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Whipple's Disease

A Review of the Literature and Report of Fifteen Patients

By

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With 22 Figures in the Text

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In recent years WHIPPLE's disease has been reported with increasing frequency. In fact, more than half of the 83 acceptable cases from the literature were published in the last two decades. This increase is probably more apparent than real. In part it may be due to a greater awareness of the disease pattern, and in part it may reflect recent developments in the understanding of the disease; namely, (a) the demonstration of a strong periodic acid-Schiff (PAS) reaction of the characteristic foamy macrophages, and (b) the recognition of widespread specific lesions outside the intestinal tract.

Although WHIPPLE's disease is relatively rare, it must be realized that until recently the disease was diagnosed almost exclusively on the autopsy table or after laparotomy and intestinal or mesenteric lymph node biopsy. This necessity of laparotomy for diagnosis doubtless constituted a barrier to recognition, and therefore less severe and abortive forms of the disease may be more frequent than our records indicate. It is expected, however, that in the future the increasing utilization of the transoral intestinal biopsy and subcutaneous lymph node biopsy will greatly facilitate an accurate and early diagnosis.

The difficulty of *clinical diagnosis* is well demonstrated in our material. A correct diagnosis of WHIPPLE's disease was made only in 10 of our 15 patients. All of these, however, were made after laparotomy and mesenteric lymph node biopsy. In 5 patients the diagnosis was not made until autopsy and only in one instance was WHIPPLE's disease included among the differential diagnoses. In the other four the diagnoses ranged from idiopathic steatorrhea to BOECK's sarcoid, pancreatitis, ADDISON's disease, collagen disease, and rheumatoid arthritis.

Detailed reviews of the literature have been given by ROSEN and ROSEN, SCHUTZ et al., CLEMMESEN, PLUMMER et al., PUITE and TESLUK, and CRANE and AQUILAR.

The purpose of the present study is to correlate the clinical aspects with the anatomic observations and to clarify the natural course of the disease. The study is based on the evaluation of 15 autopsy cases with WHIPPLE's disease from the files at the Armed Forces Institute of Pathology (AFIP) and on a review of 83 case reports from the literature.

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Materials and methods

The rarity of WHIPPLE's disease is attested by two facts: First, apparently only 83 patients have been reported in the literature (some of them more than once), and only 15 patients with autopsies were found among more than 900,000 records in the files of the AFIP. Four patients, previously reported in the literature, are now included among the 15 patients in our own series because autopsy records and material have become available. Six of the cases reported in the literature were excluded because they were at great variance with the clinical and histologic findings of the disease. The case of PALUMBO and RUGTIV and the 3 patients of PEMBERTON *et al.* presented mainly granulomatous thickenings of the small bowel mesentery without alterations of the small bowel mucosa. These 4 are probably examples of sclerosing mesenteric lipogranuloma. PEARSE reported a case in which the entire abdominal cavity was studded with multiple fibrous nodules filled with an oily substance. This finding, in conjunction with a history of previous operation for abdominal adhesions, suggests oil granuloma rather than WHIPPLE's disease. LUNA's and LATIENDA's case of a 17-month-old boy is interpreted as possibly being one of diffuse lipogranulomatosis, as described by FARBER *et al.*

Our series consists of 15 autopsied patients, of whom 11 had lymph node biopsies (including 8 mesenteric lymph node biopsies).

Sixty-five deaths due to WHIPPLE's disease are recorded in the literature; 14 other patients so diagnosed were alive at last follow-up. The patients include 42 with autopsy only, 20 with autopsy and biopsy, 14 with lymph node or small bowel biopsies, and 2 with only clinical data (BASSLER).

The complete clinical records, surgical reports, and autopsy protocols were analyzed. Sections were prepared from all paraffin blocks or wet tissue available and stained with hematoxylin and eosin and the PAS reaction after diastase digestion. Serial sections of the mesentery were prepared in one case in order to study the relationship of afferent lymphatics and cystic spaces within the mesenteric lymph nodes. In addition a variety of histochemical procedures were performed (Table 6).

Clinical observations

Age and sex incidence. Fourteen of our 15 AFIP patients were males, but this preponderance of the male sex may not be significant, since the AFIP material has many more specimens from men than women. A male preponderance, however, is also recorded in the literature: of the 77 patients in which the sex was stated, 64 were males. Except for one case reported in a Negro woman (SUGARMAN et al.) all patients were of the white race. As yet no instance of the disease has been reported in Mongolians.

The peak age incidence fell in the fifth decade in our series, as well as in the patients from the literature. The median age of the 15 AFIP patients was 38 years at the onset of symptoms and 49 years at the time of last hospitalization; of the 79 patients from the literature, 40 and 47 years, respectively. Of all patients reported, only two were below the age of 20. The youngest was an 11-year-old boy. The other child, a 14-year-old girl, showed both the features of WHIPPLE's disease and lupus erythematosus (KAMPMEIER and PETERSON). The oldest patient was 77 years of age (Table 1).

Of the 97 cases reported (our series and those from the literature combined), two-thirds originated in the United States and Canada. The remaining one-third was reported from Europe and South America. There does not appear to be any occupational preponderance.

In our series no hereditary studies were attempted. PUITE and TESLUK reported, however, WHIPPLE's disease in 2 brothers and suggested a hereditary component. Another instance of WHIPPLE's disease in brothers was reported by GROSS *et al.* Such a familial incidence, however, has not been known in any other instance, although the possibility of the existence of undetected subclinical cases remains.

Table 1. WHIPPLE'S *Disease — Age and Sex*

Age group	AFIP			Literature		
	Total	Male	Female	Total	Male	Female
Total	15	14	1	77	64	13
10—19	—	—	—	2	1	1
20—29	1	1	—	5	4	1
30—39	3	3	—	12	10	2
40—49	4	4	—	30	26	4
50—59	3	3	—	16	15	1
60—69	3	3	—	10	7	3
70—79	1	—	1	2	1	1
Median age	49	46	—	47[1]	46	46
Range	(24—75)	(24—66)	75	(11—77)	(11—74)	(14—77)

[1] Two patients aged 49 and 53, respectively, with sex not stated, were excluded from the table but were included in the median.

Clinical course. Clinically, the course of the disease may be divided into three stages: a first indeterminate stage with insidious onset of arthralgia, general weight loss, fatigue, and anemia; a second stage with various abdominal symptoms, primarily diarrhea and steatorrhea; and a terminal stage with severe steatorrhea, malnutrition, and cachexia. Death usually comes suddenly, and its immediate cause is often difficult to determine.

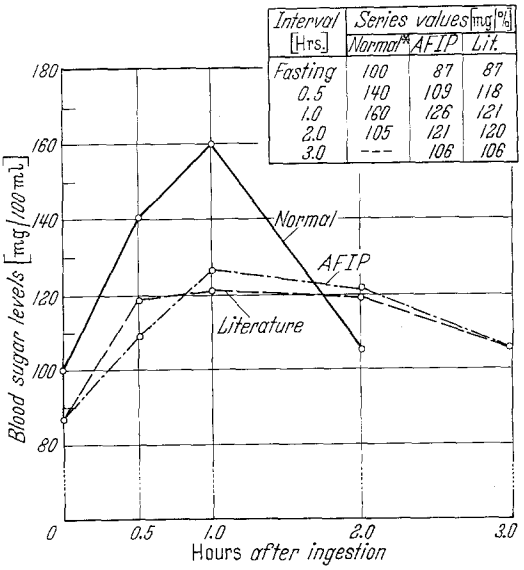

Fig. 1. Glucose tolerance levels (average mg/100 ml) in WHIPPLE'S disease

The disease is always chronic. The initial symptoms are vague and remain so until abdominal symptoms dominate the clinical picture. The actual duration of the disease can therefore only be approximated. The duration from onset of symptoms varied considerably but exceeded 5 years in about half of the patients. In about one-fourth of the patients, however, it was 10 years or more. The age at onset did not appear to be related to the length of the clinical course. The relation between duration of the disease and the sequence of symptoms is indicated by the survival rates, based upon onset of specific symptoms. For example, the 5-year survival rate from onset of arthralgia was 83%; from onset of abdominal pain, 23%; abdominal distention, 22%; and diarrhea, 19%.

Arthralgia. 73% of our patients had arthralgia; in 9 (60%) it was the initial symptom. This corresponds well with the observations in the literature in which 86% of all patients complained of arthralgia and 62% noted it as the first manifestation. Arthralgia was often combined with fatigue, weight loss, and anemia. In most patients the joints were swollen and painful, but in a few only slight stiffness and tenderness were noted. The pain occurred most frequently in the smaller joints, particularly the ankle, wrist, shoulder and back. It was often migratory and persisted in most patients during the entire course of the disease.

The mean duration of arthralgia was about 7 years. In 1 patient the joint symptoms terminated in an acute purulent arthritis (842374).

Intestinal manifestations. Abdominal pain, abdominal distention, diarrhea, and steatorrhea were the most frequent intestinal symptoms. Tables 2 and 3 reflect their incidence and sequence of appearance. Diarrhea and steatorrhea as a rule followed the abdominal pain and distention by 1 to 12 months. Constipation was less frequent (5 patients) but also seemed to precede the onset of diarrhea by several months. A palpable mass in the upper abdomen was noted in 4 patients. Abdominal pain was almost always epigastric. It tended to occur and become more severe after meals. Food intake was also reported to provoke diarrhea (606873).

