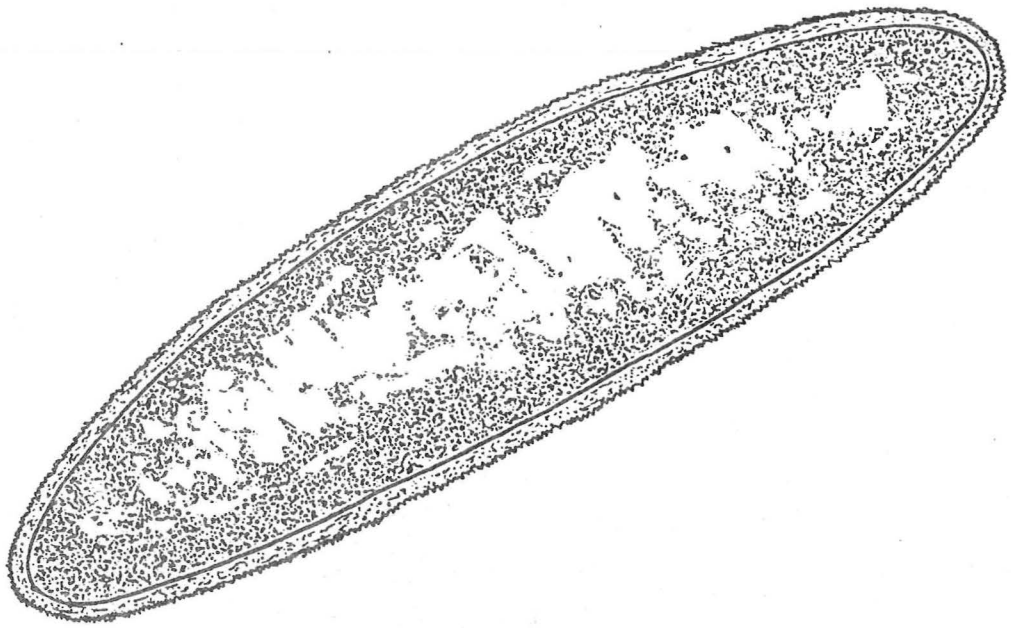
Infectious

WHIPPLE'S DISEASE:

A SYSTEMIC BACTERIAL INFECTION



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"As one looks back upon the history of this case in connection with the remarkable observations at autopsy, it is difficult to resist the conclusion that we are dealing with a definite and hitherto unrecognized clinical picture with which we shall meet again"

(George H. Whipple, 1907)

INTRODUCTION AND HISTORICAL ASPECTS

In 1907, 29 year old George H. Whipple, an instructor in the Pathology Department at Johns Hopkins University, who later shared a Nobel Prize with Minot and Murphy for work on liver extract in pernicious anemia, published a paper entitled "A Hitherto Undescribed Disease Characterized Anatomically by Deposits of Fat and Fatty Acids in the Intestinal and Mesenteric Lymphatic Tissues". The report concerned a 36 year old male physician who died after a 5 year illness characterized clinically by polyarthritis, weight loss, weakness, and chronic diarrhea. The striking findings at autopsy were (a) the absence of tuberculosis or neoplasm; (b) the presence of triglyceride and fatty acids in dilated lymph channels within the small intestinal villi; and (c) an infiltration of the lamina propria of the small intestine by large, foamy mononuclear cells which, rather unexpectedly, did not stain for fat. Fatty deposits were also prominent in the adjacent mesenteric lymph nodes, as were large mononuclear foamy cells and multinuclear "foreign-body type" giant cells. Whipple was most impressed with the accumulation of fat in the intestinal lymphatic system and stated "... this suggests very strongly that we are dealing with some obscure disease of fat metabolism. In searching for a name to designate this condition great difficulties were encountered. It would seem that no suitable name can be applied to it until the etiologic factor is determined. The term Intestinal Lipodystrophy is suggested..."

Whipple's description was quite exceptional for at least 4 reasons:

1. He recognized that he was examining a patient with a "new" disease, although it is thought by some that the first case was described in 1895 by Allchin and Hebb.

2. He recognized on sections of mesenteric lymph nodes large numbers of intracellular rod-shaped organisms that were argyrophlic and "about the diameter of the spirochete of syphilis but... rarely exceeding 2 μ in length." In the Discussion of his paper, Whipple stated: "It is not claimed that this is the etiologic factor in this disease but its distribution in the glands (sic nodes) is very suggestive." It is now recognized that these rod-shaped bacilliform organisms are the cause of this disease. It is of considerable interest that Whipple inoculated one of the patient's smaller mesenteric lymph nodes subcutaneously into a rabbit and the rabbit died 7 weeks later without evidence of tuberculosis, suggesting that the node contained a transmissable agent other than the tubercle bacillus.

3. Whipple emphasized the importance of arthritis which preceded intestinal symptoms in his patient. Unfortunately, Whipple did not have the opportunity to examine joint tissue at autopsy.

4. Whipple described other systemic features of the disease which we now know are sometimes present in these patients, including a) polyserositis (peritonitis, pleuritis, and pericarditis; b) endocarditis involving the aortic valve; and c) retroperitoneal lymphadenopathy. However, Whipple did not believe that these features were definitely related to the intestinal disease he was describing.

Whipple's disease is rare: the next case was described in the literature 16 years after Whipple's and the first case which was diagnosed prior to death, at laparotomy, was in 1947. In 1949, Black-Shaffer reported that the large foamy macrophages described by Whipple in the lamina propria of the small intestinal mucosa and in the mesenteric lymph nodes stained intensely with the periodic acid-Schiff (PAS) method. The presence of PAS-positive macrophages in the small intestinal mucosa at light microscopy then became a major method for diagnosing the condition.

Prior to 1950, every reported case was fatal. In the early 1950's, reports of successful antimicrobial treatment of isolated cases of Whipple's disease appeared. In the late 1950's, it was demonstrated that the disease could be diagnosed by small intestinal biopsy, obviating the need for laparotomy. In 1959, Sieracki and Fine emphasized the systemic nature of Whipple's disease, finding PAS-positive macrophages in a number of extraintestinal sites at autopsy. The organs involved in their study are shown in Table 1.

TABLE 1. ORGAN INVOLVEMENT AT AUTOPSY IN 4 PATIENTS WITH WHIPPLE'S DISEASE (FROM SIERACKI AND FINE)

Small Intestine	4/4	Lung	3/3
Colon	3/3	Blood Vessels	1/2
Esophagus	3/3	Kidney	2/3
Stomach	4/4	Urinary bladder	0/3
Mesenteric Nodes	4/4	Prostate	0/3
Peripheral Nodes	4/4	Testes	0/3
Serosal Membranes	3/3	Seminal vesicle	0/2
Liver	4/4	Thyroid	0/2
Spleen	3/3	Adrenal	3/3
Gallbladder	1/3	Brain	2/2
Pancreas	3/3	Skin	0/2
Heart	3/3	Bone	2/2

(number involved divided by number available for examination)

In August 1961, two laboratories reported simultaneously that rod-shaped bacillary organisms were visible on electron microscopy (EM) in single cases of Whipple's disease. These two groups of investigators included Drs. Chears and Ashworth at this medical school and Drs. Yardley and Hendrix at Johns Hopkins. These organisms are now recognized as the cause of Whipple's disease. Demonstration of these organisms in various tissues by EM is now accepted as the preferred method for diagnosing Whipple's disease, as there are other causes of PAS-positive macrophages in tissue. The exact organism which causes Whipple's disease still has not been identified.

In the past 25 years, it has become apparent that Whipple's disease is not just a small intestinal infection, but a systemic disease with protean manifestations. Although small intestinal involvement usually dominates the clinical picture, this may not be true in certain cases. Thus, a patient may initially be referred for rheumatological, neurological, cardiac, or hematological evaluation. For this reason, it is important that internists be familiar with Whipple's disease, even though it is uncommon. Once initially fatal, this condition is easily treatable in most cases if diagnosed early. In the past 8 years, I have had the privelege of caring for two patients with Whipple's disease at the Dallas VA Medical Center. These two cases will be described in detail in this Grand Rounds. Both cases have been published and both illustrate that this disorder is a systemic one that may be confused with other conditions.

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CASE REPORTS

Case 1. A 64-year-old white man presented to the Dallas VA Medical Center in March 1977 with fever to 104° F, chronic diarrhea, melena, abdominal pain, and a 20 kg weight loss over 2 months. He had had intermittent fever and nondeforming arthritis of the ankles, elbows, and knees since 1967, as well as low back pain and neck pain. He was febrile, emaciated, had skin hyperpigmentation and bilateral knee effusions. A small bowel x-ray showed mild dilatation. D-xylose absorption test was abnormally low. Stool weight was 345 gm/24 hr (normal, less than 200 gm/24 hr) and the stool fat was 5.7 gm/24 hr (normal, less than 5 gm/24 hr). X-rays revealed severe degenerative arthritis involving the lumbo-sacral spine, cervical spine, hips, and knees. An HLA B27 antigen test was negative.

A jejunal biopsy just distal to the ligament of Treitz showed diffuse infiltration of the lamina propria by foamy macrophages containing PAS-positive material. EM showed many bacillary organisms within macrophages, and the diagnosis of Whipple's disease was made. The patient was treated with procaine penicillin, 600 000 U intramuscularly twice daily for 14 days, with resolution of all symptoms within 36 hours. He was discharged, asymptomatic, on oral penicillin G, 500 mg twice daily.

Over the next several months he gained approximately 20 kg and remained asymptomatic except for one transient episode of vertigo. A repeat jejunal biopsy 3 months after initiation of therapy showed persistence of PAS-positive macrophages but fewer organisms on EM. After 8 months of penicillin therapy, no bacillary organisms were seen by electron microscopy. Penicillin was continued for another 6 months and then discontinued in June 1978. Three weeks later he developed fever, arthralgias, and loose stools. Oral penicillin was reinstituted in the same dosage with resolution of all symptoms within a few days. Jejunal biopsies in November 1978 and January 1979 again showed no organisms by EM and fewer PAS-positive macrophages, with return of the villous architecture towards normal.

