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Commentary

The Tryp and the Pendulum

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The Brazilian microbiologist, Carlos Chagas, made the discovery of trypanosomes in the gut of reduviid bugs in 1908. He named them *Trypanosoma cruzi* in honor of his mentor, Oswaldo Cruz, and subsequently established their etiologic role in a new infectious disease to be called Chagas disease. Over more than a century, study of this complex disease has led to widely differing conceptualizations of the pathogenesis and immunopathogenesis that has led to equally differing paradigms for clinical management in terms of the role of antiparasitic drugs and vaccines. The fascinating article by Niborski et al. in this issue of *EBioMedicine* [1] is the latest contribution to a decades' long debate, with several swings of the pendulum, about the role of autoimmunity in the pathogenesis of Chagas disease.

Following infection into the mammalian host, *Trypanosoma cruzi* rapidly replicates and disseminates throughout the body during an acute phase typically lasting 4–8 weeks. Various components of the immune system including complement, antibodies, and cell-mediated processes control, but do not eliminate the parasite. The host then enters the chronic phase of the infection which persists for the life of the individual unless they are successfully treated with antiparasitic drugs. Of note, in 1909 Carlos Chagas made the first discovery of trypanosomes in the blood of a human, a two-year old girl named Berenice, who lived to the age of 73 and died of unrelated causes. She was infected with *Trypanosoma cruzi* for her whole life as was confirmed by isolation of parasites when she was 55 and 71 years of age [2]. Approximately, 70% of individuals with *T. cruzi* infection will live out their lives without evidence of disease, however, the remainder develop clinical manifestations usually involving inflammation of the heart or gut that are typically fatal. The factors responsible for the development of disease manifestations remain poorly understood, but may be related to host genetics, parasite strains, and possibly the frequency or dose of exposures to the parasites.

The causes of end-organ damage in Chagas disease have been the subject of the longstanding debates referenced above. Early autopsy studies showed tissue inflammation in the presence of minimal or absent parasites leading investigators to question whether cardiac pathology could be entirely explained by direct damage from lives parasites and associated inflammatory reactions. Research in the 1970s gave rise to an autoimmune theory of Chagas disease with seminal experiments showing that lymphocytes from *T. cruzi* infected animals destroyed embryonic cardiomyocytes in culture [3]. These and related discoveries led researchers to caution those working to develop *T. cruzi* vaccines because of the potential risk of inducing dangerous autoimmune reactions [4]. There was also concern that antiparasitic drugs would not be useful since the disease was thought to be driven by immune reactions [5]. The pendulum had swung. Additional research supporting autoimmune mechanisms mounted over the decades with data indicating that cardiac autoimmunity could be initiated by (1) parasite-induced damage to cardiomyocytes leading to a breakdown in self-tolerance resulting in immune reactions to self-proteins (bystander activation) or (2) molecular mimicry between immunologically similar epitopes of *T. cruzi* and host proteins [6]. Numerous *T. cruzi* antigens were identified that induced autoantibodies that reacted with human epitopes [6].

In the 1990s, research using molecular techniques showed that parasites and parasite antigens were detectable in tissues, reinvigorating the notion that the pathology was in fact parasite driven [7]. The discoveries led to renewed interest in antiparasitic drugs and therapeutic vaccines to eliminate the parasites responsible for a smouldering infection [8]. The pendulum had swung again.

The article by Niborski et al., provides another example of molecular mimicry as demonstrated by an autoantibody from chronic Chagas patients that cross-reacts with *T. cruzi* tubulin and mammalian tubulin that is only found in nervous tissue [1]. This discovery provides a new variation on the theme of molecular mimicry as shown by the dependency of a posttranslational modification of the target protein only present in neural tissue. The direct role of this antibody to disease pathology will need further study, but the research adds to the corpus of information that autoantibodies are abundant in patients with chronic *T. cruzi* infection. Most researchers in the field now agree that autoimmunity plays a role in the pathogenesis of Chagas disease [6,9], but the contribution of autoimmunity to tissue damage depends on parasites persistence to drive the inflammatory response [10]. The pendulum appears to have settled somewhere in the middle.

Declaration of Competing Interest

Dr. Buckner has nothing to disclose.

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