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Review Article

The cause of sarcoidosis: the Centurial enigma solved

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Abstract I am an experienced pathologist (4 decades), and I can now confidently perceive the cause of sarcoidosis. I can see clearly now because of 2 things: (1) modern evidence indicating a genetic-based immune dysregulation as an essential predisposing causal cofactor and (2) a century of accumulated pathology observations relevant to the point. The first factor helps explain numerous environmental, clinical, and research uncertainties, contradictions, and puzzles. The second factor, not readily available to clinicians, allows me to perceive the answer. The argument: (1) although most pathologists are vague in their conception of a "granuloma," the discerning pathologist realizes that a "true," well-formed epithelioid granuloma has only a very limited number of possible causes; (2) these causes do not include autoimmune diseases nor "self-perpetuating" granulomas to a "cleared" infectious agent; (3) the only feasible 2 causes are an infection or a reaction to a foreign particulate; (4) the only possible infections are ones where the infectious agent can be seen under the microscope; (5) experienced infectious disease pathologists do not see a microorganism (after a century of looking); (6) foreign particulates are therefore the cause (the only feasible cause remaining). This is not a new speculation; what I contribute that is new are pathology perceptions that confirm it beyond speculation. The reason the particles are not seen microscopically is that they are nanoparticles (less than a micrometer in largest dimension); larger particles are cleared from the lung efficiently by mucociliary transport. Direct evidence for this nanoparticulate theory is abundant. A recent case I studied has some compelling details. The nanoparticle theory should be accepted and acted upon, guiding further research, and there are risk-free measures that probably could benefit patients now.

Keywords: Sarcoidosis; Cause of sarcoidosis

1. Introduction

What can a contemporary surgical pathologist, using the same methods available to pathologists a century ago, say to internists about the cause of sarcoidosis that could be of any significant value? Actually, I have determined the cause of the disease. Alas, the most important parts of my assertion are based on simple light microscopic observations, and therefore, the arguments will not seem compelling to physicians who are not pathologists. It will seem to most that my points all have been ones of previous speculation. Thus, this narrative will tend to be viewed by most as nothing more than my opinion, without "hard data" and with nothing new. It is much more than that. What is new is a clarification, an epiphany, of reliable pathologic information based upon 35 to 50 years of my experience and that of some of my colleagues who are highly specialized in the pathology of infectious diseases. When this is added to the large amount of clinical research information gathered from studies over the last century, the pieces of the puzzle snap into place and, the resulting picture becomes brilliantly illuminated. An opinion is a belief based upon something less than scientific fact. When scientific facts or knowledge enter the picture, we are in the realm of hypothesis and theory, with theory being the stronger. My narrative is a theory of the general cause of sarcoidosis. It is a theory with strong evidence, and like other strongly supported theories, it should be acted upon with the assumption of truth until proven wrong.

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2. Genesis and evolution of the theory

Although the possible causes of sarcoidosis that I consider are ones that have been speculated about previously, I now can limit the feasible causes to one. There are 2 main factors that allow me to see farther than did pathologists a century ago. The first factor is the very important evidence of recent decades that indicates some persons are genetically predisposed to the disease [1]; this helps solve numerous contradictions, uncertainties, and other problems within the huge amount of conflicting data garnered over the last century. This genetic-based dysregulated hyperimmune response in patients with sarcoidosis can be viewed as a cause of the disease. It is, however, only a necessary causal cofactor and not a sufficient cause by itself. Needed also is the initiating antigenic stimulus, the underlying proximate cause. The second factor, and the one I newly contribute, are experienced pathologic perceptions that have not been so well observed by many of my colleagues. This has enabled me to clearly see the class of the causal sarcoidogenic antigen(s).

2.1. What is a granuloma?

A reasonably precise definition of a histologic granuloma is a localized and well-defined (circumscribed, well-demarcated) nodule composed of epithelioid (manifesting abundant pink cytoplasm) histiocytes with or without scattered multinucleated giant cells. When defined this way, the word granuloma is pathologically clinically useful because the number of possible causes for such granulomas is relatively limited and a particular cause on the list can be specifically determined in most instances. The problem is that most pathologists have a loose or vague conception of granuloma such that the term starts to lose its useful meaning [2]. For some pathologists, the most nonspecific, mixed chronic inflammation, as long as a few histiocytes are included, can qualify. Why pathology in general has been persistently so poor in the use of this term is something I have tried to understand and explain, but it mostly remains a mystery to me. The important point is that pathologists have contributed greatly to the misleading perceptions that clinicians have about what are, and what are not, granulomatous diseases. That perception is indeed poor for most clinicians, which has been a major impediment for being able to find the cause of sarcoidosis.

2.2. The surprising specificity of sarcoidal granulomas

Among epithelioid granulomas, the sarcoidal granuloma is the archetype example. It is usually relatively uniform (in size and shape) across multiple granulomas, both within a given biopsy, a given patient, or even among different patients. These features lead one to "just know" that it must have a specific cause because it is so strikingly different from the vague, heterogeneous, ill-defined patterns of less specific inflammatory changes. It is true that there are many different causes of granulomas that are slightly less well developed than a "good" sarcoidal granuloma, and if a biopsy is small or there are only very few granulomas to examine, it may not be possible with the given biopsy to adequately judge whether a granuloma is truly sarcoidal or not. If, however, a biopsy specimen is generous and has many granulomas, attention to detail will usually allow a pathologist to decide how well-developed, epithelioid, and sarcoidal the granulomas are. From over a century of pathologic experience, there are only 2 feasible causes of the sarcoidal granuloma (as has long been suspected), infection or foreign body reaction.

2.3. The possible infections

Although a fair number of infectious agents have been suggested as candidates for causing sarcoidosis [3], the actual possibilities are quite limited. For example, a number of viruses have been suggested [4], but viruses do not cause anything like an epithelioid granuloma. An amazing example of how clinicians have been misled is found in a case report purporting to show a sarcoidal granuloma within a Herpes simplex viral infection [5]. Examine the photomicrograph in this report. The mistake is flabbergasting.

