REVIEW ARTICLE

MEDICAL PROGRESS

Whipple's Disease

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The discovery of Whipple's disease and its causative bacterium, *Tropheryma whipplei*, is a prime example of how modern technologies have contributed to medical knowledge. Although Whipple's disease was first described in 1907,[1] the first successful culture of *T. whipplei* was performed nearly a century later, in 2000. This accomplishment led to a new level of understanding of the disease.

During the 20th century, knowledge of this chronic disease slowly accumulated (Table 1).[2-6] At the dawn of the 21st century, two major events — molecular amplification of the 16S ribosomal RNA (rRNA) of *T. whipplei* by polymerase-chain-reaction (PCR) assay and cell culture of the organism — greatly improved our understanding of Whipple's disease.[7-9] Initially, the organism was named *Tropheryma whippelii*, from the Greek *trophi* (food) and *eryma* (barrier), because of the malabsorption frequently observed in the disease.[8] The successful isolation and serial culture of the bacterium[9] were followed by the sequencing of its genome[11,12] and made it possible to define the organism's antibiotic susceptibility.[13,14] The name was subsequently changed slightly to *Tropheryma whipplei*.[10]

Whipple's disease is rare, though there is no valid estimate of its actual prevalence. Only about 1000 cases have been reported to date.[15] In postmortem studies, the frequency of the disease is less than 0.1%.[16] Although it occurs in people of all ages throughout the world, the typical patient is a middle-aged white man.[17]

Whipple's disease is characterized by two stages — a prodromal stage and a much later steady-state stage. The prodromal stage is marked by protean symptoms, along with chronic nonspecific findings, mainly arthralgia and arthritis. The steady-state stage is typified by weight loss, diarrhea, or both, and occasionally there are other manifestations, since many organs can be involved.[17] The average time between the prodromal and the steady-state stages is 6 years. If a patient has received immunosuppressive therapy, such as treatment with corticosteroids or tumor necrosis factor antagonists, a more rapid clinical progression may occur.[18,19] For example, diarrhea has been reported to develop shortly after the initiation of immunosuppressive therapy for chronic arthritis in patients with Whipple's disease.[19]

Roughly 15% of patients with Whipple's disease do not have the classic signs and symptoms of the disease.[20,21] Accordingly, the diagnosis should be considered in many different clinical circumstances. Indeed, Whipple's disease is in the differential diagnosis for a wide spectrum of diseases that includes inflammatory rheumatic diseases, malabsorption with small-intestine involvement (celiac disease, sarcoidosis, and lymphoma), Addison's disease, connective tissue diseases, and a variety of neurologic diseases. Characteristic signs and symptoms of Whipple's disease are listed, along with their frequencies, in Table 2.[15,16,21-25] Some cases have been diagnosed in the absence of classic signs when typical histologic lesions were found on periodic acid–Schiff (PAS) staining of specimens from small-bowel biopsies.

Table 1. Milestones in the History of Whipple's Disease and *Tropheryma whipplei*.

Date	Investigators	Advance
1907	Whipple[1]	First description of the disease
1947	Oliver-Pascual et al.[2]	First diagnosis before the death of a patient
1949	Black-Schaffer[3]	Development of periodic acid–Schiff staining for diagnosis
1952	Paulley[4]	First reported efficacy of antibiotic treatment
1961	Chears and Ashworth,[5] Yardley and Hendrix[6]	Detection of bacteria in macrophages by electron microscopy
1991	Wilson et al.[7]	Partial sequencing of 16S rRNA of an unknown bacterium
1992	Relman et al.[8]	Confirmation and extension of the 16S rRNA sequence; first naming of the bacterium: *T. whippelii*
2000	Raoult et al.[9]	First cultivation of the Whipple bacillus
2001	La Scola et al.[10]	First phenotypic characterization of the Whipple bacillus; renaming of the bacterium: *T. whipplei*
2003	Bentley et al.,[11] Raoult et al.[12]	Full sequencing of two genomes from two different strains of *T. whipplei*

Table 2. Demographic and Clinical Features of Classic Whipple's Disease.*

Feature	Patients with Whipple's Disease
	no./total no. (%)
Male sex	770/886 (87)
Arthralgia or arthritis	244/335 (73)
Diarrhea	272/335 (81)
Weight loss	223/240 (93)
Fever	128/335 (38)
Adenopathy	174/335 (52)
Melanoderma	99/240 (41)
Neurologic signs†	33/99 (33)
Ocular signs†	6/99 (6)
Pleural effusion	26/190 (14)

* Data are from reports on seven case series, all published since 1960, by Chears et al.,[22] Enzinger and Helwig,[16] Kelly and Weisiger,[23] Maizel et al.,[24] Dobbins,[15] Fleming et al.,[25] and Durand et al.[21] Total numbers refer to the total number of patients evaluated for Whipple's disease. The ages of the patients at diagnosis ranged from 1 to 83 years.

