Occupational causation of sarcoidosis

Sarcoidosis is an uncommon disorder of unknown cause characterized by widespread granulomas, a distinctive tissue response resembling that caused by tuberculosis. A number of articles have appeared within the past few years inferring occupational causation based on a higher incidence in fire-fighters and World Trade Center Disaster (WTC) workers. The purpose of this communication is to point out the shortcomings of those inferences, which are influenced by "observer effect" (OE) and which lack direct evidence of causation.

Observer effect: Heisenberg's uncertainty principle—that the position and the velocity of an object cannot both be measured exactly, at the same time, even in theory—is the archetypical example that the act of observation may influence the measurement. In Medicine, OE is evident in distortions of incidence (number of new cases per year per 100,000 persons). For example, what many regard as a melanoma pseudo epidemic may be attributable to a higher rate of biopsy (OE) of tiny pigmented skin lesions. The incidence of sarcoidosis is subject to OE:1) two-thirds of chest radiograph-identifiable sarcoidosis are clinically silent; 2) the bulk of cases occur in the 20-40-year age-range; 3) there is an ethnic incidence differential, most evident in the marked susceptibility of African-Americans. Thus, an observer's decision to annually screen WTC or firefighters with chest radiographs will spuriously increase their incidence vs. the (unscreened) population from which they are drawn as will the selection for screening of any occupation which largely employs individuals in this age range. Failure to correct for differing ethnic composition of the investigated population vs. the population at large may affect the incidence computation. Potential sources of a spuriously elevated incidence justify reservations about the validity of the reported statistical association between these occupations and sarcoidosis.

Evidence of causation: The purpose of incidence assessment is to identify risk factors that guide investigations searching for direct evidence of causation. Following demonstration of a valid statistical association, establishing causation rests on criteria advanced by Bradford-Hill:

Strength of the association: The differential incidence of lung cancer in cigarette smokers, a well-recognized causal relationship, is 9:1, far higher than the differential incidence of sarcoidosis in the cited occupations.
Biological credibility: Tobacco smoke, the principal cause of lung cancer, contains known carcinogens. The pulverized residual of the WTC disaster has not been shown to generate a granulomatous response. A positive (granulomatous) response to Kveim suspension, a test for sarcoidosis, requires 4-6-weeks to evolve. Some authors have reported that the annual incidence of sarcoidosis peaked 7-9-years after WTC exposure; they supplied no explanatory mechanism to account for the latency. Investigators inferring a causal relationship of sarcoidosis to firefighting have not identified a fire-generated agent known to induce a granulomatous response.
Consistency with observations in other settings: London and Berlin were repeatedly fire-bombed and pulverized during WWII. To my knowledge, there are no extant reports of

sarcoidosis in the exposed workers. If ". . . inhalation of particulate matter may trigger a systemic inflammatory response, which can ultimately result in granuloma formation in any organ."—were valid, one would expect to see reports of sarcoidosis case clusters in industrial demolition occupations. To my knowledge, none exist. A large case-control study of sarcoidosis analyzing environmental and occupational risk factors did not identify any occupations associated with sarcoidosis that were remotely related to WTC exposures. Dose-response relationship: A single WTC case series reported a weak correlation between the duration/intensity of exposure and the development of sarcoidosis. The fire-fighting series did not provide this evaluation. The statistical limitations cited above apply.

In summary, the inference that exposures to firefighting and WTC disaster cause sarcoidosis is open to question: both are based solely on challengeable statistical methodology, and neither is bolstered by direct evidence of causation.

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