Legionella (in red) infecting amoeba

In July 1976 while the nation was celebrating its bicentennial of independence in Philadelphia, the American Legion held its annual convention with over 2000 attendees. Soon after the convention’s conclusion, several attendees began to complain of pneumonia symptoms. Within the week, a local epidemic was apparent with 182 people, mostly Legionnaires, hospitalized. Twenty-nine deaths were documented from the then unknown respiratory infection called Legionnaires disease. To determine the outbreak cause, the CDC (Center for Disease Control and Prevention) mounted an unprecedented investigation, leading to the discovery six months later of a new bacterium, *Legionella pneumophila*, found in the cooling tower of the convention hotel air conditioning system.

*Legionella pneumophila* is naturally found in freshwater but also exists in up to one-third of potable drinking water distribution systems. Exposure to this pathogen occurs through inhalation of contaminated water mists, most commonly generated by air conditioners, humidifiers, hot tubs, spas, sprinklers and decorative fountains. Infection can manifest in two ways; life-threatening pneumonia or a flu-like illness called Pontiac fever. Healthy individuals are typically resistant to infection. Susceptible individuals include people with weakened immune systems, older ages > 65 years, smokers and those suffering from chronic respiratory conditions.

*Legionella pneumophila* is a leading cause of community-acquired pneumonia with 7,500 cases reported annually and 27 outbreaks of disease from 2000 to 2014 in the U.S. Because individuals infected with *Legionella pneumophila* typically present with flu-like symptoms, there are no unique features that distinguish it from other types of pneumonia. As it is challenging to grow in the clinical laboratory, *Legionella pneumonia* is often under-diagnosed. Other methods to detect *Legionella* exist but do not identify all *Legionella* types and species. Experts estimate that the reported cases in the U.S. are grossly underestimated with predictions closer to 20,000 per year in the United States. While there are highly effective antibiotics to treat *Legionella pneumophila*, antibiotics typically chosen to treat respiratory infections such as penicillins do not affect this organism, as it lacks the cell wall components found in bacteria such as streptococci or E. coli. *Legionella pneumophila* is among the most virulent of pathogens that cause community-acquired pneumonia. Up to 30% of cases are lethal, demonstrating an urgent need for more effective strategies to prevent and treat disease. Although many bacteria inhabit water environments, *Legionella pneumophila* has proven difficult to eradicate from potable drinking water systems. Its enhanced survival appears partly due to its ability to survive both in biofilms and at high temperatures. A crucial additional technique is the bacterium’s preferred living habitat with a one-celled animal, the amoeba. Early studies with *Legionella pneumophila* demonstrated that this bacterium prefers to replicate within amoeba that also inhabit freshwater environments and water systems. Growth of *Legionella pneumophila* within amoeba protects them from chemicals disinfectants used to decontaminate drinking water. These properties of the bacterium likely allow it to persist in drinking water reservoirs, thereby increasing human exposure to this pathogen.

Within the lung, *Legionella pneumophila* replicate within a specialized form of white blood cell, called macrophages, that are the first line of defense against such invading pathogens. Macrophages share many common features with amoeba; both
After years of stagnant federal research funding levels, investment in tick-borne disease research has gotten a significant boost this year. The National Institutes of Health (NIH) has annually spent about $23 million on Lyme disease within a $56 million tick-borne disease research portfolio. As the most common vector-borne disease in the United States with an estimated 300,000 annual Lyme disease cases, this level of funding has been insufficient to make significant progress in fostering advancements understanding the mechanisms of disease, new vaccines and improved diagnostic tests. Private philanthropy has stepped in with foundations providing more than $60 million over the past decade to spur advances.

Recognition by federal funding sources lends urgency and helps stimulate bringing new investigators to the field. An additional $6 million devoted to Lyme disease in 2020, represents a 26% boost in research funding by the NIH, and the Centers for Disease Control (CDC) Lyme disease budget will grow by 12% to $12 million. Both represent significant advances in funding that likely developed from several efforts including advocacy by patient groups and professional societies.

Advocacy helped shape the 2016 21st Century Cures Act that included a Congressionally-mandated formation of a Tick-borne Disease Working Group (TDWG), including academic and government scientists as well as patient advocates. The first report from this group was issued this past winter. Recommendations included pushing for the development of next-generation Lyme disease tests and development of an effective Lyme disease vaccine. The second two-year cycle of the TDWG is just underway and this recomposed panel is charged with examining current federal efforts and issuing recommendations to the Secretary of Health and Human Services.