† Supranuclear ophthalmoplegia is included as a neurologic sign but not as an ocular sign. Two patients presented with supranuclear ophthalmoplegia.

Thus, there are several presentations linked to *T. whipplei* infection: histologic lesions in the gastrointestinal tract in association with diverse clinical manifestations (classic Whipple's disease), endocarditis with negative blood cultures, and isolated neurologic infection.

Without treatment, Whipple's disease is ultimately fatal. Even with a specific antibiotic regimen, clinical relapse occurs in 2 to 33% of cases after an average of 5 years; relapse is usually characterized by neurologic involvement.[26]

CLASSIC WHIPPLE'S DISEASE

The most common gastrointestinal symptom of classic Whipple's disease is weight loss, often associated with diarrhea.[15,21,24,25] Occult bleeding from the intestinal mucosa is observed in 20 to 30% of patients. Abdominal pain may be present. Hepatosplenomegaly and, occasionally, hepatitis may occur.[15] Ascites has been reported in about 5% of patients.[15]

Joint involvement has been reported in 65 to 90% of patients with classic Whipple's disease.[17,21,24,25] The presenting symptom in most patients with joint involvement is intermittent migratory arthralgia, arthritis, or both.[17,21,23,25] Polyarthritis is most common, but oligoarthritis may occur. Although joint involvement alone is uncommon, Whipple's disease should be considered in the differential diagnosis in any middle-aged man with intermittent episodes of unexplained polyarthritis or oligoarthritis of the large joints, even in the absence of digestive symptoms.[17,27] Less frequent in Whipple's disease is chronic seronegative polyarthritis, which can be destructive and is often mistaken for rheumatoid arthritis.[17] On rare occasions, spondyloarthropathy, hypertrophic osteoarthropathy, and infection of a knee prosthesis have been described in patients with classic Whipple's disease.[28] Skeletal muscle myalgia and cramps in skeletal muscle may be present.[15]

Neurologic involvement has been reported in

6 to 63% of patients with classic Whipple's disease.[15,18,29] However, in a small autopsy series, central nervous system lesions were described in 10 of 11 patients (91%).[16] The neurologic manifestations of classic Whipple's disease are diverse and can resemble those of almost any neurologic condition (Table 3).[18,29] Cognitive changes are common, affecting 71% of patients with neuro-

Table 3. Clinical Features of Neurologic Whipple's Disease and Blood Culture–Negative Endocarditis Associated with *T. whipplei*.

Feature	Value
Neurologic Whipple's disease[29]	
No. of patients	84
Cognitive change — %	71
Supranuclear ophthalmoplegia — %	51
Altered level of consciousness — %	50
Psychiatric signs — %	44
Upper motor neuron signs — %	37
Hypothalamic manifestations — %	31
Cranial nerve abnormalities — %	25
Myoclonus — %	25
Seizures — %	23
Oculomasticatory, or oculofacialskeletal, myorhythmia — %	20
Ataxia — %	20
Sensory deficits — %	12
Blood culture–negative endocarditis associated with *T. whipplei*[30-38]	
No. of patients	17
Male sex — no. (%)	14 (82)
Previous valvular disease — no. (%)	7 (41)
Acute rheumatic fever	3 (18)
Bicuspid aortic valve	2 (12)
Aortic bioprosthesis	2 (12)
Antecedent — no. (%)	12 (71)
Arthralgia or arthritis	8 (47)
Seronegative polyarthritis	2 (12)
Psoriatic arthritis	1 (6)
Myalgia	1 (6)
Interval between onset of symptoms and definite diagnosis — range (mean)	2 mo–20 yr (5 yr)
Involved valves — no. (%)	
Aortic	8 (47)
Mitral	4 (24)
Tricuspid	1 (6)
Aortic and mitral	3 (18)
Aortic and tricuspid	1 (6)
Fever — no. (%)	2 (12)
Cardiac vegetations — no. (%)	13 (76)
Congestive heart failure — no. (%)	10 (59)
Arterial emboli — no. (%)	10 (59)

logic signs, and may even extend to dementia.[29] Psychiatric symptoms such as depression and personality changes are observed in roughly half the patients who have neurologic involvement. Similarly, half have supranuclear ophthalmoplegia at presentation.[29] Myoclonus is observed in one quarter of patients with neurologic involvement. Hypothalamic involvement, evidenced by polydipsia, hyperphagia, a change in libido, and changes in the sleep–wake cycle, is present in less than one third of patients with neurologic signs. Movement abnormalities of the eye muscles, termed oculomasticatory, or oculofacioskeletal, myorhythmia, are considered pathognomonic for Whipple's disease.[29]