Diarrhea was present in all our patients, and steatorrhea was noted in 14 of our 15 patients and in 92% of the patients from the literature. In contrast to the steatorrhea in pancreatic insufficiency, the stool amylase and lipase values were entirely within normal limits, and neutral fat as well as fatty acid were present in the stool. In one case the pancreas was removed and the analyzed amylase, lipase, and trypsin contents of the tissue were within normal limits. The total fecal fat varied considerably. Fat values from slightly above normal to 57% of the dry substance were reported.

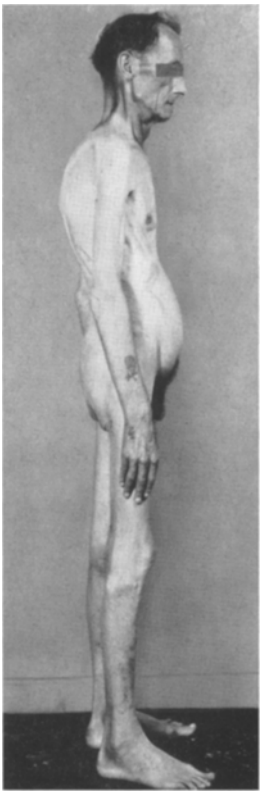

Fig. 2. Sixty-five-year-old patient with WHIPPLE'S disease of 3-year duration. Note severe weight loss, protuberant abdomen and hyperpigmentation of exposed portions of body. AFIP Neg. No. 59-345

Triolein and oleic acid marked with J^{131} was given in 2 patients. In both the recovery of the radioactive material was considerably delayed, and indicated markedly defective absorption. Occult blood in the feces was recorded in 12 of our 15 patients and in 71 of the reported patients. The early occurrence of melena and anemia and their persistence throughout the disease suggest a causal relationship. A hemorrhagic tendency in the lower colon was observed on sigmoidoscopy in 2 patients.

Cardiovascular manifestations. Heart murmurs were detected in 5 of our patients and in 15 of those reported in the literature. In all of our patients the murmur was systolic, but in 2 from the literature the murmur was diastolic in 1 and systolic and diastolic in the other. Although the significance of heart murmurs is difficult to evaluate in the presence of anemia, they seemed to be closely related to the valvular lesions observed at autopsy. In fact, in all instances in which heart murmur was reported, valvular endocarditis was observed at autopsy.

Respiratory manifestations. Chronic cough was reported in about half of the patients. It was never severe and was the initial symptom in only one instance. Suspected relationship between cough and chronic pleuritis is supported by the presence of pleuritis at autopsy in 72% of the patients with a history of a cough.

Skin manifestations. Hyperpigmentation occurred in two-thirds of our patients. In general, accentuation of the pigmentation was over the exposed areas of the body (Fig. 2). One of our white patients was so deeply pigmented that on one hospital admission her race was recorded as Negro. Similar hyperpigmentation was present in 47% of patients reported in the literature.

Hemorrhagic and hyperkeratotic lesions were frequently recorded. While the hemorrhagic lesions were seen only in the late stages of the disease, hyperkeratotic lesions occurred relatively early but did not precede diarrhea.

Hemorrhagic skin lesions (petechiae, ecchymoses, purpura) and follicular hyperkeratosis or a "dry, scaly skin" also were seen in 5 of our patients and in 18 from the literature. In a few it was associated with an erythematous rash. In one instance the hyperkeratosis was so severe that a diagnosis of ichthyosis was considered by the dermatologist (TRACEY and

BROLSMA). The hyperkeratotic changes were not confined to any particular region and were present over the trunk and extremities. In 3 patients a butterfly erythema was noted, but a biopsy was taken in only one, a 14-year-old girl who was reported by KAMPMEIER and PETERSON to have WHIPPLE's disease associated with lupus erythematosus.

RUTISHAUSER and DE WECK reported dermal lesions presumably specific for WHIPPLE's disease; comparable lesions, however, were not seen in our material.

Sensory and mental disturbances. Sensory and mental disturbances occurred in a few patients, but their significance must remain doubtful, since no definite correlations with anatomic changes could be established. Mental disturbances, psychoses, or disorientation were present in 1 of our patients (606873) and in 6 from the literature (FREI, KORSCH, PAULLEY, ROSEN and ROSEN, TRACEY and BROLSMA, WALLACE). CASSELMAN *et al.* reported in their second patient a paranoia-like picture that coincided with onset of cortisone therapy. Dementia praecox of the hebephrenic type was present in a case reported by ODESSKY and BURDISON.

In 2 patients sudden blindness of the right eye was reported (JONES and PAULSEY, TRACEY and BROLSMA). Disturbances of vision occurred in 1 of our patients (515813) (presumably as a result of terminal nocardiosis) and sudden hearing loss in 2 (199317, 703455). Impairment of vision for 1 year was reported by HENDRIX *et al.* In 2 other patients seizures of the grand mal type were observed (PETERSON and KAMPMEIER, RUSSO).

Peripheral lymphadenopathy. Enlargement of peripheral lymph nodes is a frequent finding and was observed in 10 of our patients and in 39 from the literature. It was reported most commonly in the axillary and cervical regions. Although the lymph nodes could be palpated easily, they were only moderately enlarged and clinically indistinguishable from the lymphadenopathy of other disease processes.

Weight loss. Anemia and weight loss occurred early and often preceded diarrhea or the abdominal symptoms by several years. Weight loss and arthralgia were probably the most significant symptoms of the early disease. Progressive weight loss was recorded in all patients. Some patients lost more than half of their initial weight during the course of the disease.

Past history. A relatively high incidence of venereal disease in the past history is noteworthy. Gonorrhea was recorded in 3 of our patients and in 10 from the literature. Serologic reactions for syphilis were positive in 5 patients, 3 of whom were women. It is possible that these reactions were "false biologic positives", however, and due to a circulating lipo-protein complex. This interpretation is supported by a negative treponema immobilization test in 1 of these patients (PERRY).

Laboratory findings. Although the general tenor of the laboratory data was similar for most patients, the individual values varied considerably because of the frequent remissions and exacerbations so characteristic of the disease.

The reported high incidence of anemia is also borne out by our findings. Anemia of moderate degree was present in all of our patients. Once the anemia was established, there was little increase, although usually it was slightly more severe in the late phases of the disease. The type of anemia varied, and both hypochromic and normochromic pictures were observed in the same patient at different stages of the disease. In contrast to sprue, however, megalocytic or macrocytic anemia was not found. Various therapeutic agents such as oral and parenteral iron, vitamin B_{12}, and folic acid apparently had little if any effect upon the anemia. Platelet counts and bone marrow examinations were within the range of normal.

Leukocyte counts varied from normal to as much as 30,000 and averaged between 8000 and 15,000. Leukocytosis was usually greater in the early stages of the disease and was always accompanied by neutrophilia. Exceptions were noted only in some literature patients in which relative and absolute lymphocytosis was reported (BIE, FITZGERALD and KINNEY, REINHART and WILSON, ROSEN and ROSEN).

The blood sugar levels were slightly lowered in 13 of our 15 patients. In the literature, 38% of the patients showed values lower than 90 mg/100 ml. A flat glucose tolerance curve was present in 9 of our patients and in 25 from the literature on whom data were available (Fig. 1). A similar lack of response to starch or galactose tolerance tests was recorded.

Serum total protein was also lowered. The decrease was usually slight early in the disease and greater in the terminal stage. Serum total protein averaged between 4.0 and 5.0 g/100 ml. The low extremes were 3.2 g/100 ml. in our series and 2.2 g/100 ml. in the reported

group. Serum globulin was usually less affected than serum albumin. It must be emphasized that inversion of the albumin/globulin ratio occurred only in a few isolated instances. Electrophoretic studies in 2 patients showed a relative elevation of alpha and gamma globulins in one instance and low gamma globulin in another (854481, 842374). Total protein-bound polysaccharides and serum glycoprotein were determined in 2 individuals, and both fractions were elevated (GAERTNER, SAILER and MCCANN).

Gastric acidity, as in sprue, was absent or markedly lowered in more than half of the patients.

Data on blood cholesterol were available in 43 cases. Assuming that the range of normal is between 150 and 270 mg/100 ml (BODANSKY), the averages in 34 of 43 patients were below normal (our series was 144 mg/100 ml, literature 123 mg/100 ml.). In 3 of our patients, the values were 70 mg/100 ml or less. Cholesterol esters were reported in 24 patients, and in 17 of these the esterized portion was below the normal range (60% of total cholesterol).

The concentration of total serum lipids was known in only 11 patients. In 5 of these the total lipids were less than 500 mg/100 ml. The few reported data on neutral fat, fatty acids, phospholipids, and lecithin varied, and in view of the variations inherent in the methods, the number of determinations seemed too small to be informative. Absence of the usual elevation of serum lipid levels after meals was reported in one instance (WEIGEL and SPIES). Vitamin A determinations were made in 1 of our patients and in 11 from the literature, and in 8 the values were below normal. A similar decrease in the carotene levels was noted in 5 of 7 patients on whom data were known (NEWMAN and POPE, TODD and SANFORD).

Vomiting as well as diarrhea were responsible for excessive fluid loss and concomitant disturbances in the electrolyte balance. Numerous data on blood serum sodium, potassium, phosphorus, and calcium were recorded; and in general, values ranging slightly below the norm were frequent. Hypokalemia was common, though severe forms were seen only in a few patients. Hypocalcemia was recorded twice but both times without clinical evidence of tetany.