In February 1979 he complained of intermittent vertigo and tinnitus. Examination by neurology and otolaryngology consultants failed to demonstrate any abnormalities except for a mild sensorineural hearing loss on audiography. In May 1979, penicillin was again discontinued. Two days later he developed fever, headache, anorexia, ataxia, oscillopsia, and profound disorientation, for which he was admitted on 13 May 1979. The family mentioned that they had observed gradual memory impairment and personality changes in the patient over the past 1 to 2 years. His temperature was 39.7°C. He was disoriented to time and place, had a wide-based shuffing gait, and was unable to tandem walk. In addition, he had ataxia of upper and lower extremities bilaterally. Deep tendon reflexes were bilaterally symmetrical, and no pathologic reflexes were elicited. He had no tremor or asterixis.

The leukocyte count was 12,200 with 71% neutrophils and 6% band forms. As shown in Table 2, cerebrospinal fluid (CSF) protein was 102 mg/dL and the CSF leukocyte count was 390/mm^3 (59% neutrophils and 41% mononuclear cells). Gram stain, India ink preparation, VDRL, and acid-fast bacillus smear of the CSF were negative. Bacteriologic and fungal cultures of CSF were negative, including cultures on hypertonic medium. Fungal titers, coxsackievirus, and adenovirus titers were nondiagnostic. Computed tomography (CT) of the head showed minimal cerebral atrophy. Cytologic studies and EM examination of several cell blocks from CSF disclosed no PAS-positive macrophages or organisms. Jejunal biopsy continued to show no organisms by EM. The patient was treated with intravenous aqueous penicillin G, 3 million U every 4 hours as well as chloramphenicol, 1 g intravenously every 6 hours. On this regimen there was rapid clearing of his mental status and gradual improvement in his gait disturbance and ataxia. Serial changes in CSF leukocyte count and protein are shown in Table 2, correlated with his clinical status and antibiotic treatment.

He was discharged on 2 June 1979 on oral penicillin G, 500 mg; probenecid, 1 g; and chloramphenicol, 250 mg, all given four times daily. Repeat lumbar puncture in August 1979 showed no leukocytes. In October chloramphenicol was discontinued, but by November his CSF leukocyte count had increased to 16/mm^3. Amoxicillin, 500 mg every 6 hours, was substituted for penicillin. Two weeks

later ataxia, an intention tremor, and a positive rebound sign developed. Pleocytosis was again noted in the CSF and oral chloramphenicol reinstituted with rapid resolution of all symptoms. Repeat lumbar puncture in December showed no leukocytes and a protein level of 42 mg/dL. He remained well until July 1982 when he again developed ataxia. CSF leucocyte was 2/mm^3 and a trial of dimenhydrinate (Dramamine) and meclizine (Antivert) were unsuccessful in controlling the symptoms. Because of a fear of a CNS reactivation of his Whipple's disease, chloramphenicol was increased to 500 mgm qid. His symptoms improved gradually.

TABLE 2. CLINICAL AND CEREBROSPINAL FLUID FINDINGS IN CASE 1

DATE	CLINICAL STATUS	CEREBROSPINAL FLUID FINDINGS		ANTIBIOTIC TREATMENT
		LEUKOCYTE COUNT	PROTEIN	
		mm^{-3}	mg/dL	
5/13/79	Fever, confusion, ataxia	390	102	None (penicillin withdrawn 5/9/79)
5/14/79	Improved	450	130	Chloramphenicol, penicillin
5/16/79	Afebrile, oriented, less ataxia	166	68	Chloramphenicol, penicillin
5/30/79	Asymptomatic	12	68	Chloramphenicol, penicillin
8/9/79	Asymptomatic	0	70	Chloramphenicol, penicillin
10/15/79	Asymptomatic			Penicillin (chloramphenicol stopped)
11/2/79	Asymptomatic	16	48	Amoxicillin (penicillin stopped)
11/14/79	Ataxia, intention tremor, positive rebound sign	14	49	Chloramphenicol, (amoxicillin stopped)
11/16/79	Resolution of all symptoms			Chloramphenicol 250 mgm qid
12/12/79	Asymptomatic	0	42	Chloramphenicol 250 mgm qid
7/15/80	Ataxia	2	52	Chloramphenicol 500 mgm qid
10/28/80	Less ataxia; decreased visual acuity	0	68	Chloramphenicol 250 mgm qid
11/12/80	No change in visual acuity			Bactrim (chloramphenicol stopped)
10/14/81	Visual acuity normal			Bactrim

In October 1980 he developed decreased visual acuity. Ophthalmalogic consultants diagnosed bilateral optic neuropathy, secondary either to chloramphenicol or Whipple's disease. A CSF examination showed no white cells and chloramphenicol was decreased to 250 mgm qid. Two weeks later, visual testing showed no improvement and chloramphenicol was discontinued. Trimethoprim-sulfamethoxazole (Bactrim) was started in a dosage of 2 tablets bid. His visual

acuity dramatically improved over the next few months and he remained well with only mild ataxia and decreased hearing until his death in an motor vehicle accident in February 1982.

Comment. This patient's presentation was quite typical for Whipple's disease. Despite a prolonged course of penicillin which successfully eradicated his intestinal infection, central nervous involvement was not prevented and, in fact, he developed acute meningoencephalitis following withdrawal of antibiotics. Although CNS Whipple's disease was not documented by EM in this patient, his clinical presentation and dramatic clinical response to antibiotics that pass easily into the CNS argue strongly in favor of CNS Whipple's disease. He had extensive degenerative arthritis which resembled ankylosing spondylitis but he was HLA B27 negative.

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Case 2. A 50-year-old white man was hospitalized at the Dallas VA Medical Center for evaluation of fatigue and weakness. He had a 3-month history of anorexia, a 42-kg weight loss, intermittent burning epigastric pain, and foul-smelling diarrhea containing no overt blood, pus, or mucus. Several weeks before admission he developed a rash on his extremities. The patient had no history of fever, night sweats, lymphadenopathy, hematemesis, melena, or change in skin pigmentation and denied having had any significant illness. He had chronic low back pain and had had a lumbar laminectomy in the recent past which had not relieved his symptoms. He admitted to consuming three cans of beer daily; his diet consisted mainly of cereal, soup, milk shakes, hamburgers, and desserts. He took no medications.

On admission the patient was thin and appeared chronically ill. Vital signs were normal. There were nonpalpable ecchymoses on the dorsal forearms. Numerous hyperkeratotic follicular papules with hemorrhage into the follicles were seen. Several follicles had fragile short "corkscrew" hairs. Dentition was poor with several small bleeding sites in the gums. Other examination findings were normal, except for an intermittently guaiac positive stool and slightly enlarged inguinal lymph nodes bilaterally.

Chest and abdominal roentgenograms were normal. The hematocrit was 28.5% (mean cell volume, 73 μm^3). The leukocyte count was 11,500 cells/mm^3 with 73% neutrophils, 13% bands forms, and 14% lymphocytes. The platelet count and prothrombin time were normal. Serum iron level was 16 µg/dl (normal, 40 to 150 µg/dL). Serum albumin was 3.0 g/dL and total protein was 6.6 g/dL. Serum cholesterol was 98 mg/dL. Serum carotene was 23 µg/dL (normal, 70 to 250 µg/dL) and results of a qualitative stool examination for fat were positive. Upper gastrointestinal roentgenograms showed mild dilatation of the small bowel without thickening of mucosal folds. An abdominal CT scan showed extensive retroperitoneal and mesenteric lymphadenopathy. A skin biopsy demonstrated follicular hyperkeratosis and perifollicular hemorrhage, consistent with scurvy.

Endoscopic examination showed diffuse patchy erythematous mucosa in the stomach, duodenum and colon. The mucosa was not friable. Biopsy samples from the

duodenum, stomach, and colon showed hemorrhage into the lamina propria and collections of foamy macrophages. The macrophages stained positively with the PAS stain and were diastase resistant. Some blunting of the small intestinal villi was seen. EM showed the presence of bacilliform bodies throughout the large and small bowel, as well as in an inguinal lymph node that had been excised.

After endoscopic examination, the patient was treated with ascorbic acid, 1 g/day. Serum drawn 24 hours after the administration of the first dose had a vitamin C level of 0.1 mg/dL (normal, 0.4 to 1.5 mg/dL). The patient's skin abnormalities resolved during the next week. Repeat upper endoscopic examination after 6 days of vitamin C therapy showed normal gastric mucosa. In the duodenum, the mucosa was without erythema but several small yellowish-white plaques were seen. Biopsy samples showed a remarkable decrease in the submucosal hemorrhage but a persistence of foamy macrophages and bacilliform bodies.

He became asymptomatic on oral penicillin and gained weight, but was lost to follow-up after discharge. Eighteen months later he returned to the Emergency Room with a 2-week history of diarrhea and weight loss. He had not taken penicillin in over a year. He was started on tetracycline and referred to GI clinic, where he was seen by me two weeks later. By then his diarrhea had completely resolved and he had regained 10 pounds. An endoscopic small bowel biopsy showed active Whipple's disease with numerous bacilliform bodies. He remains asymptomatic on tetracycline, except for low back pain for which he takes ibuprofen. Back films revealed spur formation and narrowing of the L5-S1 interspace. A repeat small bowel biopsy is planned after he completes 1 year of therapy. We are currently considering switching to trimethoprim-sulfamethoxazole in hope of eradicating or preventing central nervous system Whipple's disease (see below).

Comment. This patient presented with malnutrition and scurvy, which was probably a result of both malabsorption and dietary deficiencies. Because of GI bleeding and iron deficiency, endoscopy and biopsies were carried out which demonstrated foamy macrophages in the small bowel, colon, and stomach. Recognition of these macrophages led to a PAS stain and EM which resulted in a diagnosis of Whipple's disease. The patient also had lymphadenopathy, a condition which was confused with lymphoma or metastatic carcinoma clinically and on CT scan. As in case 1, the patient had severe degenerative arthritis of the spine.