The prognosis for patients with central nervous system infection remains poor. More than 25% of such patients die within 4 years, and the same proportion of patients have major sequelae.[39] Asymptomatic neurologic involvement in classic Whipple's disease has been demonstrated through detection of DNA from *T. whipplei* in cerebrospinal fluid by means of a PCR assay.[40] Ocular involvement, excluding ophthalmoplegia, occurs in up to 11% of patients with classic Whipple's disease.[15,24,41] Anterior or posterior uveitis, usually chronic and bilateral at diagnosis, is the most frequent ocular manifestation.

Cardiac involvement has been reported in a wide range of patients with classic Whipple's disease (17 to 55%).[21,42] However, two older autopsy studies showed nearly invariable involvement of the pericardium, myocardium, or endocardium; PAS-positive macrophages were found in 79% of reported cases.[16,43] Pericarditis occurs in more than half of people with Whipple's disease.[24] Myocarditis occurs far less often and is sometimes first evident with the onset of heart failure or with sudden death. Pulmonary involvement occurs in an estimated 30 to 40% of patients with classic Whipple's disease,[15] and pleural effusion, pulmonary infiltration, or granulomatous mediastinal adenopathy was often described in the earliest reported cases.[15]

Noncaseating epithelioid- and giant-cell granulomas, most often lymph-node granulomas, have been found in 9% of people with classic Whipple's disease.[15] Involvement of the abdominal, especially the mesenteric, lymph nodes is not uncommon, but peripheral lymphadenopathy is rare. Cutaneous manifestations vary.[15,44] Melanoderma is a classic finding, but like other researchers,[21] we have found that it is rarely observed these days, since Whipple's disease is recognized earlier in its course. Kidney involvement, which is only occasionally described, typically occurs late in the course of the disease.[15] Other manifestations, such as hypothyroidism, epididymitis, and orchitis, have occasionally been reported in cases of classic Whipple's disease.[15,45,46]

ENDOCARDITIS ASSOCIATED WITH *T. WHIPPLEI*

T. whipplei may be associated with blood culture–negative endocarditis. This was initially observed by chance in one patient in a study by Goldenberger et al. in which cardiac valves obtained from 18 patients with endocarditis were screened with a broad-range PCR strategy that targeted the 16S rRNA sequence of *T. whipplei*.[47] Four additional cases were reported two years later.[30] To date, 17 cases of blood culture–negative endocarditis associated with *T. whipplei* (Table 3) have been described,[30-38] most of which have involved native cardiac valves in men with an average age of approximately 60 years. Arthralgia or arthritis, often preceding the diagnosis of blood culture–negative endocarditis by some years, has been the predominant extracardiac symptom in these cases.[30] Clinical signs of infection appear to be rare.[30]

Physicians often use the Duke criteria to diagnose endocarditis,[42] but in patients with blood culture–negative endocarditis, two of the criteria — fever and a history of valvulopathy — are absent, making it difficult to diagnose endocarditis associated with *T. whipplei*.[48] To date, this manifestation of Whipple's disease has generally been confirmed by a PCR assay of DNA taken from surgically obtained cardiac valves, although in one case, an assay of intestinal tissue specimens was positive.[30]

ISOLATED NEUROLOGIC MANIFESTATIONS

Neurologic manifestations occur in three situations: neurologic relapse of previously treated Whipple's disease, neurologic involvement in classic Whipple's disease, and isolated neurologic symptoms due to *T. whipplei* without histologic evidence of intestinal involvement. Thirty-two patients with isolated neurologic infection (18 males and 14 females) with a mean age of 46 years (range, 4 to 72) have been described.[15,18,29,40,44,49-58] Nineteen of these 32 patients had systemic symptoms, such as fever (10 patients), weight loss (8), articular pain (7), and peripheral lymphadenopa-

thy (2). PCR assays of intestinal tissue specimens were positive in 4 of the 32 patients. The predominant symptoms included cognitive impairment, ophthalmoplegia, ataxia, and upper motor neuron disorder. Of the 30 patients for whom follow-up data were available, 18 (60%) had improvement, and 10 died (33%); in 1 patient, the disease stabilized. Whether earlier detection and treatment would have improved the outcome is unknown, though arguably likely.