The critical point is that the feasible infectious agents are all ones that can be found under the light microscope (with special stains). The only reasonable candidates for an infectious agent are a few fungi (actually, fewer than often supposed) and a few bacteria, mainly mycobacteria. The crucial thing to note is that these agents all are demonstrable in tissues with special stains. (One hypothesized exception would be cell wall–deficient mycobacteria, but see the answer to Objection 1 below).

My colleagues at the Armed Forces Institute of Pathology (AFIP) who specialize in infectious diseases have great experience in examining biopsies with epithelioid granulomas; they are, of course, asked to search for an infectious agent. When biopsies are generous and manifest multiple granulomas, they usually can decide initially (from an H&E-stained slide) whether the findings are suggestive of sarcoidosis or rather possible infection. Over the last half-century, these pathologists have examined tens of thousands of such cases. If the cases were formally studied and blindly divided into the 2 categories (suggestive of sarcoidosis or infection), the results after special stains for microorganisms would be roughly as follows: in the cases suggestive of sarcoidosis, the unexpected finding of an infectious agent would occur in not more than 1% or 2% of the cases. In the group suspected of being possible infections, the infectious agent would be found in about 50% to 60% of cases. (The remaining 40% to 50% of cases in this group would require further follow-up to try to ascertain the likely cause. The possibility that some of these cases without a causative microbe found might subsequently be considered as sarcoidosis with a slightly atypical histologic appearance is not germane to this discussion; the fact would remain that sarcoidal granulomas, whether typical or slightly atypical, lack an infectious agent).

The *P* value for statistically significant difference between these 2 large groups would be very small. (Although the study has not formally been done, the outcome of such is clear; it does not matter whether the *P* value would be .001, .0001, or .00001. There is no practical difference among different infinitesimals.) The infectious agents that could cause sarcoidal granulomas should be findable, and they are not found.

It is true that occasionally some fungi and some bacteria (especially mycobacteria) may be difficult to find and sometimes might not be demonstrated by a pathologist when an infection is actually present. But with an adequate tissue sample, the pathogens usually will be found. This is especially true for my AFIP colleagues. They have great experience, exhibit high diligence, and have always had high quality laboratory support for reliable special stains. These colleagues are very good at their specialty; they do not miss much. If sarcoidosis were caused by an infectious agent, they would have perceived it.

In individual cases, particularly if it is difficult to judge typical versus not-so-typical, the outcome may not be certain, and of course, pathologists must continue doing the special stains for microbes to avoid the occasional mistake. However, the "big picture" clearly shows that sarcoidosis is not an infection.

The clinical community seems unaware of the significance of this pathology information. These data provide evidence against sarcoidosis being an infection that is much more compelling than the meager evidence suggesting otherwise. The genetic-molecular biologic evidence suggesting infection, especially when involving polymerase chain reaction (PCR), is an example of the false leads and misinformation that can result from having techniques that are overly sensitive. If one still insists that fragments or molecules derived from infectious agents could be causal in some instances, it is clear that the mechanism will not be an actual infection. Thus, such agents would be within the spectrum of the true cause, that is, a foreign nonviable particulate.

2.4. The answer

Sarcoidosis is caused by foreign nanoparticulates (particles <1 μm in largest dimension). The particulates are inhaled and/or enter through the conjunctival membrane and through skin contact. They are not seen under the light microscope because they are too small. (Some slightly larger particles are occasionally seen, but they are dismissed as coincidental—see Objection 8 below.) Electron microscopy is very inefficient and unreliable in trying to demonstrate their presence. More sensitive x-ray and other spectrographic methods encounter problems of tissue location and difficulties in quantitation of any minerals discovered, resulting in difficulties in judging the significance of results.

The reason significant numbers of larger visible particles are not also seen in the lung is that such particles are efficiently cleared by the mucociliary blanket. Much smaller nanoparticles are (for physical-chemical reasons) efficiently adsorbed to alveolar and bronchial liquids and then entrapped within tissues.

Well-known studies [6] strongly suggest that common minerals are the most frequent cause; organic substances may be a lesser cause. The latter would be more biodegradable and less persistent than the former. Organic substances could include fragments or molecules derived from microorganisms, but if so, this would still be a foreign body type reaction and not an infection.

The reason that this is the cause is that it is the only feasible cause (based on histopathologic parameters) left standing. If you want more direct evidence, it is available. Especially important in this regard are reports of cutaneous sarcoidosis that have, upon diligent observation, a few granulomas manifesting a little bit of foreign particulate material [7-10]. The number of patients of this type that have been studied now amounts to dozens, and this compromises about 22% of patients with cutaneous sarcoidosis [10]. The thrust of most of these articles [8-10] is to emphasize that finding some foreign body granulomas in the skin does not eliminate the possibility of sarcoidosis (as the cause of the granulomas without obvious particles). The hypothesis is that, in a patient with dysregulated hyperimmune response that characterizes sarcoidosis, the granulomatous response can occur to both foreign material (in a scar with silicates, in a tattoo, etc) and to whatever other "thing" that causes sarcoidosis in the skin. One coincidentally finds foreign body granulomas and granulomas developing to whatever causes sarcoidosis, and these two things are unrelated except that they both are responded to by the abnormal sarcoidal response. However, when one finds numerous cases with granulomas that, in each individual patient, vary in their content of minerals from a lot, to less, to a tiny amount, to amounts that only can be demonstrated by energy dispersion spectrographic analysis of x-rays [8], clearly there is an alternative and more attractive interpretation. Walsh et al [7] perceived this more reasonable interpretation. In reading this article, I can tell that the senior author (a pathologist) glimpsed the truth: that the foreign body reactions and the sarcoidal granulomas are the same disease, that is, the reactions are to the same antigen(s).

