Whipple Disease Research Accelerates

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(See the article by Moussawi et al, on pages 44–50.)

The face of Whipple disease is changing rapidly. The disease was originally described in 1907 by the pathologist George Hoyt Whipple [1], but it was not until 1961 that electron microscopic studies showed it definitively to be caused by bacteria [2, 3]. The causative organism could not be cultivated, and the cell wall ultrastructure was considered ambiguous, so there was even uncertainty as to whether the pathogen was Gram positive or Gram negative. In the early 1990s, ribosomal DNA sequence analysis showed it to be a Gram-positive actinomycete, and the organism was named on the basis of this sequence [4, 5]. The technology used to clarify the phylogeny of *Tropheryma whipplei* could also then be used to detect the organism directly by molecular means.

Over the ensuing 2 decades, there has been an explosion of publications describing the detection of *T. whipplei* in many tissues. This work has both confirmed what had previously been reported in Whipple disease [6] and described new findings [7, 8]. What has emerged is the picture of a disease with many manifestations. It most often presents as originally described by Whipple: with infection of the small bowel submucosa leading to a malabsorption syndrome, often with mesenteric lymphadenopathy. The ensuing diarrhea and weight loss may be preceded by a more subtle systemic illness, often associated with arthralgia or arthritis. *T. whipplei* may also be present in a variety of other tissues, including skin, brain, spinal cord, vertebra, lung, heart valve, myocardium, pericardium, bone marrow, prosthetic materials, lymph nodes, synovium, and other sites. The disease may present with extraintestinal involvement, or involvement of these sites may become apparent upon treatment, resulting from an immune reconstitution inflammatory syndrome–like illness [9]. Treatment is still probably less than optimal; the organism can acquire resistance to trimethoprim-sulfamethoxazole, which is the antibiotic most commonly used to treat it [10]. As a result of such resistance, and possibly because of other factors, the disease is subject to relapse, and it is common for the presentation at relapse to reflect extraintestinal infection, particularly in the central nervous system. Despite its various presentations, the disease has been considered a progressive process with a final common pathway if untreated—dissemination and death.

An understanding of the ecology of *T. whipplei* is emerging. If it were widely distributed in the environment, one would expect this fact to have become apparent by now. This apparent lack of dispersion is not surprising in light of the organism’s genome, which is small in comparison to those of most other bacteria [11, 12]. This reduced genome is deficient in genes coding for amino acid metabolism and in pathways for energy metabolism, probably reflecting obligate association with a host. The organism also appears to be capable of altering its surface proteins, presumably as a way of evading the immune system. It appears that at least one of its hosts is human. Its DNA has been found in the stool, saliva, and gingival crevice of healthy humans but not, thus far, in monkeys or apes [13]. *T. whipplei* DNA has also been found in sewage influxes, and its presence in humans is associated with work exposing the carrier to sewage water. The picture is emerging of an organism that is more often a parasite or commensal of the alimentary tract than a pathogen. We do not often think of intracellular bacteria as being parasites or commensals, but there are precedents in nature, such as *Bartonella henselae* in cats, *Wolbachia* species in insects or, for that matter, mitochondria. Because there is no evidence that *T. whipplei* benefits the host, we can call it a parasitic bacterium for now.

It is often the case that the most severe end of the spectrum for an infectious disease is the first to be described. Thus, it may not simply be the case that the parasitic organism, *T. whipplei*, occasionally kills its host. It may also cause less severe disease. Recently Raoult et al [14]...
reported that the organism was found in 36 of 241 children with acute gastroenteritis but in none of 47 control subjects. Thirty-three percent of the *T. whipplei*-positive children had another identifiable intestinal pathogen. Compared with chronic carriers of *T. whipplei*, children with diarrhea harbored larger numbers of this organism, and the numbers were comparable to those found in patients with classic Whipple disease. Furthermore, the children showed seropositivity with immunoglobulin M antibodies, a finding that generally reflects acute infection. The organism cleared within 2 weeks in almost all cases. If confirmed, these findings indicate that *T. whipplei* is associated with gastroenteritis, at least in children. In that case, the question would remain—does this organism cause gastroenteritis, does the presence of gastroenteritis give it access to the host, or both?

As a first step in addressing these questions, in this issue of the Journal, Moussawi et al. [15] report experiments using a mouse model. These studies showed that normal mice fed *T. whipplei* orally cleared the organism rapidly from the gastrointestinal tract with no noticeable symptoms or seroconversion. The only finding was an increase in water content within the distal colon. In animals that had been administered dextran sulfate to induce colitis, excretion of *T. whipplei* was prolonged; the organism could be shown to invade tissues, and the animals underwent seroconversion, as the children had in the clinical study cited above. Administration of *T. whipplei* did not increase water in the colonic contents over that caused by colitis in mice given dextran sulfate. However, it is possible that a small increase in water content was masked by the effects of colitis.

The increased water in intestinal contents of healthy animals fed *T. whipplei* was slight. However, assuming the increase is reproducible, it is hard to avoid the conclusion that it was caused by ingestion of purified bacterial cells. If so, obvious questions arise. How would an intracellular organism do this without invading tissues? Can the organism transiently attach to or invade epithelial cells? Does it produce a toxin? The dextran sulfate-treated mouse experiment strongly supports *T. whipplei*’s role as an opportunistic invader, and it may have been in far more than the 30% of children in whom a second pathogen was found. In studies of the etiology of presumed infectious diarrhea, it is common not to find a cause in a large proportion of subjects, although something must have caused the acute diarrhea. It follows that a significant proportion of the 70% of patients without an identified second pathogen probably had an unidentified primary cause other than *T. whipplei*. If so, the organism in most of these children may have asymptotically invaded damaged tissues, as in the mice. Thus, although the mouse studies increase credibility of the assertion that *T. whipplei* causes disease milder than classical Whipple disease, the extent to which this really happens in humans and by what mechanisms remain uncertain. The answers may not be easy to come by, so we are fortunate to have a group with the ingenuity of the authors of this article working on the question.

References