OTHER PRESENTATIONS

Cases of Whipple's disease with isolated arthritis,[59-61] spondylodiskitis,[62] and uveitis[63] in the absence of clinical or histologic evidence of digestive involvement have also been described. In these cases, the diagnosis was established with PCR assays of synovial fluid or tissue,[59,61] specimens from disk puncture biopsy,[62] or aqueous humor[63] or with electron microscopical examination and PAS staining of synovial tissue.[60]

ASYMPTOMATIC CARRIERS

There is controversy regarding the prevalence of *T. whipplei* in duodenal-biopsy specimens, saliva, stool, and blood from healthy persons.[64] Some PCR studies have detected the organism in people without evident Whipple's disease. For example, in one small study in which a PCR assay for *T. whipplei* was performed on blood samples from apparently healthy donors, 1 of 174 samples was positive.[65] In two other studies, *T. whipplei* DNA was detected in saliva from 19%[66] and 35%[67] of healthy subjects. PCR assays have also detected DNA from *T. whipplei* in patients with disorders other than Whipple's disease; positive findings have been reported in duodenal-biopsy samples (in 5% of patients), gastric secretions (12%), and stool (11%).[66,68,69] However, neither our laboratory[70] nor that of Dr. David Relman at Stanford University[71] has identified *T. whipplei* DNA in samples from duodenal biopsies in control subjects. Among patients without Whipple's disease, we have detected *T. whipplei* using a PCR assay on DNA isolated from saliva in 4 of 620 patients (0.6%) and from stool in 2 of 133 patients (1.5%) (unpublished data).

THE ORGANISM

T. whipplei appears to be present in the general environment, though neither its source nor its transmission is well established. Studies using PCR have demonstrated *T. whipplei* DNA in sewage plant effluent[72] as well as in human stool.[73] Furthermore, an association between Whipple's disease and *Giardia lamblia* infection has been reported.[74] Since the protozoan *G. lamblia* is present in the environment, it is plausible that both microorganisms occupy the same ecologic niche.[74] Indeed, it has been suggested that *T. whipplei* might be acquired through fecal–oral transmission.[75]

The complete genome of two strains of the bacteria has been sequenced.[11,12] *T. whipplei* possesses a very small circular chromosome (less than 1 megabase), as reported for other intracellular bacteria. Organisms with adaptive strategies involving host dependence are generally associated with genome reduction, and genome annotation in *T. whipplei* has revealed that the biosynthetic pathways for 16 amino acids are missing or impaired, suggesting a requirement for external nutrients. Recombination of regions encoding for surface proteins has been detected, possibly associated with the production of many diverse membrane proteins, which may enable the bacterium to evade host immunity.[11]

T. whipplei has been isolated from mammalian cell cultures.[9] With this approach, 18 novel isolates (7 from cerebrospinal fluid, 4 from blood, 2 from cardiac valves, 2 from lymph nodes, 1 from duodenal tissue, 1 from synovial fluid, and 1 from skeletal muscle) have been established in serial cultures.[11,76,77] According to genomic analyses, it is also possible to culture *T. whipplei* without mammalian cells, simply by adding the missing amino acids to the culture medium.[78] Using this strategy, we have recently isolated and established two strains of *T. whipplei* from cerebrospinal fluid, two from blood, one from synovial fluid, one from a lymph node, one from a cardiac valve, one from skeletal muscle, and one from stool.[79]

PATHOPHYSIOLOGY OF WHIPPLE'S DISEASE

One concept concerning the pathogenesis of Whipple's disease is that in any given population, many people are exposed to *T. whipplei* and that the disease may subsequently develop in some of these people, presumably those with as yet undefined predisposing immune factors.[80] Genetic risk factors may be suggested by the predominance of men and the higher frequency of the HLA-B27

antigen among those with the disease. However, no causal association with any specific genetic factor has been demonstrated, and some studies do not support the existence of genetic risk factors.[81]