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ETIOLOGY AND PATHOGENESIS

> "I must emphasize again that this (i.e. Whipple's) is a psychosomatic disease. All my patients illustrate this and it is important from the point of view of treatment to bring to consciousness the provocative life situation. The personality profile approaches most nearly to that found in Crohn's disease and ulcerative colitis, it is unlike that in duodenal ulcer".
>
> (J.W. Paulley, Ipswich, Great Britain, 1964)

For many years, nothing was known of the etiology of Whipple's disease. The term "intestinal lipodystrophy", coined by Whipple, along with the steatorrhea seen in many of these patients made most people think of the disease as a primary lipid metabolic disorder. Many theories concerning lymphatic obstruction were proposed, but anatomic studies have since disproved this, and, indeed, the absence of chylous obstruction became one of the criteria for a histologic diagnosis of Whipple's disease as set forth by Black-Schaffer.

In 1949 Black-Schaffer described the morphology of Whipple's disease under the light microscope and demonstrated that the foamy macrophages seen in the lamina propria of the small intestine were not sudanophilic (as Whipple had also noted), but contained granules in the cytoplasm that were PAS positive, indicating that these cells had a high concentration of glycoprotein. Thus, the histological features of Whipple's disease under the light microscope as described by Black-Schaffer were non-lipid PAS-positive macrophagocytosis in the lamina propria of the small bowel and occasionally the colon, lipogranulomatosis of the mesenteric lymph nodes, and absence of evidence of lymphatic obstruction.

The description of PAS-positive macrophages renewed interest in Whipple's disease, and many workers became concerned about a possible etiologic relationship of these inclusions. Attention became focused on carbohydrate rather than lipid metabolism. Several theories were proposed prior to 1960, including a primary defect of the intestinal mucosa, a state of mechanical obstruction, a rheumatic, collagen, or hypersensitivity reaction, a disorder of cellular proliferation, possibly neoplastic, or a primary metabolic or enzymatic defect. It is safe to say that in 1960 no more was known of the etiology of Whipple's disease than was known in 1907.

In 1960 and 1961 a dramatic step toward understanding the etiology of Whipple's was made: sections of tissues from patients with Whipple's disease were submitted to electron microscopy. Cohen, et al. in 1960 examined the PAS-positive inclusions in intestinal macrophages and described a complex ultrastructure comprised of a series of membranes, vesicles, and granules and they postulated a viral origin. Hollenberg found "minute cylindrical bodies, both intracellular and extracellular" in biopsy specimens of the duodenum and he suggested a rickettsial or large viral particle. However, most observers believed the particles to be bacterial. Chears and Ashworth in Dallas described numerous gram positive bacilliform bodies in the intercellular spaces and in the macrophages of the small intestinal lamina propria. These bodies were demonstrated by light microscopy with gram and Giemsa stains and by EM. They stated "it is our interpretation that these bodies are bacteria, and a possible etiologic role for them is considered as well as an alternative explanation of their presence by secondary invasion". The bacilli were less than half the size of E. Coli, M. tuberculosis, or Proteus species and were closest in size and interior structure to Listeria.

Yardley and Hendrix in Baltimore, also in 1961, gave an extremely detailed description of the "bacillary bodies" seen in the extracellular spaces of the lamina propria in large numbers just beneath the basement membrane and around many of the PAS-positive granule-containing cells. Many of these bodies appeared round or slightly ellipsoidal in electron micrographs, and thus they suggested the body may be a coccobacillus. The particles were 0.15-0.20 μ wide and slightly more than 1 μ in length, contained a thick outer jacket, about 25 millimicrons thick, limited internally by a dark thin membrane. Adjacent to

this outer jacket, presumably analogous to a bacterial cell wall, was a clear zone of 6-7 millimicrons and then internally a rather indistinct membrane. The interior consisted mainly of very electron-dense material which had a coarsely granular appearance, but centrally the "bacillary body" revealed one or more indefinite areas of lesser density and granularity, which looked like large sharply outlined vacuoles. They thought that the granular material may be analogous to bacterial cytoplasm with ribonucleoprotein in high concentration, and the central less dense region may represent the bacterial nuclear material. Yardley and Hendrix also pointed out that these bodies were also seen in otherwise normally appearing epithelial absorptive cells and that clusters of these bodies located extracellularly were visible by light microscopy. These same clusters of gram positive material were PAS-positive and revealed individual rod-shaped bodies. These clusters stained as dark blue masses with the Giemsa stain; acid-fast stains were negative. An EM picture of the bacillary organism is shown in Figure 1.

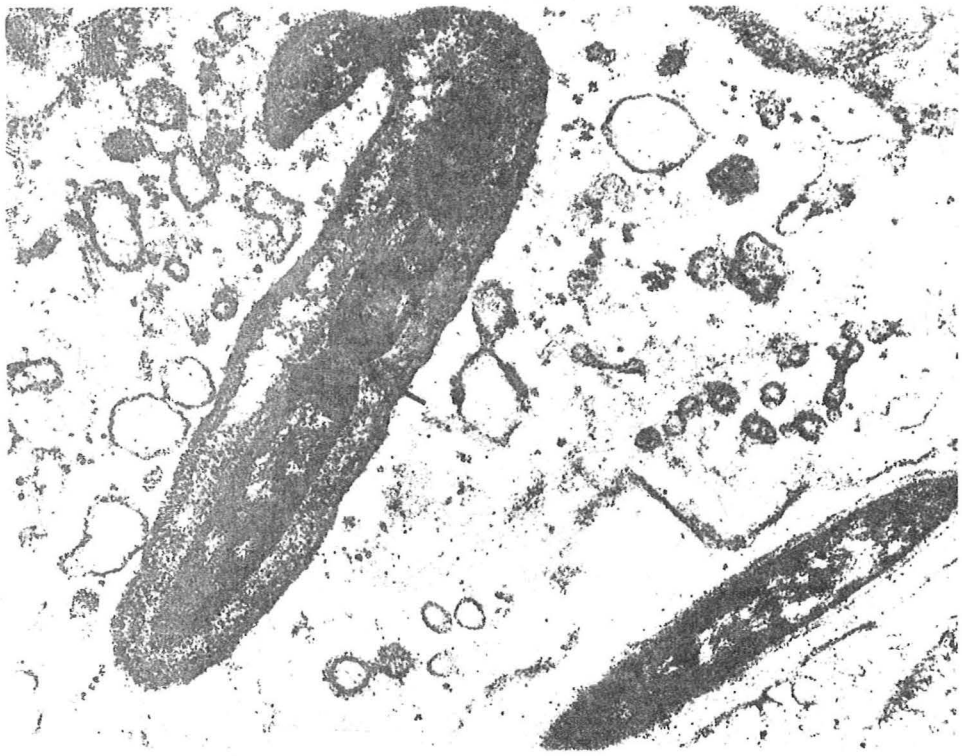

Figure 1. EM (X 55000) of a bacillus "B" extracellularly and an organism within a macrophage undergoing binary fission (F, arrow) in a patient with Whipple's disease (from Trier JS, et al, Gastroenterology 47: 684, 1965)

Yardley and Hendrix made two observations that made untenable the suggestion that the "bacillary bodies" were viral particles, as Cohen, et al. had speculated. The first concerns their size: the larger viruses, such as those of the psittacosis group, measure only about 400 millimicrons in their greatest dimension, and most types are much smaller. The "bacillary bodies" measured at least 1 μ in length, even in ultrathin sections. Second, the ultrastructural morphology of the particles was more complex than that of viruses. Large numbers of bacillary forms seen extracellularly and the failure of the organism to take up the Macchiavello stain made a Rickettsiae unlikely. The presence of the outer jacket excluded mycoplasma. The fact that the bodies stained with PAS, more a distinguishing characteristic of mycotic organisms, is unusual for bacteria, but the absence of internal organelles such as definite mitochondria, internal membrane systems, and a membrane delineated nucleus would make fungi or actinomyces unlikely. On the other hand, some bacteria fall into the size range of the bacillary bodies. Included are Brucella, Pasturella, and the Bacteriodes, but curiously the bacillary bodies in Whipple's disease are gram

positive, whereas organisms of this size and location are ordinarily gram negative. Nevertheless, Yardley and Hendrix were convinced that the "bacillary bodies" were bacteria and they speculated that the PAS-positive inclusions in the macrophages were derived from the phagocytized undigestable portion of the "bacillary bodies" or were a normal or abnormal response of the host cell to the organism.

Thus, it appeared to some that the inclusions within macrophages in patients with Whipple's disease, called sickleform particles by Sieracki, may be derived from ingested bacteria, and their formation could still be related to a metabolic disorder, such as an enzyme defect. In 1962 Fisher studied these sickleform particles and concluded that they were host cell mitochondrial fragments; he postulated a disorder or reticuloendothelial cells, particularly in their mitochondria. However, most researchers at this stage believed that the sickleform particles were derived from bacteria undergoing various stages of degeneration. Later, Ashworth demonstrated that the foamy material seen in macrophages on light microscopy represented indigestible cell wall material.

The ultimate proof for a bacterial etiology for Whipple's disease will be to fulfill Koch's postulates of pathogenicity. These postulates are listed in Table 3. Although the first postulate is fulfilled (by definition), postulates 2,3, and 4 have not been fulfilled.

TABLE 3. POSTULATES OF ROBERT KOCH

1.	A specific organism can always be found in association with a given disease.
2.	The organism can be isolated and grown in pure culture in the laboratory.
3.	The pure culture will produce the disease when inoculated into a susceptible animal.
4.	It is possible to recover the organism in pure culture from the experimentally infected animal.

Many attempts to culture the organism from biopsy material have been unrewarding.* Ashworth, et al. in 1964 minced biopsy specimens and inoculated them into several media including trypticase-soy broth, thioglycollate broth, blood agar and chocolate agar plates (with and without increased carbon dioxide tension), cysteine heart agar and Dubos' albumin broth. Also a tissue culture of Chang liver cells was inoculated without the use of antibiotics. After about one week of incubation, a small gram negative bacillus was recovered from the thioglycollate broth, but attempts to subculture the organism were unsuccessful. This fleeting organism was believed to be a Bacteroides. An enterococcus was grown from the trypticase-soy broth, but since it differed in morphology from the organism seen in microscopy it was considered a contaminant. Sherris, et al. in 1965 found on gram-stained preparations of biopsy tissue that there were numerous extremely thin, weakly gram positive bacilliform bodies, more easily

* Inability to culture an organism does not rule out its possible involvement. For example, Mycobacterium leprae cannot be cultured but is universally accepted as the agent that causes leprosy.

seen when the counterstain (saffranin) was omitted. Many species were grown out in culture, including coliforms, streptococci, small anaerobic diphtheroids, and small gram negative rods resembling Hemophilus, but these organisms were considered contaminants. Biopsy material was inoculated intraperitoneally into mice and subcutaneously and into the ileal wall of two rabbits; no evidence of infection or other disease was detected at autopsy one or two months later. Sherris concluded that the organisms seen in smear preparations and EM were highly fastidious bacteria, and that they had failed to meet their growth requirements.

