Deciphering Histoplasmosis,
Systemic Noncaseating Granuloma,
and Sarcoidosis in the Literature

To the Editor:

One naturally wonders whether encrypted in the bewildering literature on the association between histoplasmosis and systemic noncaseating granuloma (SNG) there is decipherable message.

In September 1940, the brilliant English mathematician, Alan Turing, was recruited to the Government Code and Cipher School at Bletchley Park, north of London, where it had been moved from Whitehall as a safety precaution, to participate in the project code-named “Ultra,” with the objective of decrypting radio transmissions generated and read by an electromechanical device, “Enigma,” comprising five rotors and a plugboard of such baffling sophistication and complexity (there were $1.3 \times 10^{12}$ plugboard combinations for each of $1.1 \times 10^9$ rotor states) that the Germans, throughout the war, and despite compelling evidence to the contrary, believed it to be indecipherable. Decryption depended on the use of “cribs” such as duplicate messages and standard forms of address, and “Bombes,” computers exploiting the theoretical concepts embodied in the Turing Universal Machine. Validation required the achievement of “plaintext.” The remarkable success of Ultra, which led to the Allies’ victorious prosecution of the submarine war in the Atlantic, remained the most closely guarded secret of WWII; its existence was not revealed until 25 years later. If obliged to decrypt the enigmatic literature on histoplasmosis accompanied by SNG, it is a fair bet that the Bletchley Park staff would have employed similar methods.

Carter and Hunninghake (July 1997)1 infer that their patient with SNG had a pauci-bacillary form (no organisms were identified from any site) of progressive disseminated histoplasmosis (PDH) based on exposure, nondiagnostic serologic titers, and calcified hilar lymph nodes. Does dense lymph node calcification develop within this timeframe? Could the enlargement have been due to sarcoid granuloma superimposed on previously calcified nodes? Were earlier films available for comparison? Excepting the massive pleural effusion and calcified lymph nodes, their patient resembles 11 persons described by Wheat et al.,2 with SNG accompanying serologically confirmed histoplasmosis in an endemic area (Indianapolis). In about half, a diagnosis of sarcoidosis preceded by many years an acute exacerbation ascribed to histoplasmosis; in the remainder, the acute episode coincided with the recognition of SNG. One patient had organisms recovered only from sputum, one had antig-nouria, and, in the remaining nine, no organisms were identified from any site. Two patients given amphotericin B failed to respond; eight given corticosteroid therapy (CST) responded. The authors suggested that histoplasmosis could induce a sarcoid-like disorder by an immunologic mechanism; their observations are also consistent with the possibility that it might exacerbate pre-existent sarcoidosis.

Arbaquez and Sharma4 reported a 73-year-old Iranian immigrant to California recently identified with symptomatic stage II sarcoidosis in whom a histoplasmaoma appeared 1 year following CST, while the dose was being tapered. Tehib et al.5 reported a 49-year-old immigrant from Africa of caucasian ancestry with stage II sarcoidosis. The patient declined treatment and returned, acutely ill, 3 months later at which time a biopsy of a new skin lesion demonstrated Histoplasma capsulatum. The patient died of PDH, confirmed at autopsy, despite amphotericin B and CST (given for adrenal insufficiency). The authors pointed out that the initial diagnosis was, in all likelihood, correct, inasmuch as the illness had begun months before pharyngeal symptoms appeared, his tuberculin test had converted to negative, the pulmonary shadowing spontane-

ously regressed, and organisms were not identifiable in noncaseating granuloma in a tonsillar ulceration and a peribronchial lymph node initially or in the last hospitalization. Yaseen et al.6 described a 61-year-old patient with untreated sarcoidosis of 20 years’ duration who developed PDH. The import of these three cases is that persons with sarcoidosis are predisposed to develop histoplasmosis, or, for the latter two, that persons with quiescent pauci-bacillary PDH may exhibit a clinical, pathologic, and radiographic picture indistinguishable from sarcoidosis. This seems unlikely given the latency, particularly in the last case. The cryptanalyst requires a crib for this seeming contradiction: histoplasmosis is an (immunologically mediated) cause of SNG; SNG is a (predisposing) cause of histoplasmosis.

Munro et al.7 in a brilliantly conceived study employing the Kveim response as a paradigm for the pathogenesis of sarcoidosis, found that the early response, at 11 and 18 days, differed among normal and known Kveim-negative sarcoidosis patients vs known Kveim-positive sarcoidosis patients: the former but not the latter exhibited a cellular pattern characteristic of delayed-type hypersensitivity. This seems to imply that the expected granulomatous response in the Kveim-positive group is an immunologic fall back response, an interpretation supported by the report of Fasano et al.8 of a 10% incidence of sarcoidosis in their 80-patient clinical population of combined immunodeficiency disease. If one provisionally accepts this hypothesis—that the fundamental nature of sarcoidosis is an undefined and elusive flaw in cellular immunity resulting in impaired processing of certain types of antigens—the seeming contradiction is resolved. How to test it?

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REFERENCES


False-Positive Results of Carcinoembryonic Antigen in Pleural Effusions

To the Editor:

We read with interest the paper by García-Pachon et al (March 1997).1 From February 1989 to November 1990 and from