A very important confirmation and extension of Walsh's insight is found in a recent case submitted to the AFIP for consultative evaluation of head and neck biopsies from a patient who is a sandblaster. Three years earlier, he had slowly developed a left scalp skin nodule in an area irritated by his helmet. A subsequent biopsy revealed the nodule to be composed of epithelioid granulomas containing birefringent foreign particles. The remaining nodule stayed about the same over the next couple of years, but he also slowly developed left-sided upper cervical lymphadenopathy. This was biopsied, the scalp nodule rebiopsied, and the specimens were sent to the AFIP's Department of Environmental and Toxicologic Pathology for evaluation. The visible

foreign particles (within the epithelioid granulomas) in the scalp lesion were composed mainly of silica, silicates, and titanium dioxide. The neck nodes manifested a large number of noncaseating epithelioid granulomas of relatively uniform size and circular shape. They differed from the scalp granulomas in that foreign material was not apparent. The appearance was identical to what would be seen in sarcoidosis involving lymph nodes. Further very assiduous examination and concentrated search by specialized methods revealed a tiny amount of silicates and titanium dioxide in the lymph nodes. However, the finding was so meager that it was judged that the granulomas in the neck nodes could not be declared to be definite foreign body granulomas (by "usual" criteria).

One might be tempted to suggest that the patient coincidentally has 2 different conditions with different causes. To suggest this borders on the ludicrous. With the relative rarity of diseases causing well-developed epithelioid granulomas, with the close anatomic-physiologic relationship between the 2 involved locations (scalp lymphatics draining to ipsilateral upper neck nodes), and with the fact that there was some foreign material in the nodes in common with that in the scalp, there is no way that the lesions are not causally related. (There was no evidence of infectious pathogens in any of the granulomas by special stains for same.)

The case is seminal in showing the following: (1) foreign minerals can migrate in the body; (2) when they do, the size range of the migrants can be restricted to solely submicroscopic nanoparticles; (3) silicate nanoparticles can cause histologic sarcoidosis, with the foreign material not being detectable by ordinary means.

This patient now has very appreciable mediastinal adenopathy. Almost surely, he will prove to have sarcoidosis by clinical criteria. Whether he does or not, the findings described above are very important ones.

The reason that larger micrometer-sized particles are not seen in sarcoidosis in the lungs is the highly efficient mucociliary clearance of such particles; the nanoparticles, being 2 or 3 orders of magnitude smaller, are not so readily cleared. For persons not genetically predisposed to sarcoidosis, these nanoparticles comprise an insignificant total burden of foreign material. These persons require a much higher exposure to particulates to develop lung disease, one that partly overwhelms mucociliary clearance of larger particles, and this is why pneumoconioses (silicosis, anthracosis, etc) in such persons include microscopic evidence of the foreign particulates. In a person with dysregulated immune response that characterizes sarcoidosis, however, the low volume dose presented by nanoparticles is sufficient to generate disease. This no doubt is partly related to the fact that particle volume decreases with the cube of particle diameter, whereas surface area decreases only with the square. This means that the ratio of surface area to volume increases with decrease in particle size. Because it is the surface area of the particle that reacts with surrounding tissue and thus is the antigenic interface parameter, particulates become more efficient antigen generators per unit volume (dose) of particulate matter as the particle size decreases.

There are cases of sarcoidosis with some observable foreign particulates, but these are construed as coincidental findings unrelated to the sarcoidosis. Both the lungs and skin of persons without sarcoidosis often have some clinically unimportant foreign materials. Thus, it has come to be accepted that, by definition, a sarcoidal granuloma has no observable foreign material, and if a granuloma has such material, it is not a sarcoidal granuloma but is a foreign body reaction. However, this definition is arbitrarily related to the light microscopic observability of the particulates. The important point is that this arbitrary definition has hugely interfered with the ability of physicians to perceive that sarcoidosis is caused by particulates.

Current review articles all still state that the "cause of sarcoidosis remains unknown"—not to me.

3. Objections likely to be raised against the theory

In judging the theory, many apparently discrepant points, or objections, can be raised. However, these points can be shown to be meager ones that pale in import compared with the fundamental importance and compelling weight of the argument given above supporting the theory. What I have done in formulating the theory is to "separate the wheat from the chaff."

The most important points I have used in making this separation, however, are surgical histopathology observations. For a physician who is not a pathologist, perceiving the weight that these points actually have seems intractably difficult. Many of the objections that have been raised actually are trivial.

3.1. Objection 1

What about cell wall–deficient mycobacteria and mycoplasma, which cannot be seen under the light microscope?

3.2. Answer to objection 1

Mycoplasma bacteria are the smallest free-living organisms that can cause disease in humans [11]. They lack a cell wall and therefore do not stain with bacterial stains. The pathologic reaction of an infection with these bacteria has an acute component (with some neutrophils and even microabscesses, and mucosal ulcerations) and occasionally a multinucleated giant cell might be formed. But epithelioid granulomas are not a feature. Of some pertinence for this agent not being causal for sarcoidosis is the fact that among numerous hints from DNA-PCR studies of possible infectious agents, mycoplasma are not mentioned [3].

The cell wall is required for proper histologic staining. But cell wall–deficient mycobacteria cannot be a cause since, as well demonstrated by animal experiments, the cell wall is necessary for inciting an epithelioid granuloma by a mycobacterium.

It is true that occasionally fungi and especially mycobacteria may be difficult to find and sometimes might not be demonstrated by a pathologist when an infection is actually present, but with an adequate tissue sample, the pathogens usually would be found. This is especially true for my AFIP colleagues in the Infectious Diseases Pathology Division. If sarcoidosis were caused by an infectious agent, they would have perceived it, in the same manner that they found the agent of cat-scratch disease [12]. In addition, they have examined many more cases of sarcoidosis than of cat-scratch disease.