Prothrombin, bleeding, and clotting times, as well as the determinations of NPN, BUN, creatinine and urea clearance, were within normal limits. Uric acid, as determined in 4 individuals from the literature, was not altered. In 1 of our patients, however, the uric acid levels were elevated and were responsible for an erroneous diagnosis of gout.

The Kepler water test was done in 3 of our patients and in 7 from the literature and was positive in a total of 7. Ketosteroids, determined in 6 patients, were lowered in 5. Serum antistreptolysin titres, measured in 5 patients, were elevated above 200 in 2. In 1 patient the

Table 2. WHIPPLE'S *Disease — Average Duration from Onset of Symptoms to Last Follow-Up*

Symptom	Average duration (years)				
	AFIP		Literature		
	Total	Dead	Total	Dead	Alive
Number of patients in series	15	15	79	65	14
Arthralgia	7.8	8.0	7.1	7.1	7.1
Abdominal pain	3.2	3.0	2.5	2.2	4.0
Constipation	3.4	4.3	3.4	3.5	
Abdominal distention	2.7	2.5	1.7	1.6	2.4
Diarrhea	2.6	2.4	1.7	1.4	2.9

titre was initially elevated but decreased to normal levels during the course of the disease (JORGENSEN). Several agglutination tests for typhoid O and H, paratyphoid A and B, proteus X19, and *Brucella abortus* were performed and were negative. Urine, blood, and stool cultures did not yield specific organisms.

Therapy. The favorable response of WHIPPLE'S disease to steroid therapy is well documented (GLYNN and ROSENHEIM, JONES et al., JONES and PAULSEY, LEPORE, MENDES DE

LEON and COENEGRACHT, PLUMMER, WEISIGER and CARAVATI, RADDING and FRIESE, RUTISHAUSER and DE WECK, SCHAFFNER and SCHERBEL, WANG, JANOWITZ and ADLERSBERG). In most instances, however, the remissions were short and permanent cures rare. Two patients reported as examples of successful therapy (PLUMMER et al., RADDING and FRIESE) relapsed later and at autopsy showed characteristic changes indistinguishable from those seen in untreated patients. Early steroid therapy, however, seemed to be successful in a few instances. Of our 15 patients, 10 were treated with either cortisone or ACTH, but the majority only after severe symptoms had developed. Despite this, treatment was followed in most instances by temporary improvement and a decrease or cessation of intestinal symptoms. This temporary beneficial effect is well reflected in the average duration of the disease in treated and untreated patients. While the average duration in treated cases was 5.3 years, it was only 2.5 years in the group without steroid therapy.

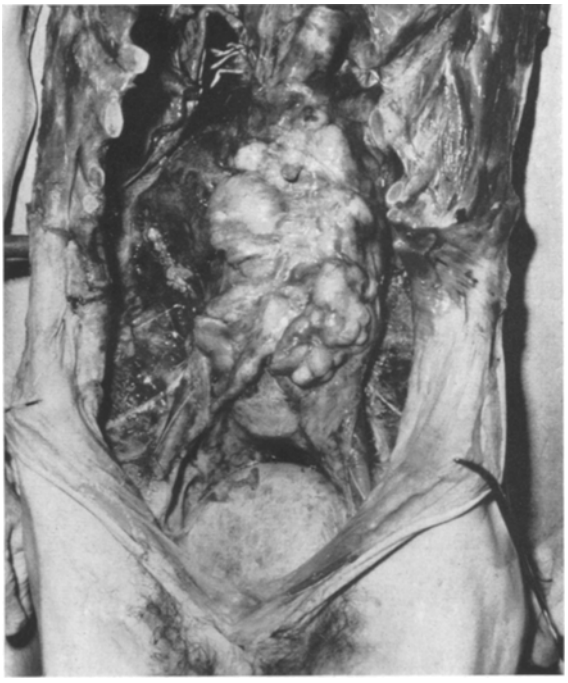

Fig. 3. Retroperitoneum at autopsy. Massive enlargement of para-aortic lymph nodes and thickening of the supravesicular peritoneum. AFIP Neg. No. 53-21947

Antibiotics, vitamins, and intravenous feeding, in addition to steroid therapy, were given most patients. In one instance a dramatic response was achieved with chloramphenicol (PAULLEY); in another patient, followed for 6 years, the disease was completely controlled by tetracycline and ACTH (ENGLAND, FRENCH and RAWSON). This and other evidence suggests that a combination of steroids and antibiotics is superior to simple steroid therapy.

Table 3. WHIPPLE'S *Disease —Clinical Manifestations*

Clinical manifestation	AFIP			Literature		
	Total with data	Present		Total with data	Present	
		Number	Per cent		Number	Per cent
Weight loss	15	15	100	72	72	100
Diarrhea	15	15	100	69	68	99
Abdominal pain	15	15	100	62	61	98
Abdominal distention	15	14	93	49	45	92
Steatorrhea	15	14	93	—	*	—
Melena	14	12	86	—	*	—
Arthralgia	15	11	73	63	54	86
Peripheral lymphadenopathy	14	10	71	—	*	—
Fever	14	10	71	—	*	—
Pigmentation	15	10	71	—	*	—
Heart murmur	15	5	33	—	*	—

* These clinical manifestations could not be accurately recorded because of the uncertainty as to their absence when not specifically mentioned.

Pathologic observations

Gross. *Intestinal tract.* Characteristic lesions in the small intestines and draining mesenteric lymph nodes were invariably present in each of our patients but varied considerably in distribution and degree (Tables 4 and 5). Generally, the small intestines were distended and their walls thickened and doughy. The mucosa had a yellowish, velvety or coarsely granular appearance and was stippled by countless yellowish-white, frondlike villi (Fig. 4). Although these villi seemed quite friable, gross ulcerations were seen in only one instance (268154). In most patients the bowel content was semisolid or of putty-like consistency, but in a few it was hemorrhagic.

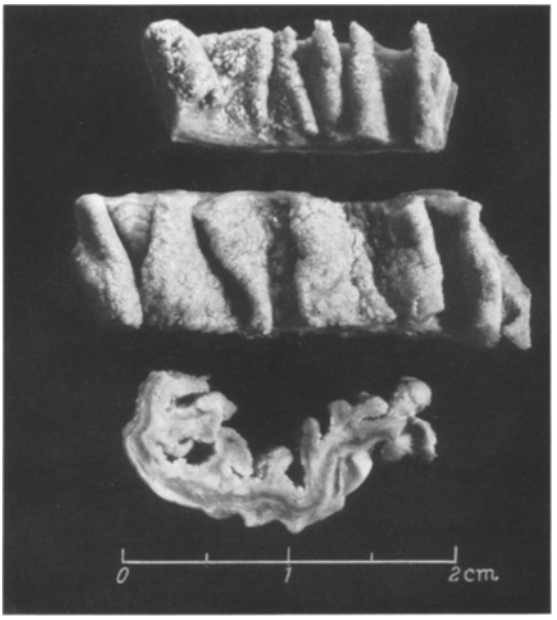

Fig. 4. Jejunum. "Furred tongue" appearance of the intestinal mucosa. Thickening of circular folds and individual villi. AFIP Neg. No. 59-1634-1

Although the origin of this hemorrhagic material is not clear, it is conceivable that many of the friable and engorged villi break off or rupture and become a source of small and frequent hemorrhages. It is likely that early anemia and melena are at least in part the result of these hemorrhages.

Table 4. WHIPPLE'S *Disease — Gross Autopsy Findings*[1]

Gross finding	Number			
	AFIP		Literature	
	Total with data	Condition present	Total with data	Condition present
Pleuritis . . .	15	14	43	32
Pericarditis . .	15	11	45	35
Valvular endocarditis . . .	15	8	40	24
Hepatomegaly	15	8	50	21
Pleural effusion	15	6	43	17
Splenomegaly .	15	6	46	19
Ascites	15	5	50	26
Peritonitis . . .	15	5	46	25
Pericardial effusion . .	15	2	45	9

[1] Includes data from 15 "AFIP" and 62 "literature" autopsies.

The mucosal alterations were always most conspicuous in the jejunum and ileum but were also seen in the duodenum, and in 1 patient extended into the

Table 5. WHIPPLE'S *Disease — Distribution of PAS-Positive Macrophages in 15 Autopsy Cases*