Massive infiltration of infected tissues by macrophages on microscopy typifies Whipple's disease.[82] After treatment, bacteria disappear, yet macrophages persist. *T. whipplei* multiplies in macrophages but not in monocytes from healthy subjects.[83] In contrast, in patients with Whipple's disease, *T. whipplei* multiplies in both monocytes and macrophages.[83] Replication of *T. whipplei* in macrophages is associated with apoptosis of the host cell,[83] which may be crucial for bacterial dissemination and is also correlated with expression and release of interleukin-16.[84] Antibodies neutralizing interleukin-16 inhibit the growth of *T. whipplei* in macrophages.[83] Serum interleukin-16 levels and markers of apoptosis correlate with the activity of Whipple's disease, decreasing to normal levels on successful treatment.[83]

Humoral responses do not appear to be implicated in Whipple's disease.[80] Several studies have demonstrated defective macrophage function in patients with the disease. Although macrophages from affected patients phagocytose bacteria normally, they appear to be unable to degrade bacterial antigens efficiently.[15] Experimental data suggest that this inability to degrade bacterial antigens is related to inadequate production of interleukin-12,[85] which may lead to diminished interferon-γ production by T cells and defective macrophage activation. A decrease in interleukin-12 production might then prevent the development of an effective type 1 helper T-cell immune response and would favor a shift toward a type 2 helper T-cell response. In support of this hypothesis, the gene expression profile of macrophages in intestinal lesions from one patient with classic Whipple's disease indicated that genes encoding CCL18 and interleukin-10 were uniquely up-regulated in intestinal lesions.[86] A similar pattern in up-regulated genes has been associated with macrophage 2, also known as alternatively activated macrophages, reflecting a predominance of type 2 helper T cells in the local immune response.

CLINICAL DIAGNOSIS

BLOOD STUDIES

Several nonspecific findings may together suggest the diagnosis of Whipple's disease. For example, before treatment there may be elevated levels of acute-phase reactants, anemia, leukocytosis, thrombocytosis, and laboratory evidence of malabsorption.[21,25] Thrombocytopenia is present on occasion.[44] Eosinophilia has also been reported.[42]

ENDOSCOPY

Pale yellow, shaggy mucosa alternating with eroded, erythematous, or mildly friable mucosa has been described on endoscopic examination of the postbulbar region of the duodenum and jejunum in patients with classic Whipple's disease.[64]

OTHER DIAGNOSTIC TOOLS

Electron microscopy may detect the distinctive trilaminar cell wall of *T. whipplei;* laboratories with experience in detecting *T. whipplei* are best at identifying this feature.[75] However, the classic tool for diagnosing Whipple's disease is PAS staining of small-bowel–biopsy specimens, which on light-microscopical examination shows magenta-stained inclusions within macrophages of the lamina propria (Fig. 1A). Several biopsy samples should be studied, because the lesions can be focal and sparse.

Depending on clinical manifestations, other tissues might be biopsied and stained with PAS.[64,75,81] However, the PAS-positive inclusions within cells are nonspecific.[64,75] For example, PAS-positive cells are also seen in patients with *Mycobacterium avium* complex.[75] Ziehl–Neelsen staining, which is positive for patients infected with *M. avium* complex and negative for those with Whipple's disease, may be used to differentiate between these two infections. Noncaseous granulomas composed of epithelioid cells, which are PAS-negative in 40% of cases, may be present in the lymphatic tissue, gastrointestinal tract, bone marrow, kidneys, synovial tissue, liver, or lungs in patients with Whipple's disease.[64,75,81]

Immunohistochemical staining for antibodies against *T. whipplei* has been used to detect the organism in various tissues, in bodily fluids such as the aqueous humor, and on blood monocytes, providing direct visualization of the bacilli (Fig. 1B and 1C).[9,41,82,87-89] Although not yet widely available, immunohistochemical staining provides greater sensitivity and specificity than does PAS staining and can be used retrospectively on fixed samples.[88,89] Recently, *T. whipplei* was detected with the use of autoimmunochemical staining in which anti–*T. whipplei* antibodies from the patient's