3.3. Objection 2

What about infections wherein the agent is "cleared" by the body and yet the granulomatous reaction to the prior agent remains, possibly to antigenic fragments or molecules from the agent?

3.4. Answer to objection 2

The most commonly cited examples of this type of process are cases of mediastinal sclerosis that seem to result from a prior histoplasmosis pulmonary infection, but in the fibrosing stage the organism is not found. This hypothesis does not hold for sarcoidosis. With the huge number of cases of sarcoidosis studied over the last century that have included surgical biopsies and/or autopsy examination, with some of the latter being incidental discoveries of sarcoidosis clinically unknown and not related to the cause of death, it is inconceivable that an infectious agent, if involved, would not have been discovered in at least some cases. There would be an early stage before the agent was degraded wherein it could be detected. The agents would not always happen to "disappear" just before pathologists start to look. After all, in mediastinal sclerosis, there are some cases where the relationship to the fungus is manifested, both clinically (evidence of prior pulmonary histoplasmosis) and pathologically (seeing the fungus). This is how the apparent infectious cause was ascertained.

A very much related contemporaneous speculation about sarcoidal granulomas that attempts to explain the fact that the cause is not seen microscopically is the concept that the hyperimmune response may involve positive feedback loops that cause a persistence of the granuloma in the absence of an inciting antigenic cause [3]. Although such loops might be a part of the immune response and might cause amplification of the reaction, the hypothesis ignores the fact that at least some persistence of the antigenic cause is required; amplifying systems do not amplify "nothing" into "something." In addition, the highly delineated, circumscribed, constrained morphology of the granuloma is important; a reaction perpetuated by the diffusely migratory elements of the inflammatory immune response, with nothing available as a topologically focusing antigenic particle, would not remain so constrained.

3.5. Objection 3

If common mineral particulates are the important cause, why did a thorough study of environmental agents such as ACCESS (A Case Control Etiologic Study of Sarcoidosis) [13] not find very significant evidence for such?

3.6. Answer to objection 3

The control subjects did not have the genetic predisposition to the disease, and the causative agents are multiple and common. The genetic component of the causation of sarcoidosis means that control persons (without the genetic predisposition to the disease) are not "true" controls, that is, they will not respond to a particulate challenge the same was as genetically predisposed individuals will. When one adds the factor of a multiplicity of common particulates as being causal, the problems of trying to ascertain relevant exposures for different individuals become daunting. The already inappropriate controls will be exposed to these substances and trying to identify subpopulations reliable for analysis and comparisons will be hopeless; any data gathered will be unreliable.

As is expressed in the first portion of the discussion section of the ACCESS study report, the authors realize these problems [13]. Indeed, they imply that because environmental substances are still suspected but the study did not have strong evidence for specific individual substances, this is some indirect evidence that the causative substances likely are numerous and perhaps mostly relatively common.

3.7. Objection 4

The histologic arguments exclude some agents because nothing like an epithelioid granuloma response occurs to the agent in a normal person; perhaps the abnormal immune response in the patient with sarcoidosis is an "all-or-none" phenomenon, completely absent in the normal person.

3.8. Answer to objection 4

To restate this objection, because clinical sarcoidosis involves a genetic-based, idiosyncratic hyperimmune granulomatous reaction, perhaps in a "normal" person, the granulomatous reaction would be totally absent to a particular agent, but in the sarcoid-disposed person, the agent would cause exuberant sarcoidal granulomas. This is not a feasible proposition. The genetic polymorphisms involved in sarcoidosis, although far from completely understood, must be complex and heterogeneous [3,6] and they would not result in a simple all-or-none granulomatous response. If the immune-inflammatory mechanisms were so radically altered in the patient with sarcoidosis, the patient surely would have other medical problems more serious than sarcoidosis. The immune response in patients with sarcoidosis seems to be altered, but it is not greatly or fundamentally changed in some drastic way. If such a basic and important function were drastically altered, almost surely the patient would be manifesting abnormalities other

than sarcoidosis and would have some impaired or otherwise abnormal response to a lot of infectious agents. Likely, the disease would be uniformly fatal because of this severe alteration of immune mechanisms. A second point that neutralizes this objection is the fact that the normal (ie, non–sarcoid-affected) person is clearly quite capable of forming good epithelioid granulomas, to tuberculosis (TB) bacilli, to histoplasma, and so on.

3.9. Objection 5

If the causal particulates are common and normal persons (ie, non–sarcoid-affected) would tend to form some granulomatous reaction to such, why are not such granulomas seen in normals?

3.10. Answer to objection 5

Almost surely they are. There are many instances wherein a few, puny granulomas are found in lymph nodes (or other tissues) biopsied for sundry reasons. A specific cause for the granulomas is looked for, not found, and the patient remains clinically unaffected by a relevant disease. These granulomas end up being essentially ignored. They are ignored because they are not clinically important. The patients do not develop sarcoidosis and, indeed, do not develop any other disorder related to the granulomas. Such instances might seem to be uncommon, but that probably is largely because, being unimportant, they are not well remembered by individual pathologists.

3.11. Objection 6

Because many patients with sarcoidosis likely have repeated or almost continual exposure to common mineral particulates, why is sarcoidosis so often a rather "self-limited" disease?

3.12. Answer to objection 6

This is a challenging question no matter what speculative cause is suggested for the disease, and thus the answer seems not important in deciding among different hypothetical causes. Probably, the answer relates to some modulation-decrease in the abnormal dysregulated hyperimmune response. The fact that the prevalence of reactivity to the Kveim test tends to decrease in patients with time supports this idea. This Kveim test data are important in indicating that self-limitation is not necessarily caused by cessation of exposure to causal antigen but rather involves an alteration in the immune reaction.