AFIP Acc. number	160449	199317	268154	279891	306393	515813	538668	606873	635629	651186	703455	706630	726887	842374	854481
Mesenteric lymph node . .	3+	2+	3+	3+	3+	3+	3+	3+	3+	3+	3+	3+	2+	3+	3+
Extramesenteric lymph node . .	1+	0—1+	1+	1—3+	1—3+	1+	1—3+	1+	—	—	—	—	1+	1+	1—3+
Subcut. lymph n.	—	0	1+	—	1+	1+	—	—	2+	—	—	3+	—	2+	—
Esophagus . .	—	—	—	—	—	1+	—	1+	1+	—	—	—	—	2+	0
Stomach	0	—	—	0	0	1+	1+	1+	1+	0	1+	—	—	1+	0
Duodenum. . .	3+	—	—	3+	3+	3+	3+	3+	1+	—	2+	—	—	—	3+
Jejunum	3+	3+	3+	3+	3+	3+	3+	3+	3+	3+	3+	3+	2+	3+	3+
Ileum	3+	3+	2+	3+	3+	3+	3+	—	3+	0	3+	3+	2+	—	3+
Colon	0	1+	1+	0	0	2+	2+	1+	1+	—	—	1+	1+	2+	1+
Epicardium . . .	0	1+	1+	0	1+	2+	0	—	2+	0	2+	2+	1+	—	0
Myocardium . .	0	0	1+	1+	0	1+	0	0	2+	0	2+	0	0	1+	0
Valvular endocardium . . .	—	—	—	—	3+	3+	0	3+	3+	—	3+	—	0	—	3+
Pleura	0	0	0	0	0	0	1+	0	1+	0	0	0	0	0	0
Liver	1+	1+	0	0	1+	1+	2+	1+	0	0	1+	1+	1+	1+	1+
Spleen	0	0	0	0	1+	2+	1+	2+	1+	1+	0	1+	1+	1+	1+
Pancreas	0	1+	0	0	0	1+	2+	1+	2+	0	0	1+	1+	1+	1+
Adrenal (capsule)	1+	3+	—	—	1+	2+	0	2+	2+	1+	—	1+	1+	1+	1+
Brain	0	—	1+	—	1+	2+	1+	3+	1+	—	1+	1+	—	2+	1+
Spinal cord . . .	0	—	—	—	—	1+	—	2+	1+	—	—	1+	—	—	2+
Bone marrow . .	—	—	—	—	—	1+	1+	0	—	1+	—	0	—	—	1+

0 =Negative. — = No sections available.

cecum and proximal portion of the ascending colon. Thus, in 10 of our patients the characteristic changes began abruptly at the pylorus and extended throughout the small intestine to the ileocecal valve. In 4 the jejunum and ileum were affected, and in 1 the ileum was the only intestinal site involved. In the literature the ileum was involved in all patients, the jejunum in 95%, and the duodenum in 58%. On occasion the serosa showed lymphangiectasia and fibrous plaques.

Lymph nodes. As a rule the mesentery was markedly thickened by numerous enlarged lymph nodes. The nodes were soft and doughy and sharply outlined against the surrounding mesenteric fat. They averaged 2 to 3 cm in diameter and were particularly large and numerous at the root of the mesentery (Fig. 5). On section, all nodes showed a uniformly cystic and spongy pattern. The cystic spaces contained an oily or creamy, yellowish-orange material that exuded upon slight pressure. Generally the spaces were small, but in a few instances measured up to 2 cm in diameter, giving the node the appearance of a multilocular cyst (Fig. 10). In all autopsy cases capsular and interstitial fibrosis of the lymph nodes was the rule and many of the nodes were fused by capsular fibrosis.

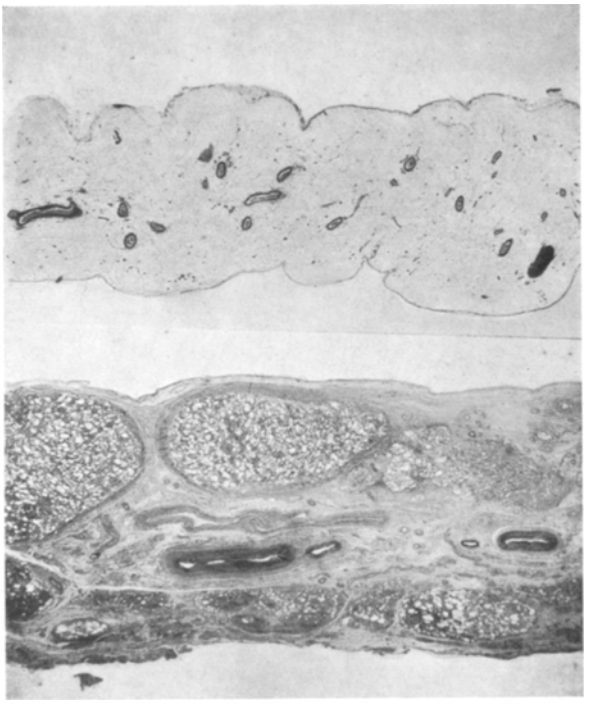

Fig. 5. Comparison of normal small bowel mesentery (top) and mesentery in WHIPPLE S disease (bottom). Note the spongelike pattern and pericapsular fibrosis. AFIP Neg. No. 59-1580. Hematoxylin and eosin. ×2

Outside the mesentery identical lymph node changes were seen only along the aorta and about the pancreas (Fig. 3). Similar cystic changes in other visceral lymph nodes, however, have been recorded (KLOOS, ROSEN and ROSEN, SIERACKI and FINE, STAEMMLER).

Mesentery, mesenteric lymphatics, and thoracic duct. As a rule the mesenteric fat was uninvolved, and the lesions were limited strictly to the lymph nodes. Interstitial inflammation and diffuse fibrosis as encountered in mesenteric lipogranulomas were not seen in our material. Such changes, however, have been reported as WHIPPLE's disease (PALUMBO and RUGTIV, PEMBERTON et al.). Severe lymph stasis was rare, though moderate distention of the lymphatic channels was noted occasionally. The thoracic duct was found patent in all 16 patients in whom it was examined. Large amounts of adipose tissue were reported in the mesentery of 3 of the patients in spite of severe emaciation.

Peritoneum. Besides pleuritis and pericarditis, mild involvement of the peritoneum and ascites have frequently been reported. Peritoneal adhesions were noted in 16 reported patients and ascites in 22. In 14 patients both lesions were present. In our material fibrous adhesions were seen at autopsy in 4 patients and ascites in 5. In 2 of the 5 the accumulated fluid was clear, but in the others it was cloudy and turbid, resembling chylous ascites. A similar preponderance of turbid ascites was found in the cases reported in the literature (15 turbid, 7 clear). The amount of ascitic fluid in our patients was usually small and reached

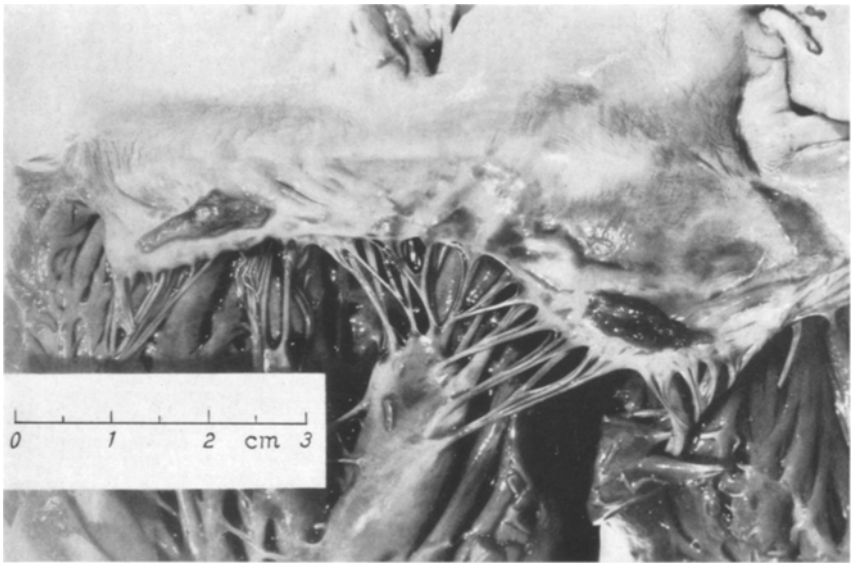

Fig. 6. Mitral valve. Two yellowish vegetations on atrial side of the mitral leaflet.
AFIP Neg. No. 53-21948

1,200 ml in only one instance. In the literature, patients with severe ascites are reported, but ascites was usually associated with symptoms of circulatory failure (PETERSON and KAMPMEIER, PUITE and DESLUK, REINHART and WILSON, SAILER and MCCANN, UPTON).

Spleen and liver. Capsular thickening of the spleen and liver, varying from mild fibrosis to heavy "sugar icing", was frequently encountered at autopsy. Capsular fibrosis was seen in more than half (56%) of the patients in our series and in exactly one-half of the patients reported in the literature. The splenic lesions were slightly more frequent than the hepatic.

Hepatomegaly and splenomegaly occurred but were not outstanding features (Table 4). Cardiac failure and congestion explained the hepato-splenomegaly in only half of the patients. In the case reported by FITZGERALD and KINNEY severe splenic enlargement was associated with a pseudoleukemic lymphocytosis.

Cardiovascular system. Valvular endocarditis was usually more extensive than anticipated from the clinical symptoms. It was present in 24 patients reported in the literature and in 8 of our patients. The distribution of lesions resembled that in rheumatic endocarditis. Thus in 5 cases the mitral valve alone was in-

volved; in 1 the aortic valve; and in 2 the mitral, aortic, and tricuspid valves. The distribution of the lesions recorded in the literature was similar. The vegetations were mostly small, firm, and nodular and often had a distinct yellowish hue. Large verrucous, friable vegetations and ulcerations were seen twice. Most of the vegetations were located on the atrial side of the valve, at the line of closure or near it (Figs. 6, 16).

