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EDITORIAL COMMENTARY

Histoplasmosis: Time to Redraw the Map and Up Our Game

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(See the Major Article by Benedict et al on pages 1003–10.)

The gradual evolution of the knowledge base about histoplasmosis in the past century has been punctuated by several revolutionary observations with regard to geographic distribution of the causative organism, clinical manifestations of the disease, host risk factors, and diagnostic strategies. Prior to the early 1940s, when Christie discovered that histoplasmosis was a common cause of pulmonary infection in the southern and midwestern United States, the infection had been considered rare and invariably fatal. The endemic area for histoplasmosis, first described in the mid-1940s, was clarified when Edwards and colleagues [1] skin tested naval recruits who had lived in 1 county their entire lives. The well-known Edwards map, published in 1969, defined the endemic area as primarily encompassing the Ohio and Mississippi River valleys (Figure 1), a kernel of knowledge that has been firmly engrained in the consciousnesses of clinicians for the past half century. As a result, the index of suspicion for histoplasmosis generally has been low beyond the defined endemic area. The times have changed.

Several factors contribute to the localization of histoplasmosis to the endemic region. *Histoplasma capsulatum* thrives in soil fertilized by starling, pigeon, or bat guano, for reasons that have never been fully elucidated. In the endemic area, covering about a third of the United States, the average annual temperature is 22–29°C and the annual rainfall is 35–50″. Humidity in this region is relatively high and the soil is slightly acidic. Knowledge about the preferred habitat of *H. capsulatum* has been informed by the investigation of multiple outbreaks of histoplasmosis, typically linked to exposure to caves, tunnels, starling roosts, chicken coops, decayed trees, or excavation and demolition projects [2]. These investigations have shown that *H. capsulatum* is not evenly distributed in the environment; microfoci containing high concentrations of the fungus exist. Conditions may be suitable for the development of microfoci in locations far removed from the Ohio and Mississippi River valleys. In 1971, Ajello [3] presciently opined that the organism eventually was likely to be identified throughout the United States, including in so-called "peripheral endemic areas" far from the heartland.

In this issue of *Clinical Infectious Diseases*, Benedict and colleagues [4] have demonstrated that it is time to rethink our notions about the geography of the histoplasmosis-endemic area, which is actually quite fluid and expanding, and is not as limited today as it appears in the 1969 Edwards map. A correct understanding of the contemporary endemic area has important diagnostic and clinical implications. Histoplasmosis has protean clinical manifestations: some life-threatening, others benign but capable of mimicking serious conditions, such as lung carcinoma [5]. Delays in diagnosis and treatment can occur if clinicians do not appreciate the risk for histoplasmosis in their patients who have not resided in or visited the traditional endemic area. For example, unnecessary biopsies might be performed in individuals not recognized to be at risk for histoplasmosis; that is, any persons who live in the endemic area. In this nationwide study of insured patients who had a coded diagnosis of histoplasmosis in 2012–14, cases were identified in each region of the United States, including areas far removed from the Ohio and Mississippi River valleys [4]. Interestingly, 44% of cases were found in the East North Central division, as defined by the US Census Bureau. This 5-state division is demarcated by the western borders of Illinois and Wisconsin and by the eastern borders of Ohio and Michigan. The finding that close to half of the cases in the United States were identified there is somewhat surprising based on conventional knowledge from the Edwards map, which showed the endemic area as roughly bisected by the Mississippi River and transected by the Ohio River. However, the remaining 56% of cases were much more widespread than would have been anticipated.

In a recent study of older adults with histoplasmosis, 10% of cases occurred outside the classic endemic area [6]. Similarly, recent surveillance data from the Centers for Disease Control and Prevention reveals striking differences in disease distribution when juxtaposed to