In 1966, Charache et al. carried out studies on one patient with Whipple's disease which raised the possibility that the etiologic agent was a bacterium with a damaged or defective cell wall. If the cell wall of a bacterium is defective, the organism will demonstrate changes in its morphology and cultural requirements and the organism may be unrecognized with routine types of cultures. Protoplasts, spheroplasts, and L-forms are examples of cell wall deficient bacteria. Charache et al. repeatedly grew out from blood and a lymph node a cell wall deficient group D beta hemolytic streptococcus (enterococcus). The bacterium on initial culture on trypticase-soy or thioglycolate appeared as clumps of gram positive and gram negative cocci or rods, but on repeated subculture they eventually reverted completely to a typical-appearing beta hemolytic streptococcus. The organism was PAS-positive on staining, was sensitive *in vitro* to several antibiotics, and induced a high circulating antibody titre in the patient's plasma. However, attempts to transmit disease to mice, guinea pigs, and rabbits with the parent strain were unsuccessful.

In 1975, Clancy et al in Canada were able to grow out a cell wall deficient form of alpha-hemolytic streptococcus from a prolonged cell culture of an axillary lymph node which had been removed from a 40 year old woman with Whipple's disease. The organism did not grow on primary culture on normal or hypertonic media, but did grow out on hypertonic sucrose medium after prolonged cell culture. In addition, the same organism, which they characterized biochemically as Streptococcus dysgalactiae, grew out from a jejunal biopsy on hypertonic medium. Monolayer cells from the lymph node culture contained PAS-positive diastase resistant material which on EM represented bacteria identical to those seen in the gut mucosa. Clancy et al. further demonstrated that the cell wall deficient strain was sensitive to tetracycline *in vitro* and that the patient's serum had IgA antibodies which reacted against the PAS-positive macrophages, as demonstrated by indirect immunofluorescence. Although Clancy's report is provocative, the material was obtained from only one patient and confirmatory reports of this particular organism in other patients with Whipple's disease have not appeared. Table 4 summarizes some organisms which have been cultured from intestinal or nodal tissue in patients with Whipple's disease.

TABLE 4. BACTERIA IN WHIPPLE'S DISEASE

Streptococci
alpha hemolytic (including cell wall deficient S. dysgalactiae)
group D (cell wall deficient)
group G
Corynebacterium (anaerobic and aerobic)
Hemophilus species

Despite conflicting cultural studies, evidence continued to accumulate in favor of a bacterial etiology. In 1964, Ashworth et al. demonstrated that the gram positive organisms underwent transverse fission and disappeared following the use of tetracycline. Phillips and Finlay in 1967 reported similar findings to Chears and Ashworth, also witnessing binary fission. Ashworth et al. described the particles as having a complete lack of identity with any normal intracellular or extracellular structure or intermediate stage thereof. They pointed out that bacilliform bodies had been present in all cases of Whipple's disease submitted to EM prior to antibiotic treatment and that descriptions of the bodies by several workers have been virtually identical. They proposed that the origin of the PAS-positive material in the foamy macrophages was bacterial, the major evidence being the "striking morphologic similarity and gradations between cell walls of intact bacilliform bodies and the collapsed ring-like structures, packets of which comprise the sickleform PAS-positive bodies" previously described by Sieracki. They further emphasized that persistent inclusions in macrophages may occur in other bacterial diseases such as the globi of Neisser of the foam cells in leprosy. Ashworth, et al. concluded that the PAS-positive inclusions in the macrophages were derived from polysaccharide-containing cell walls of phagocytized bacteria. In 1967 Dobbins and Ruffin documented bacterial invasion of epithelial cells as well as intestinal lymphatics. In 1969, Schochet et al. studied at autopsy the brain of 4 patients with Whipple's disease and neurological symptoms. With EM, they found bacilli morphologically identical to those observed in the small bowel and undergoing the same sequence of degenerative changes. The PAS-positive material was intact even after organisms had disappeared in certain areas.

Because no consistent organism has been cultured from tissue of patients with Whipple's disease, some investigators have considered the possibility that more than one bacterium could be etiologic. Several workers have tried to identify specific bacterial antigens in macrophages using immunofluorescence staining of tissues. This approach is attractive in the sense that bacterial antigens are detected rather than attempting to grow out the bacteria. Using a battery of antibacterial antibodies in several patients with Whipple's disease, the antigenic staining profiles were remarkably similar from patient to patient, implying that there is only a single etiologic bacterial agent in Whipple's disease. However, because of the wide cross-reactivity of antibacterial antibodies across bacterial species, these immunofluorescent techniques are not helpful in pinpointing which organism is the etiologic agent. For example, Whipple's disease macrophages contain antigens which react strongly with antibodies raised against Streptococci (groups A,B,C, and G), Shigella (group B), and E. Coli (group A). It is likely that the unknown bacteria which causes Whipple's disease shares common antigens with Streptococci and various enteric organisms. Perhaps the use of species-specific monoclonal antibodies will clarify the nature of the bacterium in intestinal and other tissues in patients with Whipple's disease.

Although the etiology of Whipple's disease is now believed to be infection with an unusual bacterium, the pathogenesis of Whipple's disease is unclear. Most investigators favor the gastrointestinal tract as the portal of entry. The duodenum and proximal jejunum are more conspicuously involved than the more distal small bowel, suggesting an oral portal of entry. Bacilli have been identified by Watson and Haubrich not only in epithelial cells and the lamina propria but free in the small intestine adjacent to the glycocalyx of the enterocyte's microvilli. Organisms have with one possible exception been iden-

tified in the small intestine in every untreated patient with extraintestinal Whipple's disease, suggesting that the disease usually begins in the intestine before systemic dissemination. Whipple's disease was present in the small intestine of one patient 7 years before clinical manifestations of the disease appeared. In patients receiving antibiotics, however, organisms may disappear from the gut yet still be present in extraintestinal sites, especially the central nervous system (see below).

A number of observations suggest that the organism which causes Whipple's disease is not highly virulent to the host. First, large numbers of organisms are easily demonstrated in involved tissues, yet tissue injury is usually minimal. Second, the organisms usually elicit little or no inflammatory response. Tissue injury proceeds very slowly, over months to years. There is a striking similarity to lesion of Whipple's disease and the lepromatous form of leprosy. Both diseases are characterized by large numbers of organisms, local accumulations of macrophages, phagocytosis of bacteria by macrophages, lack of tissue necrosis, and formation of foam cells from undigestible remnants of cell walls from phagocytosed bacteria.

Evidence suggests that the organism enters both the lymphatics and reaches the mesenteric lymph nodes and also enters the systemic circulation. Whether the organism usually enters the systemic circulation via the lymphatic system and thoracic duct or via the vascular system of the gut through the portal vein is unknown. PAS-positive macrophages have been identified in both thoracic duct lymph and in the systemic circulation, and bacteria have been seen invading both lymphatic and capillary endothelium within the lamina propria of the gut.

It is unknown whether Whipple's disease is caused by a rare, but intrinsically pathogenic, bacterium or by an ordinarily nonpathogenic bacterium in a compromised host. Several studies have raised the possibility that patients with Whipple's disease have an underlying defect in cell-mediated immunity which predisposes them to opportunistic infections. On the other hand, weight loss and malnutrition, regardless of cause, lead to a decrease in cell-mediated immunity. The evidence for and against a role for immunologic dysfunction in the pathogenesis of Whipple's disease will be described below.

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CLINICAL FEATURES

Incidence. Less than 500 cases of Whipple's disease have been reported. The actual incidence and prevalence of the disease is not known. The fraction of patients with Whipple's disease who are asymptomatic or who are free of GI symptoms is also not known, but such patients have been reported.

Genetic Factors. Symptomatic Whipple's disease is 5- to 6-times more common in men than in women, for uncertain reasons. Two pairs of brothers with the disorder have been reported. An association with HLA B27 has been suggested, but not proven (see below).

Race. Most patients are Caucasians. The disease is rare in blacks and American Indians.

Age. Whipple's disease tends to affect middle-aged individuals, with a peak age incidence at diagnosis of 40-49 years. However, patients as young as 3 months and as old as 83 years have been reported. A case of congenital Whipple's disease in a newborn has been reported from Italy.

Symptoms. The major symptoms of Whipple's disease are shown in Table 5, as well as their approximate frequency.

TABLE 5. MAJOR SYMPTOMS IN WHIPPLE'S DISEASE

SYMPTOM	PERCENTAGE OF CASES
Weight Loss	95%
Chronic Diarrhea	78%
Arthralgia	65%
Abdominal Pain	60%
Chills and Fever	40%

Signs. The major physical findings are described in Table 6, as well as their approximate frequency.

TABLE 6. PHYSICAL FINDINGS IN WHIPPLE'S DISEASE

SIGN	PERCENTAGE OF CASES
Weight Loss	95%
Hypotension (< 110/60)	70%
Lymphadenopathy	55%
Abdominal Tenderness	50%
Skin Hyperpigmentation	45%
Fever	40%
Edema	30%
Glossitis	20%
Abdominal Mass	20%
Ascites	5-10%
Splenomegaly	5-10%

Because so many organ systems may be involved in Whipple's disease, these will be reviewed separately below. It must be kept in mind that many of these organs may be involved in the absence of symptoms or physical findings. Thus, biopsy of certain organs not clinically involved (e.g., the small intestine) may be indicated in certain cases. Furthermore, the presence of bacteria in the small intestine of an asymptomatic patient may herald a clinical relapse of the disease.