Cessation of exposure or periods of decreased exposure to antigen would tend to be more likely with episodic infections than with common inorganic particulates; this makes the hypothesis of infection seem more attractive because it would more easily explain spontaneous improvement in many patients. However, this would not easily explain the synchronous decrease in Kveim reactivity because such a hypersensitivity reaction would not likely "immediately" decrease or disappear with decreased or eliminated antigen exposure. Compared with the evidence against infection as a cause, this argument in favor of infection is very weak.

3.13. Objection 7

What about an autoimmune cause?

3.14. Answer to objection 7

Not histologically possible. Known autoimmune diseases do not form anything remotely like an epithelioid granuloma; the vasculitis seen in many autoimmune diseases is not a granulomatous reaction; a rheumatoid granuloma is not an epithelioid granuloma [2]. The extremely well demarcated focality of sarcoidal granulomas enables a thinking pathologist to know that autoimmunity is not the cause; no self-antigen would be this extremely limited in distribution to a few microscopic points. The hypothesis that sarcoidosis may be an autoimmune disease [1] is invalid and is misleading to you. A list of diseases thought to be autoimmune would include: aplastic anemia, autoimmune hepatitis, celiac disease, Crohn disease, diabetes mellitus (type 1), Goodpasture syndrome, Graves disease, Guillain-Barre syndrome, Hashimoto disease, idiopathic thrombocytopenic purpura, lupus erythematosis, multiple sclerosis, myasthenia gravis, opsoclonus-myoclonus syndrome, optic neuritis, pemphigus, primary biliary cirrhosis, rheumatoid arthritis, Reiter syndrome, Sjogren syndrome, Takayasu arteritis, temporal ("giant cell") arteritis, warm autoimmune hemolytic anemia, and Wegener granulomatosis. Most of these disorders involve nothing even approaching a granuloma. Five diseases from this list require comment, mostly because of misleading comments in the literature stating that they are granulomatous. Wegener granulomatosis is not a truly granulomatous disease, as I previously have shown in the literature [2]. Rheumatoid arthritis may tend to localize in joint tissues because certain antigens are therein, but a histologic rheumatoid granuloma is nothing like a focal sarcoidal granuloma and is not nearly as limited or well-delineated, nor is it truly epithelioid. Regarding giant cell arteritis, it should be clearly understood that giant cells alone are not equivalent to a granuloma. Primary biliary cirrhosis is thought to be an autoimmune disease, and the changes can include some poorly formed granulomas. However, these are reactions to the irritative effects of extravasated bile, and they are not directly caused by the autoimmune process that is responsible for destroying the bile ducts [14]. Crohn disease sometimes has a few scattered granulomas, which sometimes can approach the appearance of a reasonably well-formed epithelioid granuloma. However, these are uncommon and not a hallmark of the major inflammatory reaction of the disease [15]; they are an "epiphenomenon," and probably, they are a reaction to some foreign particulates from the bowel lumen migrating into the bowel wall through the major fissures and tissue disruption produced by the primary inflammatory alterations.

3.15. Objection 8

What about the many literature articles seeming to provide evidence for multiple different infectious agents? How can this just be ignored? What about hypersensitivity pneumonitis, which is often caused by antigens from infectious agents and which sometimes has histologic granulomas?

3.16. Answer to objection 8

A huge number of literature articles purporting to present evidence for an infectious cause of sarcoidosis need to be partly discounted. Many of these need to be totally discounted, that is, they require explicit denunciation as totally worthless. Actually, some are worse than worthless, because they are misleading. An example is citation 102 in Reference 3. This article asserts that "In 30 consecutive cases of sarcoidosis, acid-fast bacilli were found in every instance." Of course, one could say that, by definition, the cases were not sarcoidosis, but that is not the point. This was a retrospective study and what the authors are implying is that, by some means of more diligent search, an acid-fast bacterial cause can be found in all or most cases diagnosed as sarcoidosis. It is true that in an occasional case thought to be sarcoidosis (and the patient treated for such), including a negative TB skin test, absent mycobacteria histologically, and negative culture results, later retrospective examination might uncover a mycobacterial cause histologically. But even in the 1950s and 1960s (treatment times for patients in this article), such cases were quite uncommon. To imply that in 30 unselected "consecutive" cases (previously examined by multiple different pathology laboratories including ones in different countries) a misdiagnosis in 100% of cases was uncovered by the authors' small group of pathologists using the same methods available to the world is absurd. Clearly, there were major selection biases for the study cases, and there are clues to some of these in the article. The important point is that articles like these need to be explicitly dismissed in current review articles, but this is not happening. Current review articles continue to cite such incorrect articles and thereby lend them (falsely) some credence. Thus, internists are giving credence to totally erroneous studies while giving none to my compellingly supported exposition of the cause of the disease. The irony is intense.

To turn now to points regarding hypersensitivity pneumonitis, the granulomas in this disorder are different from sarcoidal granulomas in that they are "looser" and not nearly as epithelioid. Hypersensitivity pneumonitis is usually a more acutely presenting disease, and it usually tends to regress rather quickly with cessation of exposure to the causal agent, much more quickly than is the course of sarcoidosis. This provides some support to the idea that organic molecules associated with infectious agents (or other organic molecules, for that matter) are probably degraded and cleared much more readily than most inorganic substances.

One needs to remain aware of the numerous contradictions and inconsistencies in supposed evidence for an infectious cause for sarcoidosis. After a century of accumulated research evidence, one difficulty in perceiving the cause is being unable to "see the forest for the trees." One needs to stop concentrating on individual trees, especially if said trees are dead or dying. The bottom line is that the evidence for an infectious cause is much less compelling than that for inorganic particulates. One important part of the latter evidence are individual cases wherein a reaction that is clearly sarcoidal has been definitely, unequivocally caused by foreign mineral particulates. No case of typical sarcoidosis can be said definitely to have been caused by an infectious agent.