In our series serofibrinous pericarditis was present in 11 patients and in a large number of the literature cases. In most the pericardium could be separated

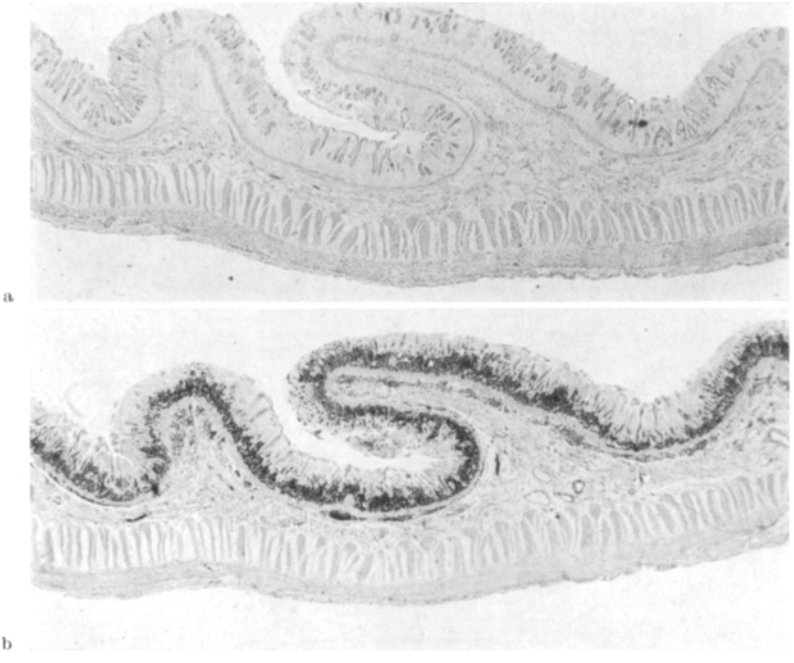

Fig. 7a and b. Small intestines. Strongly PAS-positive macrophages in mucosa and narrow zone beneath muscularis mucosae. Note absence of lymphatic distention in submucosa and subserosa. AFIP Acc. 706630. a Hematoxylin and eosin stain. b PAS with diastase digestion. ×10

with ease from the epicardium, indicating a relatively recent process. Serous pericardial effusion without organization was present only once (Table 5).

In spite of the persistent low cholesterol levels, coronary arteriosclerosis was not rare. One patient died of myocardial infarction at the age of 43, another at age 44 (854481, 726887). A third patient (age 43) had severe coronary sclerosis but without evidence of infarction. SCOTT's and HOSIE's patient also showed severe anterior myocardial infarction and mesenteric thrombosis.

Lung and pleura. The pleura was involved in 13 of our patients. Nine had pleural adhesions and 5, pleural effusions. In several instances the entire pleural space was obliterated by dense adhesions. Although the data from the literature tend to be incomplete, pleuritis at autopsy was recorded in 32 patients and pleural effusion, in 17. In a high percentage pericarditis was associated with pleural involvement (AFIP 95%, literature 87%). But no significant relationship between pleural involvement and peritonitis was demonstrable.

Miscellaneous. The brain was examined in 12 patients, the spinal cord in 6. Numerous small brain abscesses were present in 1 case (842374), probably metastatic from a suppurative arthritis of the left knee, since *Staphylococcus aureus* was cultured from both lesions. Nocardial involvement of the meninges was seen in 1 patient. No gross lesions of the spinal cord were noted in our material. Fine granulations of the ventricular lining have been reported (REVENO, SIERACKI and FINE).

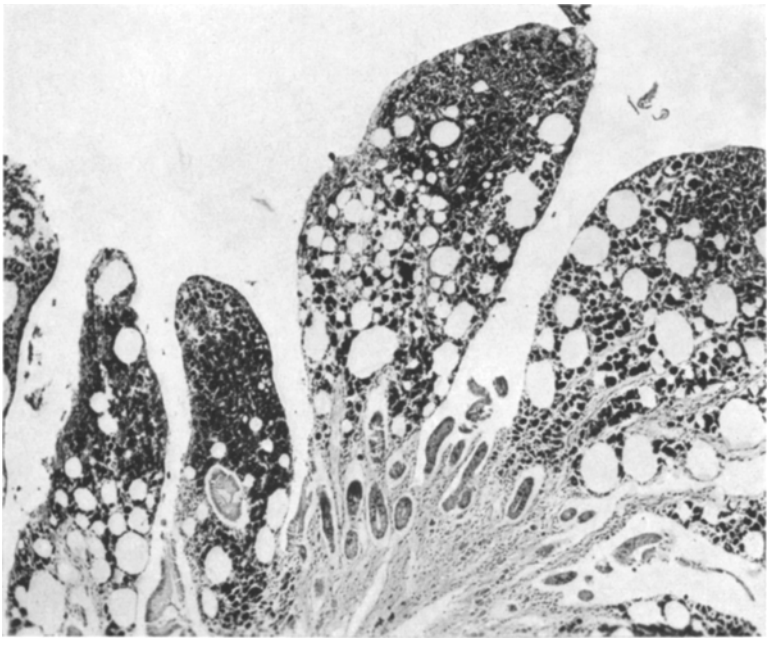

Fig. 8. Jejunum. Elongated, club-shaped villi with PAS-positive macrophages and numerous lipid-filled round spaces. AFIP Neg. No. 60-1369. PAS with diastase digestion. ×55

A gross examination of the affected joints at autopsy was not made in our material nor in that of the literature.

Microscopic. *General.* Histologically, the presence of PAS-positive particulate matter in macrophages is the hallmark of WHIPPLE's disease. While the largest number of these macrophages was encountered always in the membrana propria of the small intestines and the regional mesenteric lymph nodes, a smaller number was also found widely distributed outside the intestinal tract (Fig. 7 and Table 5).

It is noteworthy that the PAS-positive material was not restricted to one type of cell; thus, the material was present not only in the large foamy macrophages of the small intestine and lymph nodes, but also in fibrocytes and histiocytes of the loose connective tissue, in smooth muscle cells, in glia, and occasionally in Kupffer and endothelial cells. Extracytoplasmatic PAS-positive particles were often present in the vicinity of disintegrated macrophages. The amount of the PAS-positive material varied but depended largely upon the distance from the intestinal tract.

The particulate deposits assumed various shapes (Figs. 13, 14, 19). They occurred as distinct globules or masses within an acidophilic cytoplasm or formed rod- or sickle-shaped particles. SIERACKI and FINE emphasized this sickle configuration and proposed the name of SPC cells (sickleform particle-containing cells).

Intestinal tract. In the small intestines the characteristic macrophages were confined to the mucosa and in a lesser degree to the upper submucosa. In the

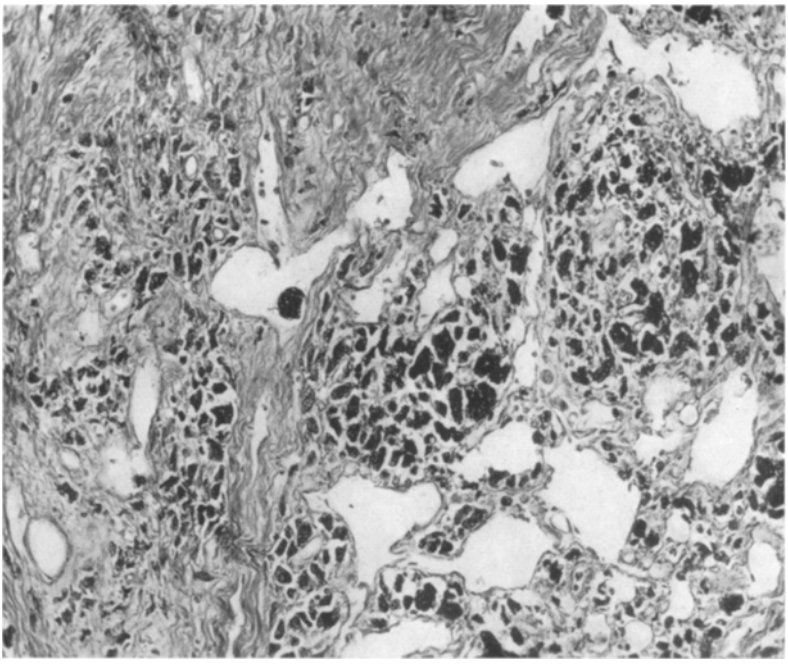

Fig. 9. Mesenteric lymph node. Macrophages, cystic spaces, and interstitial fibrosis. AFIP Neg. No. 59-582. PAS with diastase digestion. ×160

mucosa, the accumulated macrophages altered greatly the villous pattern. The individual villi were thickened, elongated or club-shaped, and often fused at their base. Not infrequently the upper portion of many villi seemed to be broken off or ruptured, and interstitial hemorrhages were common. Outside the membrana propria, macrophages were seen only in the muscularis mucosae, the uppermost portion of the submucosa, or in intestinal lymph follicles (Fig. 7). Occasional macrophages, however, were also encountered in colon, stomach, and esophagus.

The columnar epithelium of the villi was not unusual except for a relative increase in the number of goblet cells. The brush border and basement membrane of the epithelial cells were visible and seemed normal. Electron-microscopic study of 1 case supported this finding (COHEN et al.).