Gastrointestinal Tract. The most common gastrointestinal symptoms are weight loss, chronic diarrhea, and abdominal pain. Nausea and vomiting are occasionally present. Although melena is uncommon, guaiac positive stools are present in the majority of cases. Case 1 in this Grand Rounds had melena and Case 2 had guaiac positive stools and iron deficiency anemia. Thus, Whipple's disease needs to be considered in the differential diagnosis of GI bleeding. The mechanism for GI bleeding is uncertain, since erosions and ulcerations of the intestinal mucosa are not a feature of the disease. The combination of fever, chronic diarrhea, and blood in the stool should suggest Whipple's disease, in addition to idiopathic inflammatory bowel disease (Crohn's, ulcerative colitis) and other infectious diseases (e.g. amebiasis). Albumin loss into the stool also occurs commonly in Whipple's disease and may result in hypoproteinemia and peripheral edema.

In most patients, weight loss is the result of malabsorption of ingested nutrients. In other patients, anorexia and abdominal pain lead to reduced caloric intake. Furthermore, the fever which is present in almost half of patients may increase caloric requirements.

With regard to diarrhea, several mechanisms have been proposed to explain malabsorption and steatorrhea in Whipple's disease including (1) direct infection and dysfunction of absorptive small intestinal epithelial cells, preventing esterification of fatty acids to triglyceride and preventing uptake of amino acids and carbohydrates; (2) blockage of lymphatic transport of triglyceride-rich chylomicrons into lacteals due to accumulation of foamy macrophages in the lamina propria; and (3) lymphatic obstruction at the level of the mesenteric lymph nodes. The first theory is the most attractive because (1) in addition to fat malabsorption, carbohydrate and protein malabsorption occur in Whipple's disease (low D-xylose absorption, increase fecal nitrogen); and (2) malabsorption and diarrhea tends to disappear in a few days after treatment is initiated, whereas dilated lacteals and PAS-positive macrophages may require months to years for resolution. Although diarrhea in Whipple's disease is generally attributed to steatorrhea and malabsorption, it is possible that colonic involvement may contribute to diarrhea in some patients.

Abdominal pain in Whipple's disease is usually nonspecific, epigastric in location, and exacerbated by eating. Severe abdominal pain leading to exploratory laparotomy has been reported, but is quite uncommon. Ascites may result from peritonitis (see serositis, below) and be exacerbated by hypoproteinemia. In some cases, ascites is chylous. Abdominal mass may occur as a result of intra-abdominal lymphadenopathy or thickening of loops of diseased intestine.

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Joints. Arthralgia is the most common non-gastrointestinal symptom in Whipple's disease (Table 4). In most cases, arthralgia precedes GI symptoms for a number of years or even several decades. Joint symptoms usually continue unchanged when GI symptoms develop. Arthralgias are usually acute, migratory and symmetrical and there are often no objective findings of arthritis on physical examination. However, joint effusions may occur. Permanent joint destruction and deformity are uncommon, but occur. Joints which are involved, in order of decreasing frequency, are listed in Table 7. The involved joint may be stiff and have a limited range of motion. Fever is often present.

TABLE 7. JOINT INVOLVEMENT IN WHIPPLE'S DISEASE

Knees
Ankles
Hips
Fingers (esp PIP)
Wrists
Elbows
Hands (esp. MCP)
Spine

Arthrocentesis usually reveals an inflammatory arthritis, with cell counts of 6,000-75,000, often with a predominance of polymorphonuclear leukocytes. In some cases, synovial biopsy has demonstrated PAS-positive macrophages and EM studies have demonstrated the organism in synovial tissue. Other mechanisms for arthritis (e.g. deposition of circulating antigen-antibody complexes) are also possible.

Four to 8% of patients also develop a type of spondylitis, with or without sacroiliitis, which may resemble ankylosing spondylitis radiographically. These patients are almost always men who have peripheral arthritis as well. Serologic tests for rheumatoid arthritis are negative. It has been suggested that these patients may have an increased prevalence of HLA B27 antigen. Both case reports in this Grand Rounds had spondylitis which was clinically troublesome. HLA B27 antigen was negative in the one patient tested. Khan at the Cleveland Clinic studied 6 white men with Whipple's disease for the presence of sacroiliitis and/or spondylitis. One patient had typical ankylosing spondylitis, a second had sacroiliitis, and a third had low back pain with bilateral sacroiliac tenderness and normal x-rays. HLA B27 antigen was negative in 4 of the 6 patients who were tested (the patient with ankylosing spondylitis was not tested). In a series of 9 patients reported by Feurle et al, 4 of 9 patients were HLA B27 positive (44%), compared to an incidence of only 10% in controls. However, none of these patients had spondylitis.

Arthralgia responds typically in a few days to a few weeks after initiation of adequate therapy. Spondylitis may or may not respond to antimicrobial therapy and anti-inflammatory agents may be required.

A number of intestinal diseases may be associated with disease of peripheral joints and the axial skeleton. The term "enteropathic arthritis" has been used to describe these conditions, the causes of which are listed in Table 8.

TABLE 8. CAUSES OF ENTEROPATHIC ARTHRITIS

Ulcerative Colitis
Crohn's Disease
Whipple's Disease
Shigellosis
Salmonellosis
Yersinia entercolitis
Campylobacter colitis
Post small-intestinal bypass (for obesity)

The arthritis that these diseases produce can resemble seronegative rheumatoid arthritis, ankylosing spondylitis, or Reiter's syndrome.

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Skin Manifestations. Hyperpigmentation of the skin in sun-exposed areas commonly occurs in Whipple's disease (Table 5). The mechanism is uncertain, but it is not related to adrenal insufficiency. Hyperpigmentation is sometimes seen in other malabsorptive disorders such as sprue and in malnourished patients. Therefore, this sign is not specific at all.

In rare patients, subcutaneous nodules have been described and the nodule may contain PAS-positive macrophages and bacilli on EM. The presence of subcutaneous nodules, migratory arthritis, and fever in a patient with no GI symptoms as yet may lead to an erroneous diagnosis of rheumatic fever or rheumatoid arthritis.

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Nervous System. That Whipple's disease can involve the central nervous system (CNS) was first recognized in the late 1950's. The bacilli have been demonstrated at autopsy in the brain and spinal cord and on brain biopsy obtained during life. It should be emphasized that CNS involvement has been demonstrated at autopsy in some patients without any CNS symptoms or signs. Because Whipple's disease itself is rare and since CNS involvement is a relatively uncommon complication, occurring in 4 of 21 autopsied cases studied by

Schochet and Lampert at the Armed Forces Institute of Pathology, most clinical information comes from single case reports. However, a perusal of these reports emphasizes that clinical CNS involvement may occur in the absence of any intestinal symptoms. Thus, the disease may present as a primarily neurological illness. A myriad of neurological symptoms have been reported in patients with CNS Whipple's disease. These are summarized in Table 9.

TABLE 9. CNS SYMPTOMS IN WHIPPLE'S DISEASE

Mental and personality changes
Lethargy, coma
Headache
Convulsions
Motor weakness
Numbness
Slurred speech
Visual difficulties (diplopia, blurring)
Incoordination
Dizziness
Tinnitus
Hearing loss
Muscular jerks and twitches
Stiff neck
Facial pain
Sleep disorders
Polydipsia

Neurological signs that have been reported are listed in Table 10.

TABLE 10. CNS SIGNS IN WHIPPLE'S DISEASE

Dementia
Papilledema
Ophthalmoplegia
Hemiparesis
Sensory loss
Myoclonus
Hyperreflexia ($\pm$ positive Babinski)
Ataxia
Pupillary abnormalities
Nystagmus
Ptosis
Muscle rigidity
Loss of vibratory and position sense
Hearing loss

The combination of CNS symptoms and signs and GI symptoms and signs should suggest the possibility of Whipple's disease and lead to jejunal biopsy (see below). However, as mentioned earlier, there may be an absence of GI symptoms. In most cases studied, Whipple's disease is still present in the jejunum even in the absence of GI symptoms. However, cases have been reported in which the jejunal biopsy is negative in an untreated patient. Thus, in some patients, it may be necessary to biopsy other organs (e.g. lymph nodes) or even the brain in order to reach the proper diagnosis. Although Whipple's disease can cause meningitis, the organism has not been detected in cerebrospinal fluid.

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Eye. CNS involvement can lead to visual problems in Whipple's disease (Tables 9 and 10). By involving cranial nerves III, IV, and VI, ophthaloplegia and diplopia may occur. Furthermore, involvement of the optic nerve may lead to reduced visual acuity and papilledema. In addition to neurological complications, the eye itself can be directly involved with Whipple's disease. Organisms can be sometimes visualized in ocular tissue or aspirated fluids under EM. Clinical manifestations of ocular involvement in Whipple's disease are listed in Table 11.

TABLE 11. OCULAR MANIFESTATIONS OF WHIPPLE'S DISEASE

Uveitis
Chorioretinitis
Optic Atrophy
Vitreous opacities and hemorrhages
Glaucoma
Keratitis
Lacrimal duct obstruction

Ocular changes often respond dramatically to antibiotic therapy.

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Skeletal Muscle. In patients with Whipple's disease, neuropathic changes in skeletal muscle, diagnosed by electromyography or muscle biopsy, have been reported. Direct involvement of skeletal muscle has also been described. A patient presented with arthritis, fever, anemia, proximal muscle weakness without tenderness, weight loss, vomiting, diarrhea and abdominal pain. CPK was normal and symptoms did not respond to prednisolone. Jejunal biopsy was diagnostic of Whipple's disease. Muscle biopsy showed a non-specific myopathy and, in addition, a collection of PAS-positive macrophages and rounds cells between muscle fibers. No bacilliform bodies were demonstrated on EM. However, the myopathy responded to treatment of Whipple's disease with antibiotics. A case in which bacilli were present in skeletal muscle at autopsy has been reported by James and Bulkley.

Heart. Although cardiac involvement was recognized by Whipple, the strong association was not recognized until the late 1950's. Types of cardiac pathology that have been found in Whipple's disease are summarized in Table 12.