An example which proves that a sarcoidal reaction can occur to tattoo material was recently studied at the AFIP. In recent years, it has become clear that interferon therapy for hepatitis C infection can apparently sometimes initiate the immunologic dysregulation that underlies sarcoidosis, probably in individuals who are already at least partly predisposed to the disease. This case was such an example, and it occurred in a patient with a forearm tattoo that had been present longer than 20 years. Synchronously with the development of definite clinical sarcoidosis including pulmonary and mediastinal disease (supported with all the usual clinical, laboratory, and histopathologic findings), a clinically prominent dermal reaction developed in and around the tattoo. Biopsy revealed the reaction to consist of typical sarcoidal granulomas except for the presence of tattoo pigment in the granulomas. The timeline considerations in this case clearly indicate that the dermal reaction was dependent upon the development of sarcoidosis, that is, it is indeed a sarcoidosis lesion. To suggest otherwise, that is, to claim that it is not a sarcoidal lesion (by definition) because of the pigment is arbitrary and, more important, is illogical and obfuscating. A case like this proves that a sarcoidal reaction can occur to foreign mineral particulates. It does not prove that all sarcoidosis are so caused, but at least some are. This is a significant difference from infection as a hypothesized cause because no case of typical sarcoidosis has been proven to have been caused by infection (see Answer to objection 11 below).

This case is also important in showing that, in a given patient with sarcoidosis, the sarcoidal reaction can occur to different particulates within that individual patient. The sarcoidal reaction in this patient's lungs is presumably to different antigens than are present in the tattoo pigments causing the dermal sarcoidal reaction.

In addition to many other cases involving skin sarcoidal lesions that also support the fact that sarcoidal lesions can be caused by foreign mineral particulates, some intravenous drug abuse cases are relevant. "Talc" granulomatosis of the lung secondary to intravenous injection of suspended, crushed pentazocine tablets can cause a clinical picture very similar to sarcoidosis [16], except there are visible foreign particulates seen in the granulomas. This latter

difference from sarcoidosis can be explained by noting that the particulates reach lung tissue via veins rather than the airways, and thus the mucociliary blanket has no opportunity to clear the larger (ie, visible) particles.

A final illustration of the foreign body cause of sarcoidosis is derived from berylliosis. When properly viewed, chronic berylliosis can be seen to be very similar to sarcoidosis (despite some clinical differences). The histologic finding is that of sarcoidal granulomas. Although sometimes (rarely) the beryllium particles can be seen in the tissues, usually they are all tiny enough that they are not detected. Diagnosis in the latter cases has been made by compelling exposure circumstances and by the beryllium blood lymphocyte proliferation test (indicating a hypersensitivity to the metal).

The main difference is that berylliosis generally is almost solely a pulmonary disease. The difference can be explained by the fact the berylliosis results from an elemental metal particulate rather than the more common mineral (compound) particulates that cause most sarcoidosis. On a nanolevel, elemental metals can be expected to interact with tissues rather differently than mineral compounds would. Metals could be attracted to alveolar liquids and both alveolar and bronchiolar cell membranes more avidly than minerals. Absorbed into (entrapped within) tissues, they could be more fixed and unable to migrate. In addition, free metal atoms or ions (necessary for haptenic generation of antigens required for the essential immune response) would be more readily formed than free molecules from mineral compounds (because of the intermolecular forces making such compounds relatively more stable). This would make beryllium more "granulomagenic" at a lower exposure dose compared with that required for minerals. Any perceived minor differences in radiologic-pathologic (eg, specific locational distribution within lung and lobular anatomy) or histopathologic features between berylliosis and sarcoidosis are also readily explained by these 2 different "classes" of sarcoidogenic particles (ie, metals vs others). The important point is that berylliosis is another proof that sarcoidal granulomas can be caused by a foreign particulate. The same can be said for zirconium or zirconium-aluminum granulomas.

In addition, although the clinical import of berylliosis is mainly in the lungs, one should realize that other organs sometimes contain the granulomas. The one exception that has been touted and used to make a (unwarranted) distinction from sarcoidosis [3] is in the head-neck region, that is, the absence of orbital, parotid, and central nervous system (CNS) involvement. This is readily explained when one realizes that these areas most likely are affected in sarcoidosis via the conjunctival portal. That is, conjunctival entry of airborne particulates causes orbital disease, and lymphatic drainage to intraparotid lymphatics-paraparotid nodes causes parotid disease (and this linkage between the 2 anatomic regions is responsible for Heerfordt disease, uveoparotid fever). The seventh cranial nerve is intimately associated with the parotid gland, and thus, it is no surprise that this is the most common nerve affected. Perineural pathways of this nerve and possibly other cranial nerves allow transport of nanoparticles to the central nervous system. Because the anatomy and physiology of the tear system are different in a number of respects from alveoli and alveolar fluid parameters, it is easy to imagine that tears could be very effective in clearing beryllium nanoparticles, but alveolar fluids would not be. Admittedly, these points are speculative, much more so than the basic arguments for the theory, but arguing these points is not very important compared with the critical points upon which the theory rests. Therefore, this difference of berylliosis from sarcoidosis is relatively unimportant for the present thesis.

Thus, there is abundant direct evidence that sarcoidosis is caused primarily by foreign inorganic nanoparticulates. Even if some sarcoidosis cases are related to organic particulates, possibly including molecules related to infectious agents, still these would be nonviable foreign particulates and not an infection. Clearly, sarcoidosis is an environmental disease caused by noninfectious particulates.

3.17. Objection 9

Because there are many contradictory research results in the literature, how do I avoid subliminal bias that would tend to reject only the literature arguments that are against my theory and accept only ones that are in support of it?

