen.

1. Is sarcoidosis etiologically heterogeneous?
2. Is sarcoidosis an infectious disease?
3. What is the cause of the myeloid dendritic cell dysfunction? (*Vide* chapter 2, fundamental nature.)

B. Kveim test

We do not know why *ca.* half of sarcoid involved spleens are potent and specific Kveim reagent sources while the remainder lack either potency or specificity.[4]

4. Precisely what constituents distinguish sensitive and specific Kveim sources?[4]

If a positive Kveim test signified an immunologic response to an undefined antigen, one would expect it to be positive more frequently in individuals with chronic disease than in those whose disease was of recent onset.[4]

5. Why is the test negative in *ca*. 20% of individuals with Löfgren's syndrome (acute onset, stage I)? Why it is more likely to be negative than positive in individuals with stage III disease?, and why does it gradually become negative in >90% of individuals with long-standing disease?[4]

6. Does the Kveim reagent share an antigen (a nondegradable product) or hapten with the etiologic agent(s) of sarcoidosis?

7. Does the Kveim reagent generate a distinctive response by other means?

The prevalence of positive Kveim tests in healthy British individuals, 0.7-2.0 × 10^{-2},[4] is almost 1000-fold the annual incidence of clinically identified sarcoidosis in Great Britain, 3.4 × 10^{-5}.[5] We do not know whether Kveim-positive normal individuals represent the susceptible population or whether they are "true" false-positives, *i.e.*, positive in persons who are not more susceptible to the development of sarcoidosis. Does the demonstrated deficit in early cellular immune processing of the Kveim suspension exhibited by the majority of persons with Kveim-positive sarcoidosis[6] represents a fundamental and underlying feature of the disease or a secondary phenomenon? Kveim testing of individuals destined to develop sarcoidosis would distinguish between these possibilities, but we have no means of identifying these individuals.

8. Beyond an association with sarcoidosis, what, precisely, does a positive test signify?[4]

C. Prognosis

Because it is both asymptomatic and radiographically undetectable in more than 90% of cases (solely autopsy-evident, *i.e.*, lanthanic), the overall course and prognosis of sarcoidosis is unquantifiable, with the majority experiencing a benign course. Longer term intervention, even with near-homeopathic doses of corticosteroid therapy (CST), imposes insidious, drug-induced harms, to which there is a superadded potential for harm from the suppression of spontaneous resolution. Post-mortem figures underestimate the lifetime prevalence of sarcoidosis, for the majority of cases resolve. Lacking a marker similar in its persistence, sensitivity and specificity to the Mantoux test, the true incidence and lifetime prevalence of sarcoidosis cannot be accurately estimated; published estimates represent lower limits.

Aside from general prognostic guidelines such as the acuteness of onset and bone/cutaneous involvement, no simple determinant, superior to the Scadding stages, has emerged. Markers of the intensity of the response, which in general reflect disease severity, paradoxically predict a favorable outcome.

9. By what means does radiographically-apparent confinement to the hilar lymph nodes (Stage I) confer a highly favorable prognosis?

10. Has a belief that individuals with sarcoidosis, absent intervention, are at high risk of a lethal outcome generated a self-fulfilling prophesy?

D. Immunology, TH1 vs. TH2

A granulomatous response develops when innate immunity, succeeded and combined with adaptive (T- and B-cell) immunity (which largely adds antigen-specific recognition properties to the innate response), fails to eliminate/contain an antigen. The cellular, cytokine and chemokine response (referred to collectively as the effector module) that evolved to eliminate intracellular pathogens such as M tuberculosis, M leprae, L donovani, P jirovecii, and T gondii, which reside within intracytoplasmic, membrane-enclosed vesicles, is referred to as an IFNγ (for its principal effector cytokine) or T-cell helper 1 (T_H1) immunity. Based on the cellular and cytokine complement assayed by bronchoalveolar lavage (BAL) in subjects with sarcoidosis, its effector module is designated T_H1. The participating CD4+ lymphocytes are activated by dendritic cell and macrophage presentation of an undefined antigen(s) contained in the peptide binding groove of an MHC II molecule and induced to produce cytokines and a chemokine with these actions:

- IFN-γ, CD40L . . . enhance macrophage killing of engulfed bacteria.
- FasL, LT-β . . . kill chronically infected macrophages, releasing bacteria to be destroyed by fresh macrophages.
- IL-2 . . . increase CD4 (favoring T_H1) and CD8 T-cell production.
- IL-3 and GM-CSF . . . stimulate production of monocytes in bone marrow.
- TNF-α and LT-α . . . activate endothelium, inducing macrophage binding and exit in affected areas.
- CCL2 . . . attract monocytes to affected area.[7]

In the past decade, there has been increasing interest in the contribution of T_H17 cell subsets, designated as $T_H17.1$ or T_H17/T_H1 (which produce IFNγ), to the immunopathogenesis of sarcoidosis.[8]

The microbiocidal effects of a T_H1 response fails to eliminate some highly resistant intracellular organisms. The resulting, ongoing activation of macrophages mediates the formation of granulomas in which macrophages fuse and become multinucleated giant cells, or are modified to become epithelioid cells, in which the phagosomes and lysosomes are replaced by secretory features—endoplasmic reticulum, Golgi apparatus and storage vesicles. These produce TGFβ, TNFα, angiotensin converting enzyme (ACE) and RANTES. Closely associated are CD4+ lymphocytes.[9] This is the characterizing model of the sarcoidosis granulomatous response in which the putative antigen(s) is assumed to be immunologically non-degradable. The T_H1 response in clinically evident sarcoidosis typically resolves leaving a trivial or no residue, resembling in this respect the absence of residual damage in resolved pneumococcal pneumonia.

The T_H2 immune effector module largely evolved to expel/kill/wall-off extracellular parasites which are not susceptible to immune degradation, particularly helminths. The principal cytokines produced are:

- IL-13 and 4 . . . facilitate expulsion of intestinal helminths by increasing epithelial turnover, mucus production, and smooth muscle contraction.
- IL 5 . . . recruits and activates eosinophils whose product, major basic protein (MBP), kills parasites.
- IL 3 and 9 . . . generate eosinophils and basophils armed with Igε bound to FCε receptors facilitating removal of helminths.

A T_H2 response in sarcoidosis is of interest for two reasons: 1) It can be induced by corticosteroid therapy (CST); 2) Unlike T_H1, which most often resolves, it is likely to result in fibrosis (e.g., in response to schistosome eggs). "A switch to predominantly T_H2 lymphocytes may underlie a change from healing by resolution to healing by fibrosis."[9]

Kunkel et al. summarized the potential role the transition from a T_H1 to a T_H2 cytokine response:[10]

> Recent studies show that various cytokines affect fibroblast activation, proliferation, and collagen deposition during the evolution of chronic fibrotic lung disease. In particular, gamma interferon suppresses such fibroblast activities as proliferation and collagen production, while interleukin-4 augments fibroblast growth and collagen production. [These two mediators are the prototypic cytokines which functionally define either a T_H1 or a T_H2 response.] Thus, experimental

> models of granulomatous lung inflammation, which are characterized by either a T_H1 or a T_H2 response, will be useful in delineating the mechanisms which maintain and resolve chronic granulomatous lung inflammation. These experimental systems will prove to be especially important as the degree of inflammation and fibroblast activation/proliferation during the pathogenesis of chronic pulmonary inflammation may be dependent upon a balance of T_H1- and T_H2-like cytokines which are expressed during the evolution of the disease.