TABLE 12. CARDIAC INVOLVEMENT IN WHIPPLE'S DISEASE

Endocarditis
Myocarditis
Pericarditis
Coronary Arteritis

The heart is now recognized to be one of the most commonly involved organs in Whipple's disease.

Endocarditis involving the aortic valve was first described by Whipple in his original case. In 1963, Enzinger and Helwig reviewed the literature of autopsied patients and found that PAS-positive endocardial vegatations were present in 32 of 94 cases (34%). Whipple's disease may cause blood culture negative endocarditis. These patients can present with fever, heart murmur, and negative blood cultures, and they can respond to antibiotic therapy (e.g. penicillin). The most common clinical manifestation of endocardial involvement is chronic aortic regurgitation. Aortic valve replacement may become necessary. The excised valve contains PAS-positive macrophages, with or without bacilli present on EM. Whipple's disease has also been reported to cause mitral stenosis, and a case of infection of a porcine mitral valve prosthesis has been reported. Involvement of the tricuspid valve by verrucous endocarditis has also been reported.

Myocarditis has been described at autopsy in patients with Whipple's disease and bacilliform bodies have been demonstrated on EM within macrophages.

Pericarditis is not uncommon in Whipple's disease. Pericarditis may occur in association with endocarditis and myocarditis (pancarditis). Pericarditis may also occur in association with polyserositis (pleuritis, peritonitis), as will be discussed below. A pericardial friction rub may be present. Organisms have been demonstrated on EM in the pericardium in some cases, as have PAS-positive macrophages. Chronic constrictive pericarditis requiring pericardiectomy has been reported.

The actual frequency of endocarditis, myocarditis, or pericarditis in Whipple's disease has not been studied prospectively in living patients with this disease. McCallister et al. reviewed retrospectively the records of 19 patients autopsied at the Armed Forces Institute of Pathology. Eleven of these 19 patients (58%) had had clinical cardiac findings during life. These included ECG changes (non-specific ST-T changes or Q waves), systolic murmur, pericardial friction rub, or congestive heart failure. At autopsy, 15 of the 19 patients had adhesive pericarditis, 10 of 15 had mitral valvulitis or valve fibrosis, 3 had myocardial fibrosis, and 1 had severe coronary artery disease and calcific aortic stenosis. None of the other 18 patients had significant atherosclerosis. Mitral valve involvement closely resembled rheumatic mitral valve disease. Bacteria were demonstrated by EM in valve tissue and in myocardium in some cases.

Arteritis may occur in Whipple's disease. Both the endothelium and the tunica media of the artery may be involved. In one autopsy series, coronary arteritis was described in 3 of 5 patients with Whipple's disease. The aorta and pulmonary arteries have also been reported to be involved at autopsy. Clinically apparent arteritis has not yet been documented during life in a patient with Whipple's disease.

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Serosal Membranes. Whipple recognized polyserositis in his original patient. The presence of fever, serositis (pericarditis, pleuritis, peritonitis), and arthralgia or arthritis could suggest the presence of a collagen-vascular disease, such as systemic lupus. Removal of fluid from the pericardial, pleural or peritoneal cavity usually demonstrates an exudative effusion. In one case, peritoneoscopy was performed because of ascites and multiple nodules on the parietal peritoneum were seen, biopsies of which contained PAS-positive macrophages. Although bacilli have been demonstrated on EM in some cases, it is not certain that every patient with serositis and Whipple's disease has direct infection of the involved serosal membrane with the organism.

Patients may or may not have symptoms related to serositis. Chest pain, fever, cough, shortness of breath, abdominal pain, and abdominal distention are the most common clinical manifestations. These problems usually respond to adequate antimicrobial therapy.

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Lymph Nodes. After the small intestine, lymph nodes are the most commonly affected tissue morphologically in Whipple's disease. The presence of involved mesenteric lymph nodes is in keeping with the intestinal nature of the infectious process. On the other hand, any lymph node in the body may be involved clinically or pathologically by Whipple's disease.

Lymph node involvement, especially when the lymph node is a peripheral node, may suggest a diagnosis other than Whipple's disease for several reasons: (1) Whipple's disease is rare and therefore is not commonly considered in the differential diagnosis of lymphadenopathy; (2) intestinal symptoms may be minimal or entirely absent; and (3) Whipple's disease may result in granuloma formation in lymph nodes (and other tissues) in the absence of PAS-positive macrophages and bacilli on EM, with the granulomas disappearing after antibiotic therapy.

For these reasons, Whipple's disease may be confused with granulomatous disorders such as sarcoidosis or with malignancies such as Hodgkin's disease. In case 2 of this Grand Rounds, retroperitoneal lymphodenopathy on CT scan suggested a diagnosis of malignant lymphoma or metastatic carcinoma before the diagnosis of Whipple's disease was apparent on inguinal node biopsy. A case of inferior vena caval obstruction secondary to extensive retroperitoneal Whipple's lymphodenopathy has been reported.

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Lung. In addition to producing sarcoid-like granulomas in lymph nodes, Whipple's disease can result in pulmonary granulomas which may precede intestinal symptoms. The clinical presentation, chest x-rays and pulmonary function tests are similar to results in sarcoidosis. Foamy histiocytes on lung biopsy may be seen in other conditions as well such as histiocytosis X (eosinophilic granuloma), bronchocentric granulomatosis, and metabolic storage diseases (e.g. Nieman-Pick, Gaucher's). PAS staining may be helpful in distinguishing Whipple's disease from these other conditions, but PAS staining may be absent when granulomas are present.

Despite the finding that Whipple's disease may be difficult to diagnose in the lung, it should be kept in mind in the differential diagnosis. Recently, a case was reported in which bacilli within the lung were demonstrated by EM on an open lung biopsy specimen.

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Liver. As with lung disease, Whipple's may produce a granulomatous hepatitis without PAS-positive macrophages or organisms or may produce granulomatous hepatitis in which the organisms can be demonstrated on EM. The liver disease most closely resembles hepatic sarcoidosis clinically. Liver tests, when reported, have been normal except for an elevated alkaline phosphatase.

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Kidney. Renal disease in Whipple's is quite rare, but has been reported. Granulomata may be present in the absence of renal dysfunction. Two patients were focal glomerulonephritis and pericarditis have been reported. Whether the focal glomerulonephritis was secondary to bacterial endocarditis or was due to direct kidney involvement has not been determined. James and Bulkley have reported demonstration of bacilli in the kidney in one patient at autopsy (see page 27 for reference).

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Hematological Manifestations. Laboratory tests frequently demonstrate hematologic abnormalities in patients with Whipple's disease. Anemia is most common, present in more than 90% of patients in one series. Anemia is usually unaccompanied by reductions in white cells or platelets, but patients with pancytopenia have been described.

There are several mechanisms for anemia, with or without pancytopenia, in Whipple's disease. (1) Acute or chronic GI bleeding is common in this disease, although bleeding is usually occult and not gross. (2) Malabsorption of dietary iron, folic acid and vitamin B_{12} may occur. (3) Splenomegaly may occur in Whipple's disease and this may be associated with hypersplenism and pancytopenia. The spleen may contain granulomas, PAS-positive macrophages, and bacilli on EM. (4) Bone marrow involvement may occur which can interfere with hematopoiesis. The bone marrow may contain granulomas, PAS-positive macrophages, or bacilli on EM. (5) Anemia of chronic disease may occur in Whipple's disease (low serum iron and transferrin, excessive reticuloendothelial iron in bone marrow).

One-third of patients with Whipple's disease have leukocytosis with neutrophilia (see cases 1 and 2), and WBC >20,000 occurs occasionally. A few patients with eosinophilia have been reported. Leukopenia without anemia and

thrombocytopenia may also occur in Whipple's disease. In these cases, leukopenia is due to a decrease in the number of circulating lymphocytes, primarily T cells. Whether lymphopenia is a manifestation of an underlying immunological defect or is secondary to Whipple's disease is uncertain. Immunologic abnormalities in Whipple's disease will be discussed below.

Thrombocytosis has recently been recognized in some patients with Whipple's disease. Three men with peak platelet counts of 700,000 to 1,100,000 were reported by one group. These patients were anemic with low serum iron concentrations. Bone marrow examination showed megakaryocytosis and increased iron stores. Thrombocytosis has also been reported in sprue and inflammatory bowel disease and thus is quite nonspecific. It has been suggested that thrombocytosis is due to impaired splenic function. Thus, both hyposplenism and hypersplenism have been proposed in different patients with Whipple's disease.

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Immunological Abnormalities. Abnormal function of the immune system has been demonstrated in several patients with Whipple's disease. There are two theories concerning the relationship between immunologic alterations and Whipple's disease.

Theory 1. Reduced immune function is primary in Whipple's disease. A corollary of theory 1 is that chronic infection with the Whipple's bacillus occurs because the host has an underlying immunologic defect.

Theory 2. Reduced immune function is secondary to the intestinal disease. A corollary of theory 2 is that immune function should revert to normal when the disease is cured by antibiotic therapy.

There are studies in the literature which favor both theories, although most data seem to favor theory 1. A detailed review of this topic was recently published by Dobbins, who concluded that there is an underlying defect in cell-mediated immunity which promotes susceptibility to Whipple's disease. I will review some of the immunologic studies which have been carried out in patients with Whipple's disease.

Humoral immunity has been studied extensively and is generally normal. Serum IgG and IgM concentrations are normal, while IgA in serum tends to be normal or slightly increased prior to treatment. Secretory IgA in saliva and intestinal secretions is normal. These studies are of interest because there is

often a decreased number of plasma cells in the lamina propria of the small intestine in Whipple's disease. Serum complement levels are generally normal. Unusual patients have been described, however. Two cases of hypogammaglobulinemia and Whipple's disease have been reported and at least one author has speculated that hypogammaglobulinemia predisposed to infection with the Whipple's bacillus.

If Whipple's bacilli enter the systemic circulation and induce a normal humoral response, the possibility for circulating antigen-antibody complexes exists. A recent report demonstrated circulating immune complexes using a solid phase Clq radioimmunoassay, although the antigen was not identified. Whether circulating immune complexes play any role in the pathogenesis of Whipple's disease is unknown. Chronic antigenic stimulation of B cells and plasma cells could possibly contribute to the development of amyloidosis in patients with Whipple's disease.