3.18. Answer to objection 9

Most articles in the literature deal with evidence that pales in import compared with the fundamentally important factors upon which I have based my theory. Therefore, I have discounted or ignored much that is in the literature, whether it supports my argument or is against it. When the importance is minimal and the results less than reliable, discounting this "noise" seems reasonable. Another component of the answer to this objection relates to personal considerations. I have no horse in this race. That is, this publication will not further my professional status. I have over 100 peer-reviewed publications in my specialty field; I am in the latter portion of my career with no concerns about job advancement or other change. In addition, this theory will not win me any prizes nor produce any laudatory remarks; this is clear because I can hardly get anyone even to listen to me let alone find someone (in internal medicine) who sees any importance or value whatsoever in my observations.

Sarcoidosis is not important in my work nor to me personally. I have no relatives or friends with the disorder. I did not actively seek the cause. The cause that I write about entered my cognitive mind unsought, and there it flowered and matured with a kind of automaticity. I did not seek the answer, but after it blossomed into a crystal clear mind-picture, I cannot ignore it. I have to try to portray this picture so that some internists hopefully might begin to sense the

truth. Because the picture (the theory) has definite potential benefit for patients, my moral sense as a physician compels me to write this exposition.

3.19. Objection 10

Is not my contribution from pathology just visual perceptions, without good reproducibility, and not based upon experiments or objective measurements, and therefore not good scientific evidence?

3.20. Answer to objection 10

This objection seems to pervade, in a subtle way, many of the objections to the theory by nonpathologists. It seems to come from the recognized great importance of well-controlled and rigorously conducted clinical trials and other experiments for modern evidence-based medicine. This is certainly the mainstay of contemporaneous internal medicine advances, and many errors have occurred in past when studies were less well constructed. Simple observations can sometimes be misinterpreted and can be misleading. In addition, it is certainly true that in most medicine (as in most science in general), most of the things that can be learned from simple observations of nature have already been perceived. Although surgical pathologists are indispensable for tissue diagnoses for those individual patients requiring such, surgical pathology no longer is able to contribute much that is new to fundamental medical progress by simple histologic observations. However, cannot contribute "much" is not the same as cannot contribute "anything," and there are exceptions. My theory is such an exception.

Although histopathologic visual perceptions seem simple and rather nonscientific, they mostly are rather highly reliable. In thinking about this objection, one should recall the instances of very simple, but yet so very profound, scientific observations several centuries ago that have so greatly affected the advances of the age of science. The simple observation of the 4 moons of Jupiter by Galileo extended and confirmed the Copernican revolution in the most earth-shaking (and church-shaking) way possible.

In the United States, there are multiple aphorisms attributed (mostly in a humorous "tongue-in-cheek" fashion) to baseball catcher Yogi Berra. One such is the following: "You can sometimes observe a lot by just looking." There is truth in this aphorism.

When dealing with biologic-medical phenomena, we cannot expect most theories to reach the level of "mathematical proof." My theory has strong support, and it should be considered as valid (and acted upon) beyond a reasonable "medical level" of doubt.

3.21. Objection 11

What about the occasional case thought initially to be sarcoidosis, but subsequently an infectious agent is found? Could not this be an example of infection causing sarcoidosis?

3.22. Answer to objection 11

This is a very logical objection. If every time bacteria were found in a case suspected possibly to represent sarcoidosis, the case automatically ("by definition") was to be excluded from sarcoidosis, this would clearly prevent sarcoidosis from being recognized as caused by an infection. However, this objection does not hold because of the following 2 points: (1) among cases with typical sarcoidal granulomas (judged by an experienced infectious disease specialist pathologist), the percentage of cases with an infectious agent is miniscule, almost "vanishingly rare," and too tiny to be a compelling objection; (2) more importantly, there has been no case wherein, beyond the histologic granulomas, the patient has had a completely typical clinical picture (including other laboratory evidence) and subsequent course to definitely support the diagnosis of sarcoidosis. Of course, a completely typical case would include some beneficial effect from long-term steroid therapy, and such therapy would not be done in a case with a documented infectious agent; thus, I can be confident that my assertion is correct, and there is no completely typical case hiding in the literature nor one having occurred but gone unreported.

3.23. Objection 12

What about *Helicobacter pylori*? As a causative factor in gastric ulcers, this bacterium was unknown to be causal for a very long time, and this shows that a bacterial cause for a disease can remain unknown.

3.24. Answer to objection 12

This objection to my theory was raised by a journal reviewer. This reviewer had other points, but the wording of this objection indicated that he considered it to be the absolute "killer" objection to the theory. Actually, it is illogical and invalid because it is the converse, the opposite, problem presented by sarcoidosis. However, I discuss it because it provides important insight into the different viewpoints and perspectives that can exist between pathologists and other physicians. A pathologist would never make the mistake of considering this question as relevant to the theory of sarcoidosis causation.

When a pathologist hears a question or other remark involving *H pylori* and ulcers, it is automatic for a "mind's eye picture" of the bacterium to form as a memory image, at least to some degree, even if it may only be a fleeting image. In other words, the pathologist has previously seen photographs of the bacterium and has seen the actual stained organism in gastric biopsies. Thus, the pathologist has an indelible knowledge from personal experience that the organism can readily be seen histologically. The reason the causal association with ulcers went unperceived almost "forever" is simply that the hypothesized causal relationship was not conceived and properly tested. It was not because the bacterium could not be found under the microscope. This is the converse of the sarcoidosis problem, where a

possible bacterial cause has been sought (hypothesized) for a century, but the organism has not been found.

This difference in perspective between pathologists and others, arising directly from the nature of the pathologists work, is an example of how it may be difficult for internists to readily accept the validity of some contributions that pathologists occasionally can make to basic medical problems. For my theory about sarcoidosis, the histopathologic details about granulomas are essential for the logical continuity of the argument.

3.25. Objection 13

My conclusion is anticlimactic.

3.26. Answer to objection 13

This is an example of how reluctance to trust pathology contributions can contribute to the internal medicine community becoming obstinate and even obtuse. The fact that my theory confirms something that has long been considered as possibly causally relevant is perceived as a letdown, a disappointment, that is, it is anticlimactic. This disappointment may mostly be rather subliminal for many, but it nevertheless can be important in shaping viewpoints. One reviewer was vehement in expressing this objection; his comments sounded almost angry.