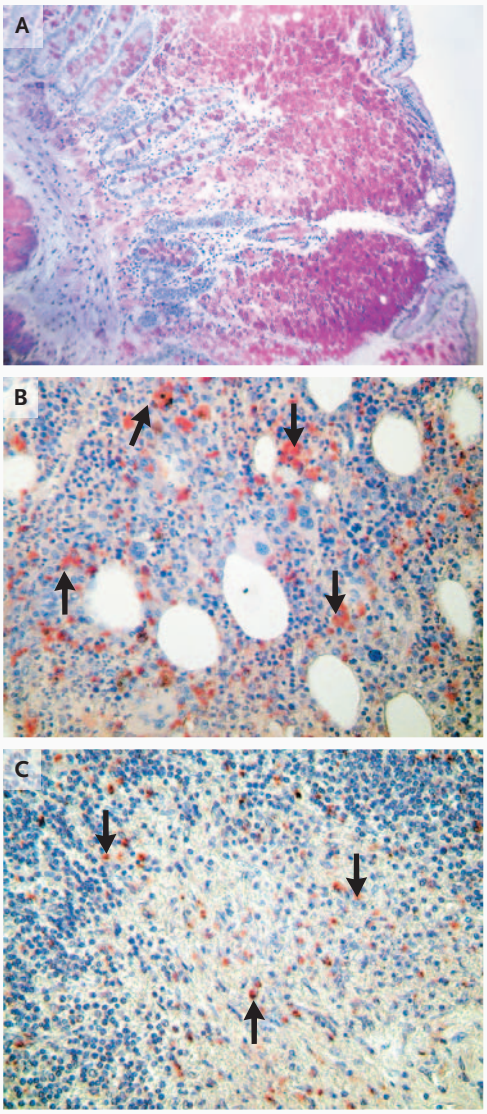

Figure 1. Detection of Whipple's Disease by PAS Staining and Immunohistochemical Analysis.

PAS staining of a duodenal-biopsy specimen shows reduced villous architecture and macrophages (magenta) in the lamina propria (Panel A). Immunohistochemical staining with polyclonal rabbit anti–*T. whipplei* antibody (at a dilution of 1:2000) and Mayer's hemalum counterstaining show *T. whipplei* in specimens of bone marrow (Panel B, arrows) and spleen (Panel C, arrows). Images courtesy of Hubert Lepidi.

own serum is used (rather than antibodies developed in the laboratory). With this technique, the organism was detected in heart-valve samples from five patients with blood culture–negative endocarditis.[90]

As noted above, PCR can be used to detect *T. whipplei* in samples from a variety of tissue types and body fluids.[91] As with all PCR assays, it is critical to avoid contamination of the DNA sample and to include positive and negative controls to validate the test. Initially, PCR assays targeting the 16S rRNA gene and 16S–23S intergenic regions of the *T. whipplei* gene were used.[8,81] More recently, a quantitative real-time PCR assay targeting this intergenic region was developed[70] that offers the advantages of a reduced detection time and a lower risk of sample contamination. Now, on the basis of genome analysis, a new quantitative real-time PCR assay has been developed that targets repeated sequences of *T. whipplei*, with substantially greater sensitivity than the earlier PCR assays and the same specificity.[92]

When amplified product is detected, the identification of *T. whipplei* should be confirmed by sequencing or by using fluorescence-labeled oligonucleotide hybridization probes in a real-time PCR assay. Discrepancies between laboratories suggest that results obtained with "homemade" (not standardized) PCR should be interpreted with caution. The many positive PCR results from people without Whipple's disease have been obtained primarily with the use of nested or seminested techniques, which carry a high risk of contamination.[66,68,69,93,94] Nonetheless, it is important to pay attention to a positive PCR assay, as suggested by the death of a patient in whom one of three PCR tests was positive but whose duodenal biopsy specimens were negative on PAS staining[95]; the diagnosis of Whipple's disease was thought to be ruled out, yet the autopsy revealed Whipple's disease. Cultivation of *T. whipplei* from various samples can be achieved, but this technique is not generally available.[9,14,41,76,77,87]

Our strategy for diagnosing Whipple's disease uses the results of PAS staining and PCR in parallel (Fig. 2). However, another group has recently proposed histologic examination of a small-bowel–biopsy specimen as the first step, with PCR performed only if the histologic findings are negative.[96] The main limitation of this approach is that the specificity of both histologic assessment and PCR is less than optimal.