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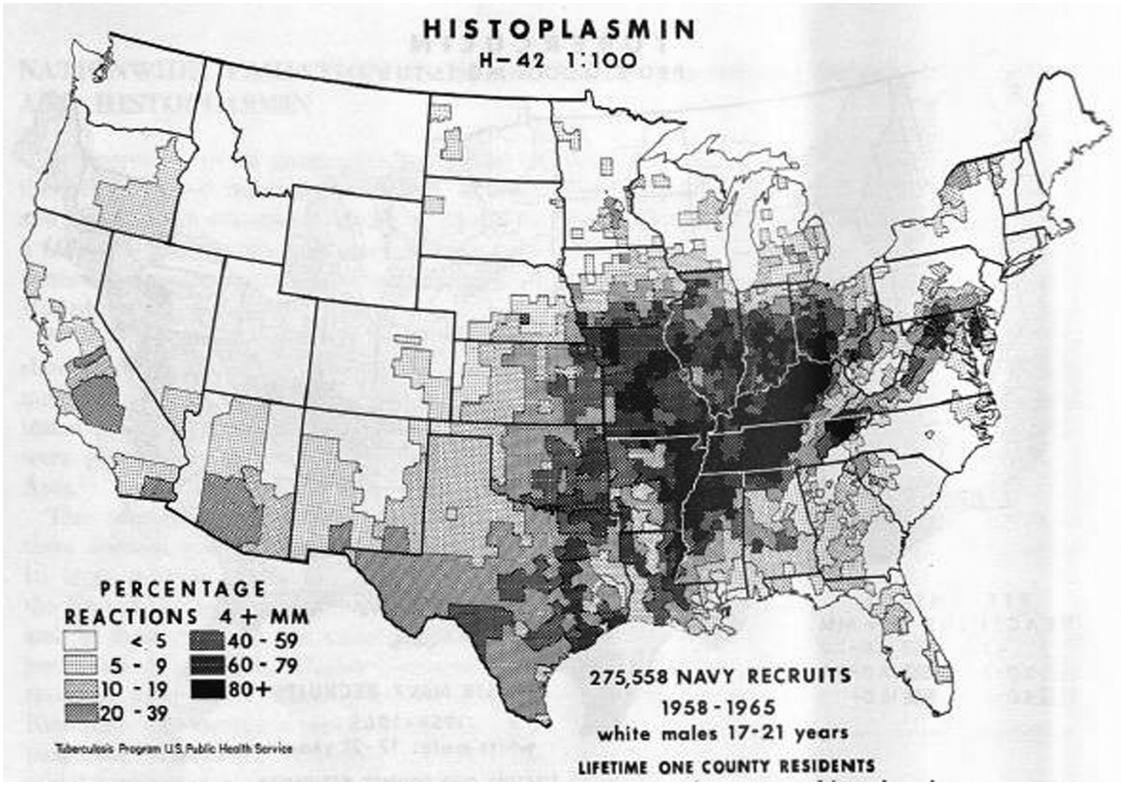

Figure 1. Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society [1].

the 1969 Edwards map [7]. For example, high prevalence was observed in western Michigan and central and southern Minnesota: regions largely unaffected in past years [7]. The endemic area has also now extended north and westward up the Missouri River valley, and autochthonous cases have been identified in the "non-endemic" states of Nebraska, Montana, Idaho, and the Dakotas [8–10]. What accounts for this apparent expansion of the endemic area? The most plausible explanations are climate change and anthropogenic influences [9, 10]. Whether or not the migration patterns of bats or starlings, the primary fertilizers of *H. capsulatum* in soil, have been altered as a result of climate change is unclear.

A shift in the forms of histoplasmosis requiring treatment is also apparent. Prior to the late 1970s, most patients who required antifungal therapy had either progressive acute pulmonary histoplasmosis (APH) or chronic pulmonary histoplasmosis. More recently, immunocompromised patients with progressive disseminated histoplasmosis have become increasingly common. From the 1980s until the mid-1990s, patients with acquired immunodeficiency syndrome comprised the largest group with life-threatening histoplasmosis [11]. The advent of highly effective antiretroviral therapy led to a significant decline in the numbers of new patients with human immunodeficiency virus–associated histoplasmosis. However, the growing number of solid organ transplant recipients and other patients requiring immunomodulating agents, including those receiving monoclonal antibody therapy, constitute a substantial proportion of recent cases of disseminated histoplasmosis in the United States.

Benedict et al's study [4] also shines light on the current diagnostic challenges in approaching histoplasmosis. An alarming finding was that many cases were identified by biopsies, presumably of lung lesions or lymph nodes. In recent years the accuracy of noninvasive studies has improved. Histoplasmosis usually can be diagnosed by ordering a battery of studies: antigen testing, serology, cytology, and/or culture [12], if a clinician suspects the diagnosis and considers these tests. However, only a third of cases reported by Benedict et al [4] had a "fungal specific test" done, suggesting that clinicians' index of suspicion for histoplasmosis is too low, and that there is a major need for education regarding manifestations of the infection and the roles of antigen and serologic testing, in particular, in establishing the diagnosis.

Benedict and colleagues [4] also provide insight into antifungal treatment prescribing for histoplasmosis in the United States. Treatment recommendations from the 2007 Infectious Diseases Society of America guidelines [13] have not changed in the past decade. For most cases of APH or for histoplasmomas, treatment is not necessary. Itraconazole is the preferred agent for severe APH, chronic pulmonary

histoplasmosis, or milder cases of disseminated histoplasmosis. A liposomal formulation of amphotericin B is recommended for more severe infections. In Benedict's study [4], 19.5% of patients were treated with itraconazole, 8.8% with fluconazole, and 2.5% with voriconazole. Fluconazole is considered a second-line agent. Controlled trials with voriconazole have not been done. The finding that more than a third of patients who received an azole were treated with a nonpreferred regimen suggests that clinicians are not widely adherent to the Infectious Diseases Society of America guidelines.

Clinicians nationwide should be alert to the possibility of histoplasmosis in their patients, even in the absence of a history of travel to or residence in one of the "classical" endemic regions. This traditional understanding is outdated. The endemic region for histoplasmosis is expanding. We need to redraw the map.

Notes

Potential conflicts of interest. The authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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