In the mucosa the macrophages were plump and round and varied from 10 to 30 μ in size. In the deeper mucosa and submucosa, however, the outline and stainability of some macrophages became indistinct; they were swollen and appeared to disintegrate in the stroma and lose their identity. Others were small and spindle shaped and seemed to be formed in situ. Occasionally giant

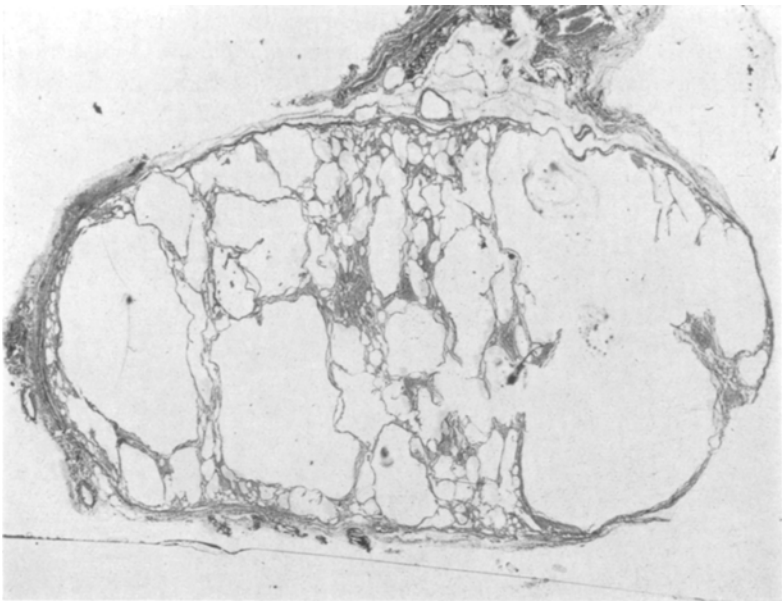

Fig. 10. Mesenteric lymph node. Marked distention of cystic spaces and transformation of lymph node to multilocular cyst. AFIP Neg. No. 59-2508. Hematoxylin and eosin stain. ×5

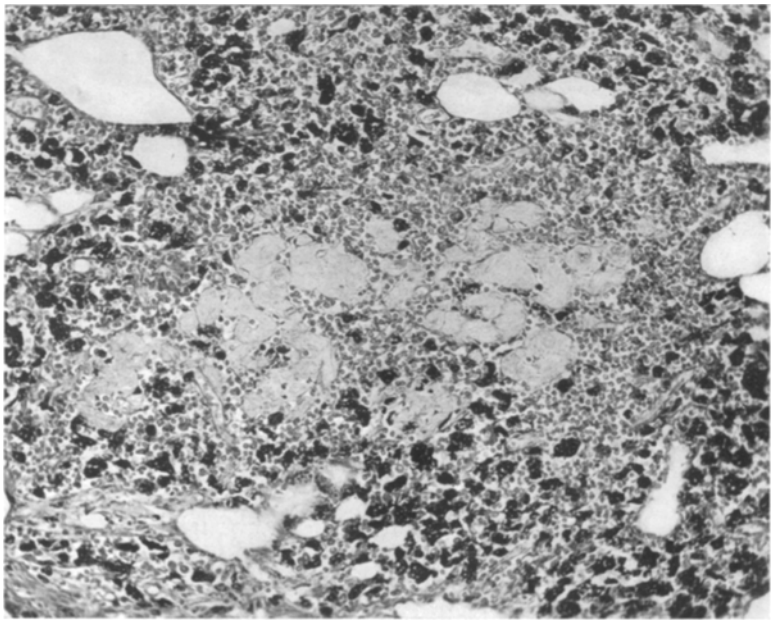

Fig. 11. Mesenteric lymph node. Hyalinization of small vessels with formation of characteristic hyaline nodules. AFIP Neg. No. 59-581. PAS with diastase digestion. ×165 (reduced to 19/20)

cells were associated with macrophages, but apart from their size and multiple nuclei their structure was similar to that of the mononuclear macrophages. COHEN et al., examining intestinal macrophages by electron microscopy, reported

short, curved membranes and some vesicular and tubular structures within the particulate deposits. They also described small dense bodies in close apposition to the macrophages and adjacent to the basement membrane (COHEN et al.).

It must be emphasized that nonparticulate or finely granular, *weakly* PAS-positive material in macrophages may be seen in the intestinal villi in sprue and various forms of enteritis. Asymptomatic accumulations of pseudoxanthoma cells in mucosa and submucosa may also be mistaken for WHIPPLE's disease (FROBOESE, FEYRTER).

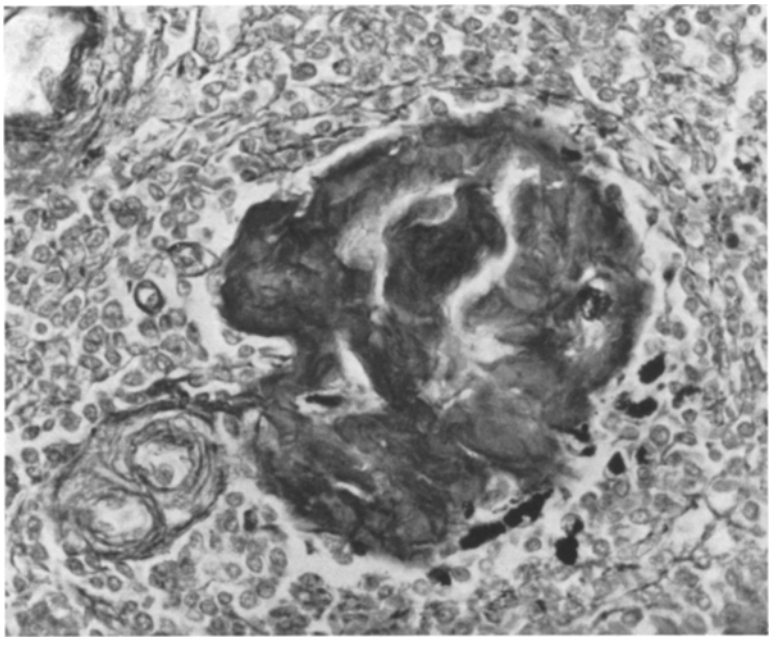

Fig. 12. Spleen. Characteristic hyaline nodule with PAS-positive macrophages in its vicinity. AFIP Neg. No. 59-586. PAS with diastase digestion. ×485

In addition to the macrophages, multiple round spaces of varying size occurred in many of the villi. Their incidence varied. Some villi were almost cribriform, usually with the larger spaces in the upper portion of the villi; others contained few spaces or none (Fig. 8). Only a few of these spaces were lined by a basement membrane and endothelial cells, and seemed to present dilated lacteals. The majority of spaces were intimately associated with macrophages. In fact, it appears that most of the spaces are formed by vacuolation and dissolution of macrophages (Fig. 13, 15).

The inflammatory component generally was negligible. In the few cases where macrophages did not fill the entire mucosa, a moderate number of chronic inflammatory cells were present. These were mainly lymphocytes, eosinophils, and plasma cells with occasional Russell bodies. In 2 transoral intestinal biopsies which we reviewed recently, small groups of polymorphonuclear leukocytes were also seen in the membrana propria. The number of mast cells was not increased.

In the intestines a close correlation of the histologic picture with duration of the lesion could not be established, although the number of macrophages and cystic spaces seemed to increase somewhat with the duration of the disease. In our material all intestinal changes seemed to be irreversible. Neither restitution nor fibrosis was noted. Even cortisone or ACTH therapy was unable to restore the changes to normal. Several recent reports about the effect of *steroid therapy* upon the intestinal lesions are conflicting. In 1 patient complete remission followed 3 months of steroid therapy, and no histologic changes could be demonstrated 9 years after the initial biopsy (HOLT et al.). Yet, in another patient the intestinal changes were not altered by 9 months of intensive steroid therapy (BRODOFF et al.). HARGROVE reports 2 patients with intestinal biopsies before and after treatment. In his first patient there was a slight decrease in the number of macrophages after 1 year of therapy. The second showed clinical improvement after tetracycline and ACTH therapy, but the biopsies before and after treatment were indistinguishable (HARGROVE et al.).

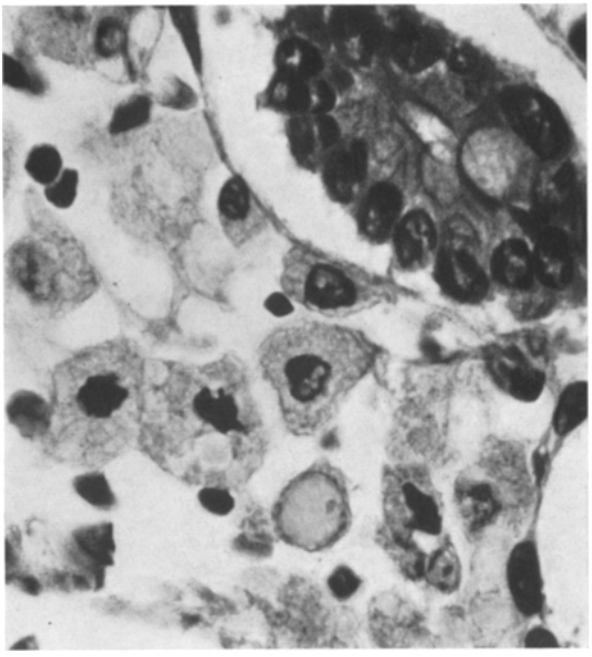

Fig. 13. Jejunum. Characteristic macrophages in the membrana propria showing vacuolization in some of the cells. AFIP Neg. No. 59-1766. Hematoxylin and eosin stain. ×1200

Abdominal lymph nodes. Examination of many sections from the abdominal lymph nodes, including mesenteric, peripancreatic, and para-aortic nodes, revealed characteristic and strikingly uniform changes. The normal follicular pattern was absent; and irregular cystic spaces, filled with an amphophilic or weakly acidophilic coagulum, replaced portions of the parenchyma. In the stroma numerous large foamy macrophages, indistinguishable from those of the intestines, were intermingled with lymphocytes and, occasionally, with plasma cells and eosinophils. Interstitial and capsular fibrosis was marked in most nodes, and in a few only a dense, fibrous capsule remained (Figs. 9, 10).