TREATMENT

Whipple's disease was invariably fatal before the advent of antibiotics. However, current recommen-

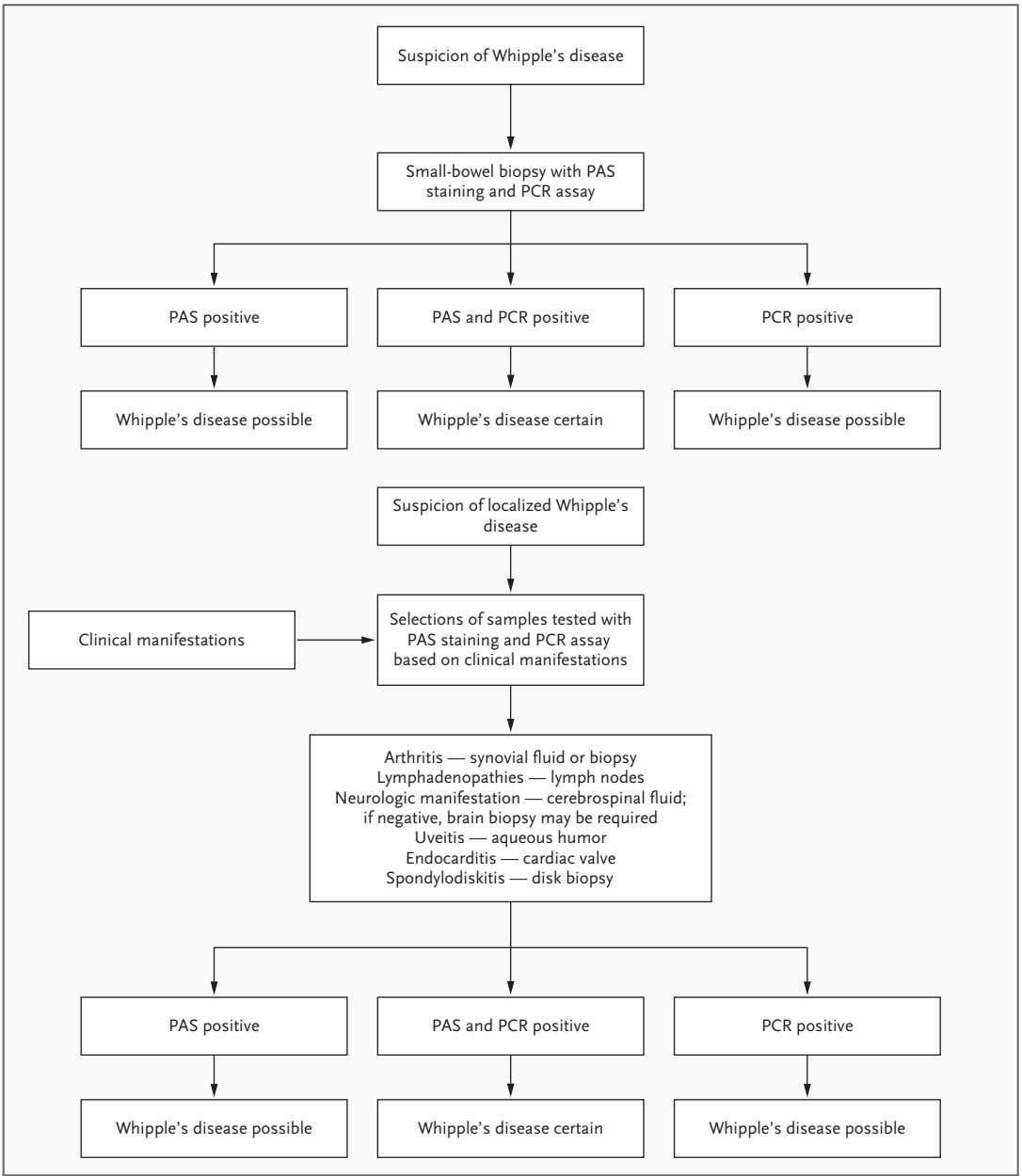

Figure 2. Strategy for the Diagnosis of Whipple's Disease Using PAS Staining and PCR Assay.

The sampling hierarchy depends on the clinical manifestations of the disease and the interpretation of the obtained results. If PAS staining of the small-bowel–biopsy specimen is positive and the PCR assay is negative, the diagnosis of Whipple's disease must be confirmed; this can be done by immunohistochemical testing with an antibody to *T. whipplei*. If this test is positive, Whipple's disease is confirmed; if the test is not feasible, other tissues must be analyzed. If the PCR assay is positive and PAS staining is negative, the result must be confirmed by using another PCR target on the same sample or by analyzing other tissues. When a definite diagnosis of Whipple's disease has been established, the cerebrospinal fluid should be tested with a PCR assay, even in the absence of neurologic signs. When the diagnosis is in doubt, samples from saliva, stool, and blood can be tested; a positive PCR assay with one of these samples in conjunction with a positive test on another tissue may be helpful in confirming Whipple's disease.

