

The Discovery and Naming of Histoplasmosis: Samuel Taylor Darling

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In 1903, international efforts to construct the Panama Canal were being threatened by the twin biological hazards of yellow fever and malaria. The French decided to leave the endeavor in the hands of the Americans after enduring more than 12,000 deaths and an estimated \$40 million loss. Tropical diseases were a deadly enemy, and if American efforts were to succeed, these diseases needed to be overcome.



Image: Samuel Taylor Darling

In that same year of 1903, Samuel Taylor Darling graduated from the College of Physicians and Surgeons of Baltimore and had trained in Louis Pasteur's laboratory. He was thrust into the tropical hospitals of Panama when he accepted an internship at Ancon Hospital and joined the medical team headed by William Gorgas, whose mission was to control malaria and yellow fever. This 32 year old professor of pathology and histology at Baltimore City Hospital soon rose through the ranks to be appointed head of the Board of Health Laboratory in Panama.

While Walter Reed discovered the role of the mosquito in malaria transmission and William Gorgas successfully initiated a prevention campaign, Darling identified an apparently new disease process occurring at the Panama Canal. Three cases piqued Darling's interest that a new disease was occurring. In 1905, he observed an unusual autopsy in a 27 year old black carpenter from the Caribbean island of Martinique who worked on the canal. His lungs were studded with granulomas, which Darling noted to be not as closely packed or as numerous as

was found in military tuberculosis. Smears from white granulomas in the lung and from the spleen, liver, and bone marrow revealed an “intense invasion of large endothelial-like cells by small round or oval microorganisms”. In 1906, a second autopsy on another black canal laborer from Martinique revealed oval microorganisms mirroring the first case. The third autopsy case finding was a Chinese immigrant laborer living in Panama for fifteen years which also showed similar microorganisms.

These three patients also presented with symptoms of an irregular fever, cachexia, and splenomegaly common among canal workers; however, these cases were expressly different from yellow fever and malaria. These patients presented with pustular eruptions and ulcers often around the face and anus, ulcerations in the gastrointestinal tract, and lymph node, spleen, liver, and lung involvement. One of his lab assistants noticed how “completely [Darling] submerged everything for the benefit of his professional duty and ambition”, preferring to work in complete isolation while he studied celloidin sections, cultures, and autopsies. Darling examined the autopsy tissue samples in more patients who succumbed to this disease and granulomas were found in the lung. The oval microorganisms were seen within alveolar epithelial cells in the granulomas, while others appeared to be free in the spleen and bone marrow. These microorganisms were surrounded by a clear refractive nonstaining rim. *M. tuberculosis* could not be isolated. He proposed that the microorganism causing this newly-discovered disease was a protozoan and named the organism *Histoplasmosis capsulatum* because it invaded the cytoplasm of histiocyte-like cells and was enveloped by a capsule. Darling recorded his observations in six classical papers published from 1906 to 1909 describing the disease (Figure 1).

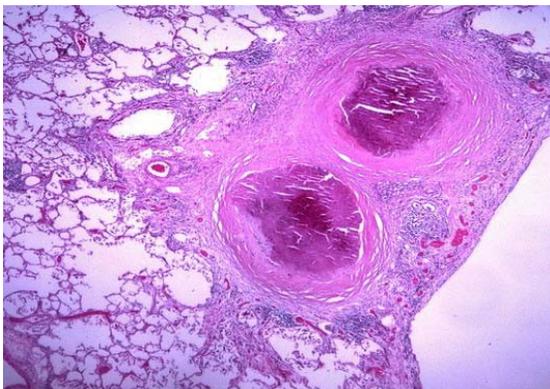


Figure 1: Numerous yeast forms of *Histoplasma capsulatum* in alveolar macrophages. The arrowhead points to a halo formed when there is retraction of the cytoplasm.” .

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Darling also performed most of the autopsies in patients who died of malaria, the major disease of the Canal Zone, second only to pneumonia. He formulated the splenic index which measured the degree of infectivity as indicated by splenomegaly in a patient. Through Darling's systematic collecting, feeding, and breeding of the *Anopheles* mosquito, he was able to observe the macrogametes within the mosquito. He identified the *Anopheles albimanus* as the main mosquito vector for both tertian (*vivax*) and estivo-autumnal (*falciparum*) fevers in Panama. With this finding, Darling initiated the first "species-specific" control system, in which sanitation efforts specifically targeted this species of mosquito, thus reducing the cost of sanitation and increasing its effectiveness. Another mosquito was later named in his honor: *Anopheles darlingi*, a significant vector of malaria in South America. Although Darling's distinction originated from his work on malaria and the histoplasmosis, he also published noteworthy observations on amebiasis, trypanosomiasis, leishmaniasis, filariasis, schistosomiasis, piroplasmiasis, strongyloidiasis, and uncinariasis.

Histoplasmosis became known as "Darling's Disease". Nonetheless, his findings had several flaws. Although the microorganism did reside in histiocytes, it was neither a protozoan nor was it encapsulated. He came to these erroneous conclusions after finding flagellated forms (most likely artifact) of the microorganism and comparing them to *Leishmania*, also elucidated in 1903.

Because the disease usually was not fatal and symptoms of histoplasmosis were so protean, the extent of the disease process and worldwide dispersion of histoplasmosis were unappreciated. In 1906, R.P. Strong also reported cases of histoplasmosis in the Philippines, although he also incorrectly linked it to Leishmaniasis. Over the following decades, reports of microorganisms with oval bodies in the mononuclear cells of the peripheral blood smear similar to those Darling described were recorded in patients throughout South America and later the rest of the world. In 1912, the Brazilian pathologist, Henrique da Rocha-Lima, obtained tissue from Darling's Panama patients and compared the organisms to Leishmaniasis. By showing the microorganism's similarity to *Cryptococcus farciminosus* Rivolta, the cause of epizootic lymphangitis in horses, he concluded that *Histoplasma capsulatum* was a fungus rather than a protozoan. (In 1985, *Cryptococcus farciminosus* was moved into the Histoplasmosis genera as *H. capsulatum* var. *farciminosum*).

References

Chaves-Carballa E. (2007). *The tropical world of Samuel Taylor Darling: Parasites, pathology and philanthropy*. Portland, OR: Sussex Academic Press.

Daniel TM, Baul GL. (2002). *Drama and discovery: the story of histoplasmosis*. Westport, CT: Greenwood Press.

Darling ST. A Protozoan general infection producing pseudotuberculosis in the lungs and focal necrosis in the liver, spleen, and lymph nodes. *JAMA* 1906;46:1283-1285.