This seems to be related to, and an accentuation of, the reaction to my theory that "it is nothing new." There seems to be an unconscious desire for the answer to the cause of sarcoidosis to be something very new, unusual, and exciting. For example, an infection by a previously unknown retrovirus, the "Misha virus," occurring synchronously with enhanced solar flare activity could qualify as a theory that is acceptably new and unexpected and therefore appropriately interesting and exciting. This type of "new" cause could result in a Nobel prize for someone. *H pylori* as a cause of ulcers was an interesting and exciting discovery. Alas, the cause of sarcoidosis is nothing like this. The cause is mundane, unexciting, and "nothing new." I cannot help this. This is not relevant to the correctness or incorrectness of my theory. To suggest otherwise, to dismiss the theory because it is anticlimactic, is truly being obtuse.

4. Discussion (consequences of the theory)

The evidence for sarcoidosis being a reaction to foreign nanoparticulates, with most particles being relatively common minerals in the environment (but possibly including some elemental metals or some organic particulates in some instances) is overwhelming. I recommend that this theory be assumed definitely to be the cause until "proven otherwise." Organic nanoparticles (including those possibly derived from microorganisms) likely would be much more biodegradable than minerals and metals. Because persistence of antigen in tissues has been deemed by many to be an important part of sarcoidosis [3], this may make organic particles less important than minerals and metals.

Additional studies to try to identify specific environmental particulates are likely to be unrewarding. Efforts now should be directed toward altering the patients' environmental exposures without requiring knowing a specific particulate cause. This of course makes some types of intervention problematic, but there are several things that can be tried, and this is where environmental research efforts should be concentrated. It may be that someday highly targeted therapy directed toward altering the abnormal immune response may tend to make environmental questions essentially moot. However, that day is not here yet, and it is unlikely that altering the complex and fundamentally very important inflammatory immune mechanisms of patients will be without some risk of adverse side effects.

For most patients, repeated or almost continual exposure to the pathogenic particles seems likely. (The fact that most cases are self-limited is not an argument against this; self-limitation requires an explanation related to modulation of the dysregulated immune response regardless of a hypothesized cause.) If an internist accepts my theory, then surely more would immediately be done to help patients possibly limit their exposure to a likely cause. Limiting continued exposure to the causative agent has at least some potential to be helpful, despite the fact that most patients may have a rather "self-limiting" disease. Because young women are frequently affected, such patients might be using talcum powder on their baby's posterior or on their own bodies. No talcum powder should be allowed in the house of sarcoidosis patients. No cosmetic powders. Because vacuuming a rug (unless there is a central vac system) stirs up many nanoparticles that are not filtered out by the vacuum device, and they hang in the air for a fair while (because they are so tiny), this may be a very important causal factor for many persons. The wife-patient should leave the house while the husband, son, or daughter does the vacuuming. If the family is planning on moving or otherwise changing homes (for reasons unrelated to the sarcoidosis patient), the presence or absence of a central vacuum system (which would be less contaminating to the household air) in the choosing of a new house becomes an important consideration. These are all things that could be done or taken into account at zero risk to the patient so that a possible benefit-to-risk ratio is astronomical, even if the likely benefit possibly may be small. The cost to the patient in terms of inconvenience is quite small. Advising patients in these specific ways is not currently being done. The most that might be done in advising a patient seems to be "don't smoke, avoid chemicals and dusts." Without being more specific and directive, this is of no help. (I can imagine patients saying to themselves, "What chemicals? OK, I will be sure and avoid the acid in my car battery; and I won't go to the desert for vacation in case I might encounter a sand storm.")

The possible benefit of measures like these could be tested readily by prospective studies with no risk to patients. In judging the degree of possible harm from a particular

"dust-type" (ie, particulate) exposure, it should be realized that estimates of amount of harmful particulates made by the visual appearance of contaminated air may be very misleading. This is because micrometer range particles are much more visible than nanometer particles, but the latter are much more harmful. Thus, exposure to a sandstorm may be much less dangerous that the nanoparticles stirred up from vacuuming a rug. This point is especially relevant when trying to judge a patient's occupational exposure risk. Nanoparticulates may be present and important for said patient, but the environment may not be judged a "dusty" workplace by general criteria.

Possibly, more efficient help would be the placement of hyperefficient subtypes of HEPA filters in every room of patients' houses and possibly their offices or other workplaces if relatively small and delimited. The size distributions of causative nanoparticles are not known (yet), but it is likely that ordinary HEPA filters might not be very helpful. The ultra low penetration air variants, however, remove particulates down to 200 nm with 99.999% efficiency [17].

Because the filters cost money, an internist friend assures me that evidence-based medicine demands that the hypothesis of possible help from such filters be tested by a proper clinical trial before this would be recommended to patients. I would urge internists to please begin such a trial, albeit to date my argument has encountered only deaf ears.

Knowing more specifically the cause of sarcoidosis can limit wasted effort and expense of misdirected research.

Because my theory can be directive in these ways, it is considerably better than the prior and current tentative speculations that have left persons writing reviews on sarcoidosis to begin their comments with the simple but overly pessimistic sentence: "The cause of sarcoidosis remains unknown" [3]. This is not true, and the inability of internists to recognize this fact represents a failure of contemporary medicine.

5. Epilogue (for pathologists)

The consequences of my theory regarding import for patients would be better communicated directly to internists. But I publish them in a pathology journal because pathologists are my only hope for "spreading the word" and acquiring some kind of audience. Internists have paid no heed, and this likely is because of the critical role that pathology observations play in my argument. If you perceive some value to my comments, I urge you to try to get your internist friends to read this article and try to help them find some value therein. I thank you for your help.

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