Although abnormalities in the humoral immune system in Whipple's disease are not prominent, defective cell-mediated immunity has frequently been reported. Cell-mediated immunity has been assessed by measuring (a) circulating lymphocyte counts; (b) responses to intradermal antigen in vivo; and (c) responses of lymphocytes to mitogenic antigens in vitro.

In 1968, Maxwell et al. reported that the lymphocytes of a patient with Whipple's disease had a subnormal response to mitogenic stimulation to the plant lectin phytohemagglutinin (PHA). The patient was studied after he had achieved a complete remission with antibiotics. Total circulating lymphocyte counts were normal. A comprehensive immunologic study of a group of patients who had been treated successfully for Whipple's disease was published in 1972 by Martin et al. Whereas humoral immunity was normal as assessed by serum IgG, IgA, and IgM concentrations, the delayed hypersensitivity response to intradermal antigens was absent in 5 of 7 patients tested. They employed a panel of 23 different fungal, viral, and bacterial antigens and calculated from skin test results in control patients that an anergic response to all 23 antigens would be expected to occur in less than 1 in 75,000 people. The sixth Whipple's patient responded to only 1 of the 23 antigens and the seventh to only 2. Martin et al. further compared in vitro tritiated thymidine uptake by lymphocytes basally and after stimulation by PHA. In healthy volunteers and patients, the ratio of ^{3}H-thymidine uptake after PHA to basal ^{3}H-thymidine uptake averaged almost 100:1 (range, 25 to 200:1), whereas in Whipple's disease patients in remission, the ratio averaged only 10:1 (range, 1 to 20:1). Thus, the study by Maxwell et al. alluded to above in a single patient and the more comprehensive study by Martin et al. strongly suggested a primary defect in cell-mediated immunity in patients with Whipple's disease in remission. Another case report by Groll et al. in 1972 also supported this notion. A patient was studied during active disease and in remission. Humoral immunity was generally maintained, but the patient had cutaneous anergy (which was only partially restored during remission), slower than normal rejection of skin grafts from unrelated donors (which did not improve during remission), and a reduced in vitro lymphocyte incorporation of ^{3}H-thymidine and ^{3}H-uridine in response to PHA (which did not improve during remission). Feurle et al. have also reported a persistent defect in circulating T cell numbers, in skin test reactivity, and in lymphocyte responsiveness to concanavalin A (conA) in a group of 9 patients with Whipple's disease.

Haeney and Ross reported a female patient with apparent Whipple's disease (no EM performed) with lymphopenia, cutaneous anergy, and reduced lymphocyte response to mitogens in vitro. After satisfactory treatment of Whipple's

disease with antimicrobial therapy, lymphopenia resolved but anergy and lymphocyte unresponsiveness persisted. The patient was then treated for 4 months with levamisole, an antihelminthic drug which is an immunostimulant, thought to activate functionally defective T cells. Levamisole had no effect of reduced cell-mediated immunity in this patient, as assessed by skin testing and lymphocyte responsiveness *in vitro*.

In 1977, however, Clancy et al. published a case report which suggested that reduced cell-mediated immunity is secondary to active disease and disappears with adequate treatment. Before therapy, the patient had lymphopenia. (Lymphopenia is present in the majority of patients with untreated Whipple's disease and could possibly be a result, at least in part, of lymphocyte loss from dilated lacteals into the gut.) Circulating B lymphocyte numbers were normal, but circulating T cells were markedly reduced. Furthermore, the patient did not respond to PPD, candida, or mumps skin tests. However, before therapy lymphocytes responded normally to PHA *in vitro*. Following therapy, the circulating lymphocyte count increased from 900 to 3300 and T cells increased from 220 to 2900 per mm^3. In addition, skin reactivity to candida and mumps antigen returned. In another case reported in 1978 by Kirkpatrick et al., lymphocyte responsiveness to mitogens PHA and conA was normal during active disease. The patient did have lymphopenia, and both T cells and B cells were reduced. A third report by Keren et al. also raised some doubt about the prevalence of abnormal cell-mediated immunity in Whipple's disease. They studied 3 patients with Whipple's disease in remission. All 3 patients had lymphopenia, which was a reflection of reduced T lymphocytes with normal B lymphocytes. Although 1 patient was anergic during active disease, none was anergic when in remission. *In vitro* responsiveness of lymphocytes to mitogens (PHA, conA, and pokeweed mitogen) were normal or very close to normal. Lymphocytes from these 3 patients were able to participate in antibody-dependent cell-mediated cytotoxicity responses but spontaneous cell-mediated cytotoxicity was normal in only 1 of the 3. Thus, the immunologic abnormalities were not impressive or consistent in these patients studied by Keren. Vincendeau found normal skin testing results, normal circulating lymphocyte counts (T and B cells), and normal responsiveness to PHA and conA *in vitro* in one patient. Thus, a number of workers have been unable to demonstrate a defect in cell-mediated immunity in patients with either active or treated Whipple's disease.

If Whipple's disease represents an infection by opportunistic bacteria in an immunocompromised host, one might expect that Whipple's disease might occur in other patients with conditions associated with reduced cell-mediated immunity (e.g. patients receiving immunosupression following organ transplanation or patients with HTLV-3 infection and the acquired immunodeficiency syndrome (AIDS)). This has not been the case, however. One brief report has appeared concerning possible Whipple's disease in a Haitian women with AIDS (she also had Pneumocystis carinii pneumonia, chorioretinitis, CMV infection, and cardiac Kaposi's sarcoma). However, EM was not done. Since intestinal infection with Mycobacterium avium intracellulare, an organism commonly associated with AIDS, can result in PAS-positive macrophages in the small intestine, the postulated association between Whipple's disease and AIDS remains unproven. One report of a patient with both Whipple's disease and giardia lamblia infection has been published. The patient had lymphopenia and had normal immunoglobulins. Whether co-infection with the Whipple's bacillus and giardia lamblia was a co-incidence or related to immune dysfunction is uncertain.

Immunologic studies in Whipple's disease are summarized in Table 13.

TABLE 13. IMMUNOLOGIC FUNCTION IN WHIPPLE'S DISEASE

FUNCTION	RESULTS
Humoral immunity	Generally normal
Cell-mediated immunity	
Lymphopenia	Very common
Reduced Circulating T cells	Common
Anergy	Common, but may disappear in some patients after therapy
Lymphocyte responsiveness to mitogens in vitro	Abnormal or normal
Other opportunistic infectious	Absent

Additional immunologic studies in Whipple's disease are warranted, with emphasis of helper and suppressor T cell populations as well as on monocyte/macrophage function.

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DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Whipple's disease is a pathological diagnosis. Thus, biopsy of an involved organ is required. The hallmark of Whipple's disease is accumulation of PAS-positive diastase-resistent macrophages. However, because PAS-positive macrophages are sometimes seen in other conditions, the exact diagnosis of Whipple's disease requires demonstration of bacilli by electron microscopy. Whipple's disease is one of the few conditions in clinical medicine where EM is imperative for accurate diagnosis. Selection of an organ to biopsy is determined by 2 factors: (1) the likelihood of the organ being involved in the pathological process; and (2) the morbidity associated with the biopsy procedure itself. For these reasons, small intestine, colon, and peripheral lymph nodes are the most commonly biopsied areas in Whipple's disease. However, in rare cases Whipple's disease has been diagnosed during life by biopsy of the bone marrow, lung, synovium, pericardium or brain. The morphologic features of Whipple's disease will be reviewed below.

Although Whipple's disease can be diagnosed only by tissue biopsy, the disease may produce somewhat characteristic abnormalities radiographically or endoscopically which may suggest the diagnosis. Small bowel series may show thickening of the jejunal and duodenal mucosal folds with or without mild dilatation of the small bowel. Marked small bowel dilatation does not occur. These findings are non-specific and may be seen in other conditions such as celiac sprue, intestinal lymphangiectasia, Zollinger-Ellison syndrome and lymphoma. It should be mentioned that Whipple's disease may be present in the small bowel despite normal x-rays.

Enlargement of lymph nodes and thickening of the bowel wall has been recognized in Whipple's disease using routine radiographic studies, lymphography, ultrasonography, and computed tomography (CT). Again, these findings are non-specific since they can also occur in neoplastic diseases as well as in other diseases (e.g. tuberculosis).

Whipple's disease may give the duodenal mucosa a characteristic appearance at duodenoscopy. The mucosa may be partially covered by yellow-white plaques, which represent accumulations of lipid in dilated lacteals. The duodenum of case 2 in this Grand Rounds had this endoscopic appearance (after the changes of scurvy disappeared). These endoscopic abnormalities disappear after adequate therapy of Whipple's disease.

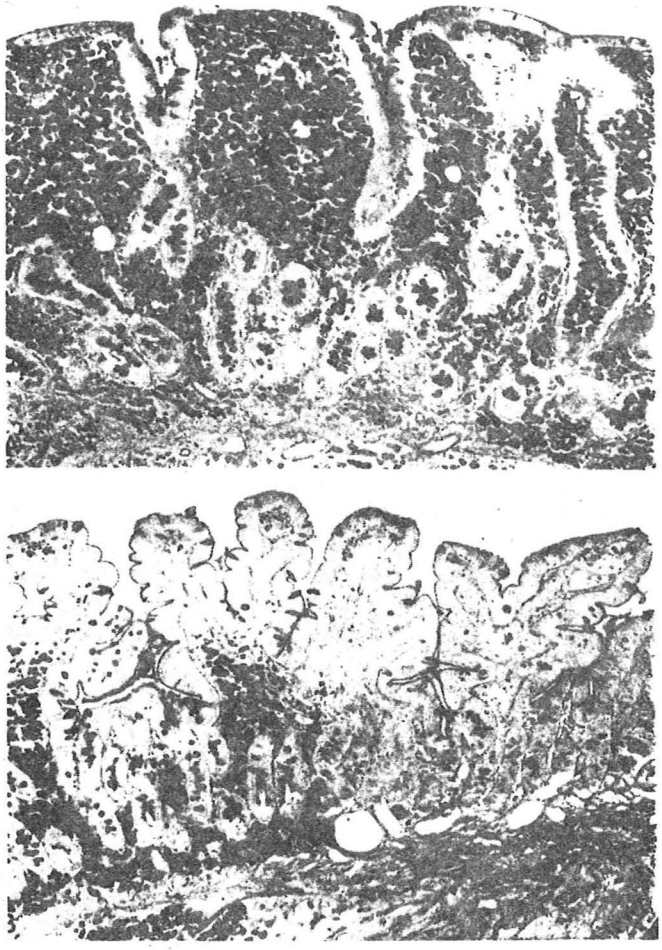

Figure 2. Jejunal biopsies from a patient with Whipple's disease before (top) and 19 months after antibiotics (bottom). PAS stain (X 75). After treatment more normal appearing villi are present and the PAS-positive macrophages are much less prominent (from Trier JS et al).