Many of the larger spaces were distended lymph sinuses that communicated with afferent and efferent lymphatics. Such a communication has been demonstrated on the basis of serial sections by GLYNN and ROSENHEIM and confirmed by us in a study of serial sections from a mesenteric lymph node. Apart from distention of preformed lymph sinuses, however, many spaces seemed to originate in the stroma. These stromal spaces were either formed by interstitial accumulation

of sudanophilic material or by dissolution of macrophages. Thus, swollen and vacuolated macrophages, apparently in the process of disintegration, were often observed (Fig. 15). Multinucleated giant cells containing varying amounts of PAS-positive material frequently lined the cystic spaces. Similar but smaller giant cells occurred occasionally in the stroma.

Two characteristic forms of interstitial fibrosis could be distinguished: 1. small and distinct hyaline nodules that originated from small, swollen, and hyalinized blood vessels (Fig. 11); and 2. areas of diffuse fibrosis within groups

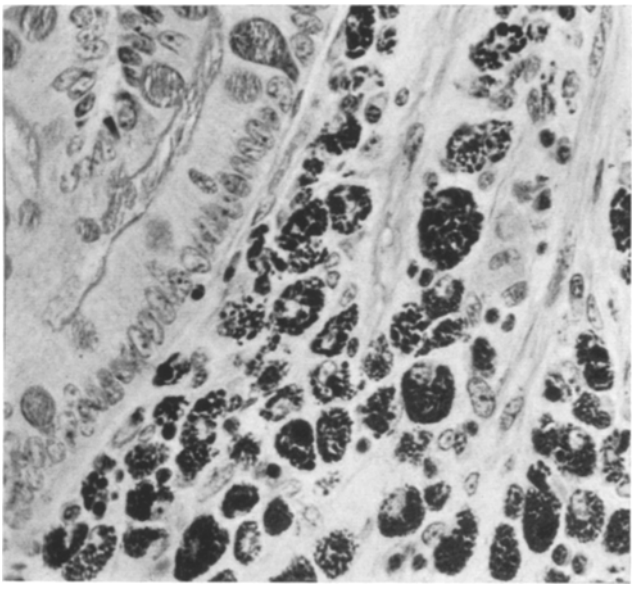

Fig. 14. Jejunum. Particulate PAS-positive deposits in the macrophages. The particles vary in size and configuration; the mucosa is unaltered. AFIP Neg. No. 59-1769. PAS with diastase digestion. ×660

of macrophages. In the latter process, macrophages were incorporated in fibrocollagenous tissue and seemed to disintegrate. Small particles of PAS-positive material similar to that in the macrophages were often scattered in the newly formed fibrous tissue. Identical changes occurred in the fibrotic capsule, where macrophages and PAS-positive droplets were often seen. Our observations strongly suggest that the PAS-positive material incites desmoplasia, but this cannot be proved unequivocally.

Thirty-two visceral lymph nodes from locations other than the mesentery were studied. Characteristic PAS-positive macrophages occurred in all but were less numerous than in the mesenteric nodes. Only the para-aortic and paraPancreatic lymph nodes showed changes comparable to those in the mesentery. Direct lymph-drainage from mesenteric lymphatics may explain the severe involvement of these nodes.

Comparison between biopsy and autopsy material. In order to gain insight into the pathogenesis of the lesions in the lymph nodes, we compared the autopsy material with lymph node biopsies taken at earlier stages of the disease. Comparable material was available in 7 of our patients. The time interval between the

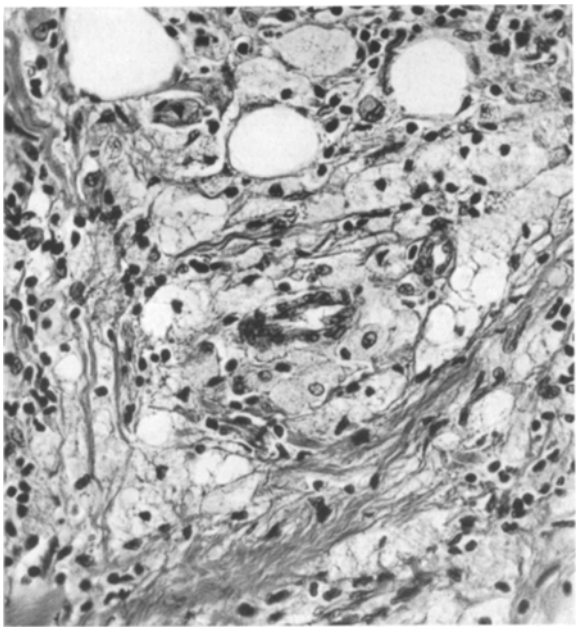

Fig. 15. Mesenteric lymph node. Dissolution and vacuolation of macrophages. AFIP Neg. No. 62-2395. Hematoxylin and eosin stain. ×660

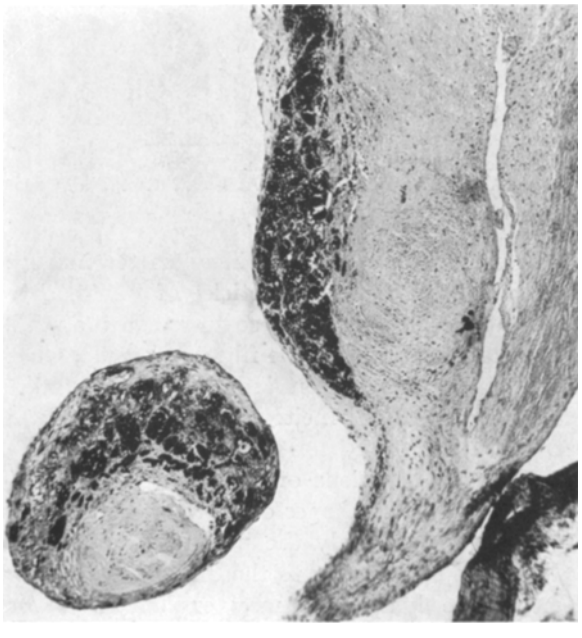

Fig. 16. Mitral valve. Subendocardial PAS-positive macrophages in mitral valve and chorda tendinea. AFIP Neg. No. 59-1578. PAS with diastase digestion. ×90 (reduced to $^{9}/_{10}$)

date of biopsy and autopsy varied from a few months to as much as 5 years. For the most part, the changes corresponded roughly to the time interval but were also dependent upon the severity of the disease. Thus, tissue changes that apparently took several years in one patient developed in a few months in another. The general tendency in each, however, was similar and centered chiefly upon the development of the cystic spaces and the progression of interstitial and capsular fibrosis. In contrast, little or no difference was observed in the number of PAS-positive macrophages. Thus, in the autopsy material the spaces were larger and more numerous, and little remained of the original lymph node parenchyma. Yet, in some of the earlier biopsies no, or few spaces were encountered. Interstitial and capsular fibrosis was absent or slight in the earlier biopsies but conspicuous in most autopsy sections. Fibrosis also seemed more severe in cases of short clinical duration. The number of giant cells paralleled more or less the development of the cystic spaces.

From this we may conclude that: 1. the number of PAS-positive macrophages is not significantly increased in the latter stages of the disease; 2. the presence of macrophages precedes the formation of cystic

spaces and spaces may be entirely absent in earlier stages of the disease; 3. capsular and interstitial fibrosis occurs late and is much more severe in the autopsy material than in lymph nodes taken earlier at biopsy; and 4. the histologic differences between lymph nodes at the time of biopsy and at autopsy are about as large as those found between mesenteric and subcutaneous lymph nodes examined at autopsy.

Mesentery. In our autopsy material (in contrast to most biopsy sections) narrowing and obliteration of mesenteric, peripancreatic, and retroperitoneal

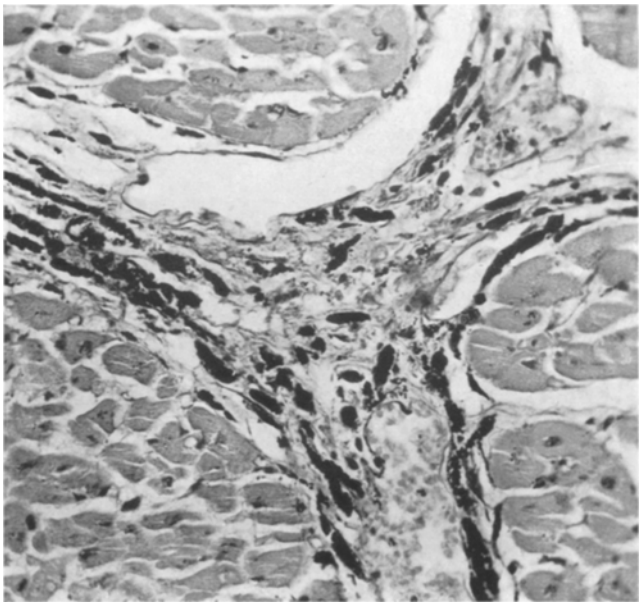

Fig. 17. Myocardium. Macrophages in the interstitial connective tissue. AFIP Neg. No. 60-1379. PAS with diastase digestion. ×305 (reduced to $^{19}/_{20}$)

lymphatics were frequent. These changes involved apparently afferent and efferent lymphatics alike. They were usually most marked in the close vicinity of lymph nodes, and the degree of change paralleled roughly the amount of capsular fibrosis. Such changes were not encountered in the intestinal submucosa and were rare in the juxta-intestinal mesentery. In general the muscular walls were hypertrophied and the lumen narrowed or obliterated by subendothelial fibrosis. A cribriform lumen developed in those instances in which the valves became fibrosed. Chronic inflammatory elements about the lymph channels were not prominent, and no acute inflammatory changes were seen (Figs. 21, 22).