The authors summarized the potential roles of the functionally defining T_H1 and T_H2 cytokines in the outcome of granulomatous lung disorders in table 1 of the reference:

> T_H1 → IFNγ, antiproliferative, anti-fibrotic; suppresses T_H2 cytokines. IL-2 → IFNγ.
>
> T_H2 → IL-4, fibroblast chemotaxis, matrix production. IL10 → suppresses T_H1 cytokines.

In 2004, Elenkov wrote:

> Evidence accumulated over the last 5-10 years indicates that glucocorticoids (GCs) inhibit the production of interleukin (IL)-12, interferon (IFN)-gamma, IFN-alpha, and tumor necrosis factor (TNF)-alpha by antigen-presenting cells (APCs) and T helper (T_H)1 cells, but upregulate the production of IL-4, IL-10, and IL-13 by (T_H)2 cells. Through this mechanism increased levels of GCs may systemically cause a selective suppression of the T_H1-cellular immunity axis, and a shift toward T_H2-mediated humoral immunity, rather than generalized immunosuppression.[11]

On the same subject, Almawi et al. reported:

> Glucocorticoids (GCs) are used as immunosuppressive and anti-inflammatory agents in organ transplantation and in treating autoimmune diseases and inflammatory disorders and they exert their effects by several mechanisms, the most significant of which is inhibition of cytokine production and action. Recent reports suggested that GCs inhibit cytokine expression indirectly through promotion of a T helper cell type 2 (T_H2) cytokine-secreting profile, thereby resulting in preferential blockade of pro-inflammatory monokine and T helper cell type 1 (T_H1) cytokine expression. The target of GCs appeared to be monocytes and macrophages, whereby altered

> regulation of interleukin (IL)-1/IL-1 receptor antagonist (IL-1ra), coupled with profound blockade of IL-12 synthesis and inhibition of interferon (IFN)-gamma-induced major histocompatibility complex (MHC) class II expression, lead to a preferential cognate stimulation of T_H2 cells at the expense of T_H1 cells.. . . Collectively, this indicates that, in exerting their anti-proliferative effects, GCs act indirectly by altering T_H1/T_H2 cytokine balance, blocking the (pro-inflammatory) T_H1 program and favoring the (anti-inflammatory) T_H2 program.[12]

The addition of Cyclosporin A to CST, in a controlled prospective trial, demonstrated a clear, adverse effect on the outcome of progressive pulmonary sarcoidosis vs. CST alone.[13] Metzger and Peterson demonstrated that Cyclosporin A "dramatically enhanced the levels of pulmonary inflammation" to injected Schistosoma mansoni eggs in mice [a T_H2 response].[14]

Similarly, Gieseck et al. concluded:

> Type 2 immunity is characterized by the production of IL-4, IL-5, IL-9 and IL-13, and this immune response is commonly observed in tissues during allergic inflammation or infection with helminth parasites. However, many of the key cell types associated with type 2 immune responses - including T helper 2 cells, eosinophils, mast cells, basophils, type 2 innate lymphoid cells and IL-4- and IL-13-activated macrophages - also regulate tissue repair following injury. Indeed, these cell populations engage in crucial protective activity by reducing tissue inflammation and activating important tissue-regenerative mechanisms. Nevertheless, when type 2 cytokine-mediated repair processes become chronic, over-exuberant or dysregulated, they can also contribute to the development of pathological fibrosis in many different organ systems.[15]

11. Might BAL-assessed, differential cytokine assemblage prove a useful prognostic marker?

12. Does CST-induced transition from a T_H1 to a T_H2 response account for excess sarcoidosis mortality?

E. Pathogenesis of isolated sarcoidosis

Based on the observation that >90% of cases exhibit intrathoracic involvement, investigators have inferred a pulmonary portal of entry of the

putative antigen(s) of sarcoidosis. Inhaled agents that elicit a granulomatous response, *e.g.*, M tuberculosis and H capsulatum, characteristically produce localized pulmonary shadowing that may progress to the ipsilateral hilar lymph nodes. Bilateral hilar adenopathy unaccompanied by pulmonary shadowing is the most frequent presentation of sarcoidosis; if pulmonary shadowing evolves, it invariably succeeds the hilar adenopathy, and it is typically diffuse.