As mentioned earlier, the definitive diagnosis of Whipple's disease requires microscopic examination of tissue. PAS-positive, diastase-resistant macrophages are the "pathognomonic" finding in the disease (Figure 2). However, PAS-positive macrophages can be found in the intestine (especially the rectum) in other conditions such as idiopathic colon histiocytosis, melanosis coli, and infection with Myocobacterium avium intracellulare. Thus, demonstration of PAS-positive macrophages should raise the suspicion of Whipple's disease, especially in an appropriate clinical setting, and should lead to an examination of tissue by EM. It is of some historical interest that Yardley and Fleming obtained tissue from Whipple's original case and demonstrated PAS-positive macrophages in the small intestine, lymph nodes, heart, and pancreas some 54 years after Whipple's original description.

In general, Whipple's disease is a diffuse condition in the proximal small intestine. Therefore, a normal small bowel biopsy should exclude this

condition. However, a case has been reported in which the disease process was patchy, present on some biopsy fragments and absent on others. It has been suggested that an endoscopically-directed duodenal biopsy, attempting to biopsy grossly visible plaque-like areas, may be more rewarding than blind biopsy with an intestinal biopsy tube.

The morphologic features of Whipple's disease of the small intestine have been reviewed in several places. The villi are preserved but are enlarged and often club-like due to an accumulation of foamy macrophages in the lamina propria. Dilated lacteals are prominent, but tissue necrosis and inflammation are usually absent. Occasionally, small rod-shaped bacteria can be seen by light microscopy using gram or Giemsa stain. Under EM, bacilli are seen both free in the extracellular space, often dividing, and intracellularly within macrophages and epithelial cells (enterocytes). Bacilli within macrophages are usually seen in various stages of degeneration. Bacilli do not destroy the epithelial cells or their microvilli. Bacilli have also been seen with lymphatic endothelium, capillary endothelium, polymorphonuclear leukocytes, plasma cells, lamina propria smooth muscle cells, intraepithelial lymphocytes, and mast cells. After therapy, bacilli may disappear in a few days, but other cases require weeks or months. An unusual patient has been described in whom PAS-positive macrophages and bacilli were found in the jejunal submucosa but not in the mucosa.

Whipple's disease has often been diagnosed by rectal biopsy. In Case 2 of the Grand Rounds, the disease was present in the colon, stomach, and small intestine. However, as discussed above, because of the non-specificity of finding PAS-positive macrophages in the rectum or colon, Whipple's disease should only be diagnosed by rectal biopsy if the clinical picture is compatible and if EM demonstrates typical bacillary organisms. The same criteria should be applied to other organs, such as lymph node, bone marrow, or synovium.

Many inflammatory fluids aspirated from patients with Whipple's disease are potential sites for demonstration of organisms. Fluids aspirated from joints, serous cavities, the spinal subarachnoid space, or the vitreous humor often contain inflammatory cells and an elevated protein concentration. Unfortunately, bacilli are only rarely demonstrated in these fluids, with the possible exception of the vitreous humor. Nevertheless, it is worthwhile to attempt EM examination of such fluids.

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TREATMENT

Before 1950, Whipple's disease was a fatal condition. Cases were often diagnosed at autopsy. Those diagnosed during life were often treated unsuccessfully with corticosteroids, alkylating agents, or radiation. In 1952, Paulley reported the first successful use of an antibiotic in Whipple's disease. The patient was apparently cured after two brief courses of chloramphenicol. Haex and Van Beck had earlier also treated successfully a patient with salazopyrin (Azulfidine), but did not report their findings until 1955.

Because the organism cannot be cultured, antimicrobial sensitivities are not available as guidelines. Furthermore, since Whipple's disease is rare, it has not been possible to carry out controlled studies of particular antibiotics. Therefore, empiric trials of various agents were carried out and if a patient did not respond to one agent in a "reasonable" amount of time, another therapeutic trial was initiated. The use of an "historical" control group was in this disease quite cogent, since death was the rule without antibiotics and survival became the rule with them. Several different antibiotics seemed to be effective: chloramphenicol, tetracycline, penicillin, sulfonamides,streptomycin.

Despite several impressive case reports, the routine use of antibiotics only took hold slowly. One reason for this was that cases of apparently successful treatment with corticosteroids, ACTH, x-ray therapy and nitrogen mustard continued to be reported in the 1950's. To complicate matters, several patients who were successfully treated with antibiotics had also received steroids. However, in 1963 Davis et al. from Duke University presented evidence that antibiotics and not steroids were the effective agent, as shown in Table 14.

TABLE 14. THERAPY AND OUTCOME IN 15 PATIENTS WITH WHIPPLE'S DISEASE AT DUKE UNIVERSITY (FROM DAVIS ET AL.)

THERAPY	NUMBER	DIED
No antibiotics or steroids	5	5
Steroids alone	2	2
Antibiotics alone	2	0
Antibiotics plus steroids	6	0

Although this study was small and uncontrolled, it was followed by several reports attesting to the usefulness of antibiotics in this disease and gradually steroids and other modalities were eliminated from the therapeutic armamentarium.

In seeking an ideal drug for Whipple's disease, several criteria should be met: (1) the drug should be able to eradicate the organism from the primary site of infection, the small intestine; (2) the drug should be effective orally, since prolonged treatment may be required; (3) the drug should be safe and relatively inexpensive; (4) the drug should be effective in extraintestinal sites of disease.

The most commonly used drugs to treat Whipple's disease are penicillin (G or VK) and tetracycline. Although both of these drugs fulfill criteria (1) through (3) above, concern has been raised recently that these drugs may be ineffective in eradicating or preventing infection within the central nervous system (see Case 1 of this Grand Rounds). Because CNS Whipple's disease is a dreaded complication which may occur despite complete eradication of intestinal disease, an emphasis on using drugs that penetrate the blood-brain barrier has been placed recently. In our Case 1, CNS Whipple's disease was successfully treated with chloramphenicol, a drug that penetrates the blood-brain barrier quite well. Of course, chloramphenicol has potential bone marrow and optic toxicity, but we felt that his condition was serious enough to take this risk. After optic neuritis developed, possibly secondary to chloramphenicol, we started him on trimethoprim-sulfamethaxazole (TMP/SMX) after consulting Dr. Jim Smith. TMP/SMX has been used successfully in Whipple's disease and penetrates the blood-brain barrier. Our patient's CNS symptoms and signs were well-controlled on TMP/SMX. A recent patient has been described by Ryser et al in whom dementia associated with Whipple's disease was reversed by TMP/SMX over a 6-month period.

Keinath et al. reviewed the literature and found 88 patients who had been treated with various antibiotics for variable lengths of time for Whipple's disease. Of these 88 patients, 31 (35%) relapsed at least once after treatment (both of our patients have relapsed). Relapses were classified as clinical (N=16, defined as recurrence of original symptoms without biopsy confirmation), CNS (N=13), GI (N=1), or cardiac (N=2). The frequency of relapses by prior treatment is shown in Table 15.

TABLE 15. TREATMENT AND SUBSEQUENT RELAPSES IN WHIPPLE'S DISEASE (KEINATH ET AL)

TREATMENT*	NUMBER	RELAPSES (%)	CNS RELAPSES
TCN alone	49	21 (43%)	9
PCN plus STM, then TCN	15	2 (30%)	0
PCN + STM	5	2 (40%)	0
PCN alone	8	3 (38%)	2
TMP/SMX	3	0 (0)	0
Others	8	3 (38%)	2
Totals	88	31 (35%)	13

(* TCN = tetracycline; PCN = penicillin; STM = streptomycin; TMP/SMX = trimethoprim/sulfamethoxazole)

Keinath et al. also found that results of treatment of non-CNS relapses were usually excellent, whereas CNS relapses were often refractory to treatment. Thus, our excellent results (Case 1) are somewhat unusual. Keinath et al. concluded, based upon their review that "tetracycline alone, or penicillin alone, is not adequate initial therapy for Whipple's disease and that central nervous system relapse is resistant to therapy. The authors recommend parenteral penicillin and streptomycin followed by 1 year of oral trimethoprim/sulfamethoxazole therapy or oral trimethoprim-sulfamethoxazole alone for 1 year as initial therapy for Whipple's disease". It must be emphasized that this recommendation is not based upon prospective studies or large numbers. Furthermore, the optimal duration of therapy is unknown.

After reviewing the literature and caring for 2 patients, I will treat the next Whipple's disease patient I see with TMP/SMX for at least 3 months, after which I will repeat a small intestinal biopsy. If organisms are absent, therapy will be stopped and the patient closely watched for relapse. If organisms are still present, therapy will be continued for another 9 months and the biopsy repeated at that time. If the patient is allergic to or cannot tolerate TMP/SMX, I will employ a 10 day course of parenteral penicillin and streptomycin followed by oral penicillin or tetracycline (rather than oral chloramphenicol because of its potential toxicity). In such a patient, chloramphenicol would be used at the first indication of CNS involvement.

In closing, I will predict that the organism which cause Whipple's disease will be discovered in the next decade, possibly by employing monoclonal antibodies against species-specific bacterial antigens. Once the organism is discovered, it will be possible to develop serologic tests, proper culture techniques and more rational (rather than empiric) antimicrobial therapy.

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