ASIP CENTENNIAL COMMENTARY

S. Burt Wolbach, Rocky Mountain Spotted Fever, and Blood-Sucking Arthropods

Triumph of an Early Investigative Pathologist

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In a series of four articles published between 1916 and 1919 in The Journal of Medical Research, precursor to The American Journal of Pathology, the investigative pathologist S. Burt Wolbach unambiguously showed that Rocky Mountain spotted fever has a tick-borne mode of transmission, the causative agent replicates intracellularly, and the disease is fundamentally a vasculitis. Although underappreciated, Wolbach’s tour-de-force work epitomized investigative pathology. These four articles should be mandatory reading for young investigators and are recommended also to seasoned investigators who seek reinvigoration in the beauty in their craft. (Am J Pathol 2013, 182: 291–293; http://dx.doi.org/10.1016/j.ajpath.2012.11.011)

“There [in the Bitterroot Valley], each spring while life was awakening, a particular ghastly death came.... Some years it killed every man who caught it.” —Paul de Kruif

Geography and S. Burt Wolbach

The Bitterroot River flows due north on the western edge of Montana, near the Idaho border. This stunning river joins the Clark Fork at Missoula, the population center of western Montana. As Lewis and Clark learned too late for it to be helpful in their expedition, the water in this drainage flows westward, eventually merging with the Snake River, then the Columbia River, and finally discharging into the Pacific Ocean. Along the border between Montana and Idaho, snowcapped peaks of the Bitterroot Range soar abruptly and majestically out of the valley floor, the highest peaks reaching more than 3000 m (>10,000 feet). The Selway—Bitterroot Wilderness area lies within the range, and this region remains largely pristine. For reasons not understood, the eastern slopes of the Bitterroot Mountains are infested with wood ticks (Figure 1), very large numbers of them. The density of these blood-sucking arthropods can be breathtaking, especially in the springtime when they emerge and venture forth along snowmelt lines, driven by questing behavior and unknown stimuli. For individuals who loathe or have pathological fear of ectoparasites, spring is a very disquieting season in the Bitterroot Valley.

One thousand miles to the southeast, in the center of our country, the Platte River flows west to east through southern Nebraska. This laconic and lengthy river, mostly unknown to easterners and westerners alike, is formed when the North Platte originating in Wyoming joins the South Platte, which has its headwaters in Colorado. Grand Island, Nebraska, is located between Kearny and Columbus, at 40°55′20″N 98°21′29″W, upstream of the confluence of the Platte River and Loop River. For early settlers and those fortunate enough to drive across our country, one realizes sometime west of Omaha and east of Grand Island that the plains truly are great and the appellation is accurate and deserved.

The goal here is not to belabor US geography. Rather, we seek to alert the reader about the early scientific discoveries of S. Burt Wolbach, an outstanding investigative pathologist whose contributions to the study of infectious disease are underappreciated and known, unfortunately, to few. The discoveries were made in the Bitterroot River valley almost 100 years ago. I believe they had their genesis in Wolbach’s early years in his hometown on the Platte River and in the surrounding Great Plains, where he...
acquired and exercised his relentless curiosity, keen powers of observation, love of nature, and grit: key characteristics that assisted his success.

Dr. Wolbach and Investigative Pathology

One need only skim the titles of articles published in The Journal of Medical Research in the early 20th century to realize how closely connected infection biology and investigative pathology were at that time. Indeed, the inextricable linkage of pathology, microbiology, and infectious disease research was underscored by the existence of many Departments of Pathology and Biology. (Of note, this tradition continues at the University of Nebraska College of Medicine, which has a Department of Pathology and Microbiology.) Wolbach’s findings were reported in a tightly clustered series of four single-author articles published between 1916 and 1919 in The Journal of Medical Research, precursor to The American Journal of Pathology. Collectively, this work is striking in scope and scholarship, and should be mandatory reading for all young investigators. The articles shed light on the workings of an inquisitive and organized mind, with strong interests and roots in natural history, as it sought answers to complicated biomedical riddles. In these four articles, Wolbach elucidated the pathogenesis of the disease now known as Rocky Mountain spotted fever.

Using guinea pigs and monkeys, Wolbach demonstrated that the disease is transmitted by ticks and that it is caused by an unusual pathogen that replicates intracellularly in endothelial cells; furthermore, he showed that the resulting disease is essentially a vasculitis. To describe the morbid anatomy associated with Rocky Mountain spotted fever, Wolbach examined tissue obtained from individuals who died of the disease, examination that confirmed the presence of intracellular organisms and critical vascular lesions. In his final report, Wolbach concluded, “The lesions of the blood vessels are due to the presence of the parasite and constitute the distinctive pathology of the disease, and warrant the definition [as] ‘an acute specific infectious endangiitis, chiefly of the peripheral blood vessels....’” (page 181 in'). The pathogenesis he described was novel at the time. Wolbach did everything our field of investigative pathology strives to accomplish but few are fortunate enough to achieve so regularly: identify the problem, proceed straight to the gist of the matter by experimental means and clear thinking, and delineate the pathological mechanism. His efforts set the standard for much subsequent work on other arthropod-transmitted agents, including the example of Borrelia burgdorferi, the causative agent of Lyme disease.