dations are not based on therapeutic trials or the susceptibility of *T. whipplei* to various antimicrobial agents. Tetracycline has long been prescribed as a first-line treatment, but the frequency of recurrence after treatment with this agent has been high (28% on average).[21,25,26] Thus, the standard for antibiotic therapy currently favors antibiotics that are capable of crossing the blood–brain barrier, such as trimethoprim–sulfamethoxazole. The recommended treatment is oral administration of 160 mg of trimethoprim and 800 mg of sulfamethoxazole twice per day for 1 to 2 years, usually preceded by parenteral administration of streptomycin (1 g per day) together with penicillin G (1.2 million U per day) or ceftriaxone (2 g daily) for 2 weeks. However, lack of a clinical response has been reported with this strategy, and recurrence is also possible (Table 4).[21,25,26,39,97-99]

Patients with a neurologic recurrence of Whipple's disease have a poor prognosis.[39] Interferon gamma has been proposed for treatment of recurrent central nervous system disease, and one report noted that a positive effect was still present at least 1 year after interferon gamma therapy had been stopped.[100] The susceptibility of *T. whipplei* to various antimicrobial agents has been tested with the use of both cell and axenic cultures.[12,13] Many antibiotics, including doxycycline and sulfamethoxazole, are active in vitro, but trimethoprim is not, as predicted from genomic analysis,[13,14,101] since *T. whipplei* lacks the coding sequence for dihydrofolate reductase, which trimethoprim targets.[101] In cell culture, cephalosporins (including ceftriaxone) and fluoroquinolones are not active.[13] In axenic medium, ceftriaxone and levofloxacin are active.[14] Vacuole acidification has been shown to be critical to the survival of *T. whipplei* in phagosomes, since agents that increase the intravacuolar pH decrease bacterial viability.[102] A regimen based on this observation — doxycycline (200 mg per day) and an alkalinizing agent, hydroxychloroquine (200 mg three times per day) — has been effective in vitro. This combination has, thus far, been the only successful bactericidal regimen against *T. whipplei* in vitro.[13,102] Whether this regimen will work in a general clinical setting is unknown, though it has been successful in four of our patients: two with classic Whipple's disease and two with blood culture–negative endocarditis (unpublished data).

On the basis of previous work,[102] we suggest using a regimen of doxycycline and hydroxychloroquine to eradicate the intracellular organisms in patients with Whipple's disease who do not have neurologic involvement (as indicated by a negative PCR assay on cerebrospinal fluid and the absence of neurologic signs). In patients with neurologic involvement, we suggest adding a high dose of sulfamethoxazole or sulfadiazine to the regimen described above. There is no established marker that can be used to determine how long treatment should be continued. By analogy with other chronic infections,[103,104] it would seem reasonable to use this regimen for at least 12 to 18 months. Clinical trials are needed to confirm our approach and to establish whether these personal suggestions are effective.

DIRECTIONS FOR FUTURE RESEARCH

The recent cultivation of *T. whipplei*, along with the complete sequencing of its genome, should provide new opportunities for investigating, understanding, and treating Whipple's disease. The reservoir of *T. whipplei* remains to be established, and transmission mechanisms remain to be elucidated. The significance of possible asymptomatic carriers must be clearly addressed. Isolates of *T. whipplei* should be routinely genotyped to identify associations among clinical forms, different strains, and geographic origin. Although PCR has expanded the recognized clinical spectrum of the disease, many facets remain elusive. In the future, the development of an assay for detection of specific antibodies in the serum may help with diagnosis of the disease. Improvement in diagnostic approaches is of paramount importance for reli-

Table 4. Initial Treatment and Subsequent Relapse in Whipple's Disease.*

Antibiotic	No. of Relapses/ No. of Patients Treated (%)
Tetracycline	43/133 (32)
Trimethoprim–sulfamethoxazole	1/46 (2)
Penicillin and streptomycin	2/6 (33)
Other	12/64 (19)
Total	58/249 (23)

* Data are from six reports on case series, published since 1985, by Keinath et al.,[26] Fleming et al.,[25] Bai et al.,[97] Geboes et al.,[98] Feurle and Marth,[99] and Durand et al.[21]

able detection. Improved detection will in turn lead to decreases in the morbidity, and perhaps the mortality, associated with the disease, which is treatable when diagnosed early but may have fatal consequences when the diagnosis is delayed. Prospective trials are needed to evaluate therapy.

Drs. Raoult and Fenollar are among the inventors named on a patent held by the Université de la Méditerranée that does not involve commercialized products. No other potential conflict of interest relevant to this article was reported.

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