13. If the putative antigen is airborne, why is its evolution retrograde and symmetrical?

14. If the inference is correct, how might an airborne agent cause clinically lone extra thoracic disease involving e.g., the integument, abdominal organs or the central nervous system?

F. Differential ethnic susceptibility

There is a marked ethnic differential in sarcoidosis incidence and manifestations, most evident in the 12-fold incidence ratio of Blacks vs. Whites.[16] Natural resistance-associated macrophage protein 1 (Nramp1), encoded by the SLC11A1 gene, whose allelic variants differentially affect resistance to mycobacterial species, is a potential causal candidate. Maliarik et al., in a case–control study of Nramp1 polymorphisms in Blacks with sarcoidosis, found an SLC11A1 allele that exerted a protective effect.[17] Dubaniewicz et al. demonstrated an association between allele 3 at the functional (GT)n promoter region repeat polymorphism of SLC11A1 and the risk of sarcoidosis.[18]

15. Are there identifiable Nramp1 alleles which account for ethnic variations in sarcoidosis incidence, prognosis or clinical manifestations?

G. Age Incidence

Unexplained variations in age incidence furnish tantalizing clues to a deeper understanding of sarcoidosis. Hillerdal and colleagues reported from Uppsala, Sweden that sarcoidosis was very uncommon before the age of 20, that there was a primary peak incidence in both sexes age 20 to 34 and a striking secondary peak incidence (see Fig 3. of the reference) in females ages 45 to 65. [19] Because chest radiography was a routine part of the population health survey, its selective application may have

contributed to the small number of individuals identified with sarcoidosis in those younger than age 20 in this survey. Other investigators, but not all, have reported similar double peak age incidence in females.

Juvenile sarcoidosis, which differs in its features from the adult form, is rare. In searching for a plausible explanation of this clinical and age differential, one might hypothesize that both are attributable to evolving, age-conditioned maturation of the immunological response. If this hypothesis is accurate, one might speculate, under the assumption of near-ubiquity of the potential causal agents, that virtually all sarcoidosis-susceptible (*i.e.,* immunologically predisposed) individuals have been challenged by age 34 (males and females) or age 65 (females); and that in individuals beyond these ages, only non-susceptibles remain. I know of no information that addresses this speculation.

16. Why, in some reported populations, do females exhibit a bimodal peak age incidence?

17. Is the extremely low incidence and different expression of sarcoidosis in children ascribable to immunological maturation/evolution? to different antigenic exposures?

18. Why is sarcoidosis rare in the elderly?

H. Seasonal Incidence

A seasonal sarcoidosis incidence has been reported by several investigators. It was not possible to infer the season of onset in some reports because they only furnished the season of diagnosis, which typically coincided with the date of the initial, diagnostic CR. Ungprasert et al. evaluated 345 incident cases diagnosed between 1976 and 2003 in Minnesota. They observed little seasonal variance except for a modest, consistent reduction in Autumn, *with a nadir in November*. [italics added] Because they included cases whose diagnosis resulted from an abnormal CR, which might have been taken for an unrelated reason, it is not possible to confidently infer the season of onset.[20]

Gerke et al. observed no seasonal pattern on the date of diagnosis of 3,791 cases among U.S. veterans, 2000 to 2007. To select for incident cases, potential prevalent cases were excluded if they had a diagnosis of sarcoidosis in the one year prior to the index date. The advanced age (mean, 50) and range (21 to 86) of the cases suggest that many had chronic

disease. The authors' published data lacked documented diagnostic confirmation and stage.[21]

Three reports cite a pattern of peak seasonal occurrence in which one can be confident:

Demirkok et al. reported on the seasonal incidence of sarcoidosis among 275 subjects diagnosed over a 38-year period, based on an analysis of medical records of the Cerrahpasa Medical Faculty, Department of Internal Medicine, Division of Lung Diseases, Istanbul between 1966 and June 2004. The investigators limited the analysis to the seasonality of symptomatic, recently diagnosed patients with sarcoidosis. *Patients with sarcoidosis diagnosed by chest X-ray scanning and not symptomatic were excluded*. [italics added]. All cases were tissue verified. They reported *an increased incidence March-April,* [italics added] and a decreased incidence in October-December. They concluded: "Our results are consistent with an infectious and/or contagious etiology as previously reported for Chlamydia pneumoniae, Propionibacterium acne, Mycobacteria, wood burning, pine pollen, allergens, farm animals, fine sandy soil and clay eating.[22]

Wilsher reported on patients with acute onset of sarcoidosis, evidenced by erythema nodosum or acute arthralgia, in a single New Zealand medical Centre. *Of 59 newly diagnosed cases, 24 presented in this fashion exclusively between April and December, with peak clustering in the spring months of August, September and October ($p<0.001$, Fisher's exact test)*. [italics added]. This cohort was more likely to have a stage I disease. The seasons are reversed in the southern hemisphere; New Zealand spring months would correspond to the same months as the peak incidence reported in Turkey, viz., March-April.[23]

Glennas et al. reported a similar experience and a similar seasonal incidence in Norway. Of 186 persons presenting with acute reactive arthritis, 17(9%) were found to have sarcoidosis. T*he onset of the sarcoidosis cases clustered in the spring (February-June) ($P = 0.01$).*[24] [italics added].

Springtime occurrence coincides with tree pollination. A search for a tree or other plant that is common to and widely distributed in Turkey, New Zealand and Norway, and which produces copious pollen, might prove productive in identifying an additional causal candidate.

19. Is there a shared, intercontinental, tree species whose springtime pollen induces sarcoidosis in susceptible individuals?

I. Increasing sarcoidosis mortality

Gideon and Mannino reported an increase of age-adjusted sarcoidosis mortality of 23% in males and 32% in females between 1979 and 1991.[25] Swigris et al. reported an increase of age-adjusted sarcoidosis mortality of 30% in males and 51% in females between1988 and 2007.[26] A French national study demonstrated a similar, secular increase in sarcoidosis standardized mortality between 2002 and 2011..[27] A secular sarcoidosis mortality increase could be attributable to increased sarcoidosis incidence, to a secular increase in its severity, or as a consequence of increasing, treatment-induced, suppression of spontaneous resolution. Increased ascertainment of subclinical cases due, for example, to increased CT imaging, cannot, by definition, be a contributor.

20. What is the cause of the secular increase in sarcoidosis mortality?

J. Worthwhile trials

1. Thalidomide in males with untreated, stable, persistent stage III sarcoidosis

2. BAL assessment of T_H1 vs. T_H2 in stable stages II, III as prognostic markers

Conclusion

The tantalizing aspect of sarcoidosis is, that in contradistinction to many disorders of unknown cause, its baffling features imply an underlying unity, an interrelatedness that might offer powerful clues to the answers. One conjures a prospective Newton, turning the lense of his unremitting concentration on these problems until the husk of mystery burns off, revealing the solutions. One imagines some future, chimeric, Alan Turing-Sherlock Holmes decrypting-deducing the answers by sheer force of intellect. One envisions him retiring to his Baker Street study at midnight with his clay pipe and a shag of tobacco, seeking the interconnection which must exist, between the characteristic pathology, etiological elusiveness, epidemiology, prognosis and Kveim findings, emerging at

dawn from a cloud of smoke, affirming to Watson that he had arrived at the one possible solution! One envisages them successfully seeking conclusive evidence, which Watson would later chronicle as *The Adventure of the Mottled Lung*.[1]

Notes

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