One cannot read these and other articles written by Wolbach without concluding that first and foremost he was a biologist and naturalist who strived to understand pathological processes and mechanisms using a broad array of the tools available at the time: superb intellect, keen powers of observation, the microscope and related modest laboratory paraphernalia, experimental animals, necropsies and autopsies, and histopathological analyses. His investigative approach is a tour de force from an early systems biologist who excelled in interdisciplinary research. The present commentary will not address Wolbach’s substantial contributions to our understanding of other infectious agents (including trypanosomes, influenza viruses, and streptococci, as well as other rickettsial diseases), nor discuss his extraordinary body of work in the field of vitamin deficiency states. Woodward et al6 exquisitely summarized many aspects of Wolbach’s career, and readers interested in the rich history of research on Rocky Mountain spotted fever are referred to Harden’s definitive work on this subject.

S. Burt Wolbach was born in Grand Island, Nebraska, on July 3, 1880, a relatively short time after the Nebraska Territory was granted statehood in 1867. This was a time in US history when the western prairie seemed to have no end, stretching to almost unlimited horizons. In 1880, Grand Island, located in south-central Nebraska and in the center of the country, had a population of less than 3000. Wolbach’s childhood was marked by a strong interest in outdoor activities common to rural areas at the time and still today, including hunting, fishing, horseback riding, and others for which observation powers were a tremendous asset.

Wolbach graduated from high school in Grand Island in 1897. He decamped for Lawrence Scientific School at Harvard College and then Harvard Medical School, from which he graduated in 1903. He was interested very early on in infection biology, as demonstrated by his publication as a medical student in 1903 with Harold C. Ernst on the tubercle bacillus. This work revealed an affinity for combining his powers of morphological observation, detailed and precise description of natural history, and analysis of pathological material from humans and infected animals.
Wolbach was also an innovative investigator, at heart a solver of practical problems. This characteristic was illustrated by his solution to the problem of how to transport live rickettsia-free lice to Poland, which he required for execution of planned studies on epidemic typhus. To ensure that the lice arrived well nourished and ready for experimental action, he and colleagues John L. Todd and Frank W. Palfrey simply strapped louse boxes to their legs, thereby permitting the lice to feed during the slow Atlantic transit. This process resulted in the “T” (Todd) and “W” (Wolbach) strains of lice. Wolbach’s work on Rocky Mountain spotted fever undoubtedly provided him the crucial expertise to subsequently discover the cause of epidemic typhus (Rickettsia prowazekii) in Poland and demonstrate its louse-borne mode of transmission. For this work, Wolbach received the Polish award of Commander of the Order of Polonia Restituta. This writer could not determine the precise confluence of events that stimulated Wolbach to travel to western Montana of his own volition and investigate the cause of the disease that was killing settlers in the Bitterroot, a problem that also had substantial detrimental economic impact in the valley. Perhaps it was the call of the northern Rocky Mountains to a man of the Plains then living on the flat East Coast? Perhaps it was simply the desire to apply his distinct investigative pathology skill set to a vexing medical problem? Some have suggested that scientific data and resulting discoveries are the by-product of the clash of human egos and scientific competition. Perhaps he felt that other investigators’ studies and conclusions were simply not up to snuff? In this regard, I cite his statement that “while Ricketts may have encountered the true parasite of the disease in ticks, he was led hopelessly astray by the occurrence of bacteria in his infected as well as non-infected ticks.” Regardless, we as investigative pathologists are fortunate that he chose to focus his attention and considerable talents on this disease.

Closing Comment

The history of biomedical research is replete with examples of individuals who due to chance, odd happenstance, or plain bad luck have not received adequate acknowledgment of their contributions. The pathologist S. Burt Wolbach is one of these. His career was largely shaped by investigative pursuits—the science of pathology, rather than the practice of pathology. He realized that a carefully conducted autopsy or necropsy could greatly inform and shape the investigative pathology experimental process. Wolbach served the scientific community as mentor to many individuals, and also as president of the American Association of Pathologists and Bacteriologists (1936) and of the Society for Experimental Pathology (1937). Although his name is known to researchers who work on intracellular bacteria in insects, many of Wolbach’s accomplishments are unknown or unrecognized by investigative pathologists today, and have even less recognition among scientists in the bacterial pathogenesis field. The four landmark articles that Wolbach published almost a century ago in The Journal of Medical Research deserve a much wider audience. I especially recommend them to young (and, one can hope, still impressionable) scientists, regardless of background and training, who seek to make a mark in any area of investigative pathology. All four are available in full online (http://www.ncbi.nlm.nih.gov/pmc). Reading this elegant quartet of articles can also reinvigorate seasoned investigators who have become habituated to reading too many articles that are stultifying in their reductionism, lack zest, and represent only an incremental advance of marginal value.

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References