Now nearly forty years since the discovery of the bacterium Borrelia burgdorferi as the cause of Lyme disease, the push toward advancing the field is very welcome. Breakthroughs may happen. However, it is better to count on incremental improvements, which are how modern medicine mostly changes.

Paul G. Auwaerter, MD, MBA
Director, Fisher Center for Environmental Infectious Diseases

Lyme Disease Clinical Research

Lyme disease is a bacterial infection transmitted by tick bites. The infection may cause symptoms such as fatigue, muscle aches, joint aches, joint swelling, and rash. If untreated, the symptoms may progress to include arthritis or neurologic disease. Current FDA-approved blood tests for Lyme disease rely on testing for antibodies that develop in response to the infection. As with any human immune response to infection, the generation of antibodies may take 2-4 weeks to form. After a tick bite, these tests for Lyme disease may be negative in the early weeks of infection leading to a delay in both diagnosis and treatment if the characteristic “bull’s eye” rash is not present. Also, antibodies cannot be used to monitor treatment effectiveness as these molecules may persist for decades after antibiotic therapy.

The Fisher Center is collaborating with MicroB-plex, Inc. of Atlanta, Georgia in the evaluation of a novel cell-based blood test for early Lyme disease that may signify the presence of the infecting Borrelia burgdorferi bacteria before traditional antibody-based assays. This testing approach may also track with response to antibiotics thereby confirming clearance of infection. If successful, the test may lead to breakthroughs in the diagnosis and management of Lyme disease.

People with early Lyme disease (symptoms less than seven days) with a rash consistent with erythema migrans may join the study. To learn more about our Lyme research, call (443) 287-4840 or visit our website at EarlyLymeStudy.org

Image source: Auwaerter, M.D.
Congratulations to Meghan Davis, DVM, PhD recipient of a 2019 Johns Hopkins Catalyst Award for promising early-career faculty members. Her selection was based on accomplishments to date, creativity and originality, and academic impact. In addition to this $75,000 grant, Dr. Davis will participate in mentoring sessions and networking events. In 2014, Dr. Davis and Elizabeth Matsui, MD received a Fisher Center Discovery Program (FCDP) grant for their research on environmental pathogen exposures and asthma exacerbation. Pilot data from the FCDP grant led to large NIH grants for both Davis and Matsui. As faculty in the Bloomberg School of Public Health, Dr. Davis continues her environmental research into the interface of bacteria and hosts to reduce disease in humans and animals.

Pneumonia Bug Remodels in a Surprising Home

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hunt down and kill bacteria. The strategies acquired by Legionella pneumophila to avoid predation by amoeba in the environment allow the bacterium to evade killing by macrophages in the lung. Importantly, early studies by Lucy Tompkins and colleagues at Stanford University demonstrated that Legionella pneumophila grown within amoeba are more infectious within human macrophages. While the mechanisms by which this interaction enhances Legionella pneumophila virulence remains unknown, the presence of amoeba in contaminated drinking water appears to be responsible for outbreaks of Legionellosis. This knowledge suggests a critical role for this bacteria-amoeba interaction in determining the incidence and severity of the infection.

In 2018, Kimberly Davis, PhD, of the Johns Hopkins University Bloomberg School of Public Health and Tamara O’Connor, PhD of the Johns Hopkins University School of Medicine were awarded a Fisher Center Discovery Program grant to study the role of amoeba in enhancing the ability of L. pneumophila to cause human disease. Their experiments produced highly significant findings demonstrating that Legionella adapt during growth within amoeba that subsequently lessens the ability of human macrophages to find and to ingest them. This leaves infected people less able to fight infection with their immune system, especially if already impaired by smoking or pre-existing conditions. Davis and O’Connor’s current research is focused on determining the specific bacterial features that are responsible for these properties and exploiting these changes to develop new strategies for water remediation and disease prevention.

Laboratory research exploring how environmental factors impact infectious disease in humans can be difficult to fund through traditional agencies. The mission of the Fisher Center is to provide initial funding for innovative, high-risk avenues of research which allow scientists to develop research programs that address critical questions at the intersection of environmental biology and human infectious disease research. “We are extremely grateful to the Fisher Center Discovery Program for enabling and supporting this research, which is essential to understanding a key phase in the transition of an environmental pathogen to humans” both Davis and O’Connor replied. Their exciting findings will play a central role in guiding the development of more effective water treatment procedures and clinical practices to prevent and treat disease.

Image Source: Jason Park and Tamara O’Connor
Thank you to those who contributed so generously to support environmental infectious disease research and education in the past six months. Such gifts help facilitate innovative research, especially targeted to early-career investigators.

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