Systemic lesions. General. Foamy macrophages outside the intestinal tract have been described by earlier investigators. Fahr (1928) reported them in the spleen; Kloos (1939) in infraclavicular lymph nodes, hilar lymph nodes, and tongue; Fitzgerald and Kinney (1945), in the periadrenal capsule. In recent years the PAS reaction greatly facilitated the recognition of systemic changes. Upton (1952) first emphasized the widespread distribution of specific PAS-positive macrophages. More detailed accounts have been given by Farnan (1958) and Sieracki and Fine (1959).

Table 5 gives the distribution of specific PAS-positive macrophages in our 15 autopsy cases. Identification of the specific macrophages was made easy

by the strong PAS affinity of the sharply defined particulate deposits. In only a few instances were special stains other than the PAS reaction needed for identification (Tables 6, 7).

Subcutaneous lymph nodes. In 7 of our patients, 13 biopsies of the subcutaneous lymph nodes were performed. The biopsies were taken between 2 months and 36 months before the patients came to autopsy. Over two-thirds of the nodes were axillary or cervical. Eleven subcutaneous lymph node biopsies were reported in the literature (BIE, FARNAN, FISHER and WHITMAN, KLOOS, KORSCH, PUITE

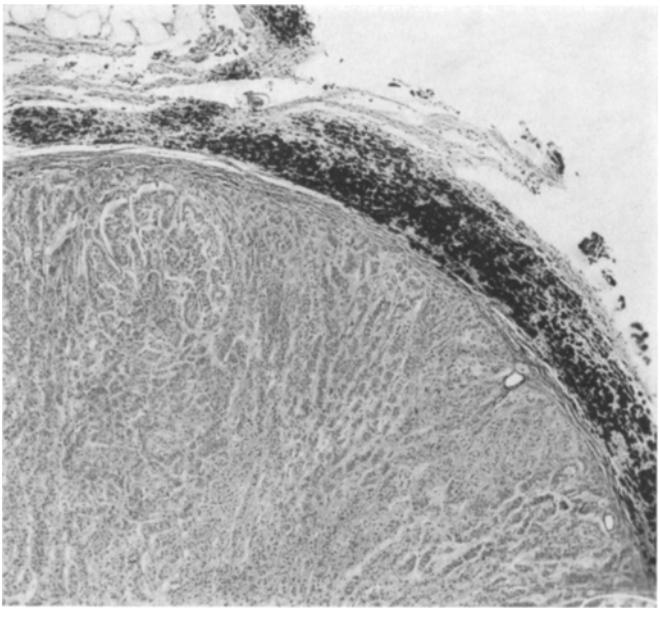

Fig. 18. Adrenal gland. PAS-positive macrophages in pericapsular tissue. AFIP Neg. No. 62-2396. PAS with diastase digestion. ×300 (reduced tv $^{19}/_{20}$)

and TESLUK, RUSSO, RUTISHAUSER et al., RUTISHAUSER and FOROUHAR, UPTON, VAUX).

More than one-half of all these biopsies of lymph nodes were interpreted originally as reactive hyperplasia, and about one-third as nonspecific granulomatous inflammation. The diagnosis of WHIPPLE's disease was made in only one instance from the biopsy alone (FISHER and WHITMAN). Yet, diagnosis by examination of lymph nodes alone is possible in most instances, although caution must be exercised in the interpretation of the PAS-positive deposits. Mast cells, atypical Russell bodies, pigmented and non-pigmented PAS-positive reticulum cells, and non-specific lipogranulomas may mimic the disease.

Under low power the over-all pattern of the lymph node often appeared nonspecific, with reticuloendothelial proliferation, loss of follicular structures, and widening of sinusoids. Under higher power, two main changes became evident: First, individual PAS-positive macrophages were scattered throughout the node, and second, small aggregates of macrophages formed tubercle-like structures. Only in a few nodes were small cystic spaces noted. In most cases

the tubercle formation was not conspicuous, but twice it prompted an initial diagnosis of sarcoidosis (OLIVER-PASCUAL et al., PORTER).

Undoubtedly the characteristic changes in the subcutaneous lymph nodes occur early in the disease and precede the intestinal symptoms. In 1 of our patients the change in the peripheral lymph node occurred 36 months before the patient came to autopsy; in another case, reported in the literature, they were seen 42 months before the patient died. In a recent case of WHIPPLE's disease not included in this report, a diagnosis was made first from the peripheral lymph node biopsy. Subsequently the diagnosis was confirmed by intestinal biopsy (Acc. 938955).

Cardiovascular. Sections of valvular lesions, examined in 7 patients, could be distinguished from other forms of nonbacterial thrombotic endocarditis by the presence of large round macrophages with strongly PAS-positive intracytoplasmic particles (Fig. 16). These macrophages were always located at the base of the vegetations and in a few instances within the overlying thrombotic material. An additional finding in 2 patients was the presence of peculiar small subendocardial myxoid or cystic lesions that were not accompanied by macrophages. Aschoff bodies and granulomatous changes with giant cells in the myocardium have been described in the literature (JARCHO, REVENO) but were not seen in our material.

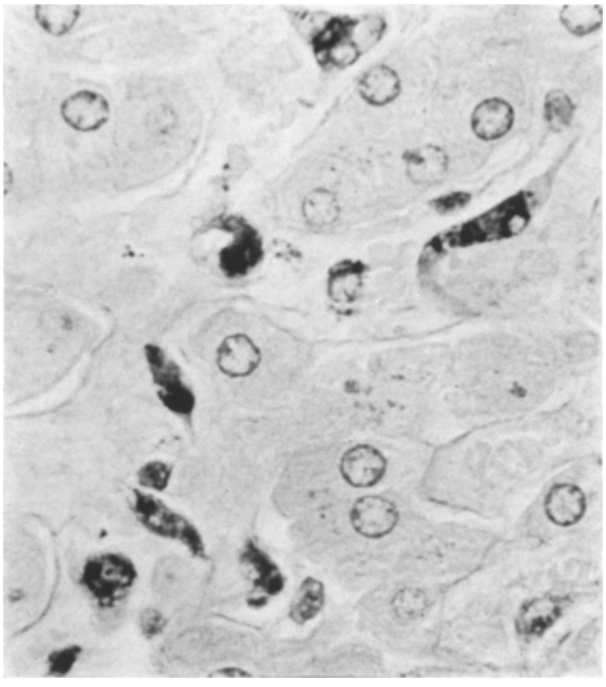

Fig. 19. Liver. PAS-positive particulate material in partly desquamated Kupffer cells. AFIP Neg. No. 60-1376. PAS with diastase digestion. ×850 (reduced to 19/20)

Small groups of PAS-positive macrophages were seen between the myocardial fibres in some hearts (Fig. 17), but as in the epicardium, the macrophages could not be related to interstitial fibrosis.

The serofibrinous inflammation in epicardium and pericardium was usually mild and in the majority of patients accompanied by fibrous organization. Foamy PAS-positive macrophages were found mainly in the deeper portions of the subepicardial fat.

Spleen and liver. In the spleen foamy macrophages were seen in 9 of our 14 cases. They were located almost exclusively in the proximity of the Malpighian follicles and sometimes along the trabeculae. Frequently they surrounded small,

distinct hyaline bodies that had replaced portions of the follicles (Fig. 12). These bodies did not accept stains for amyloid. Since in some cases foamy macrophages

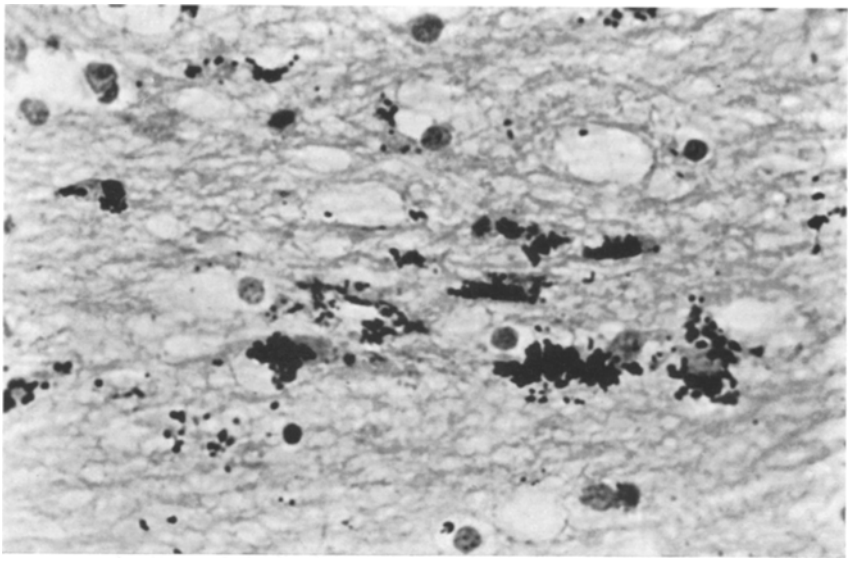

Fig. 20. Brain. PAS-positive deposits in glial cells in vicinity of nocardial cortical abscess. AFIP Neg. No. 60-1371. PAS with diastase digestion. ×660

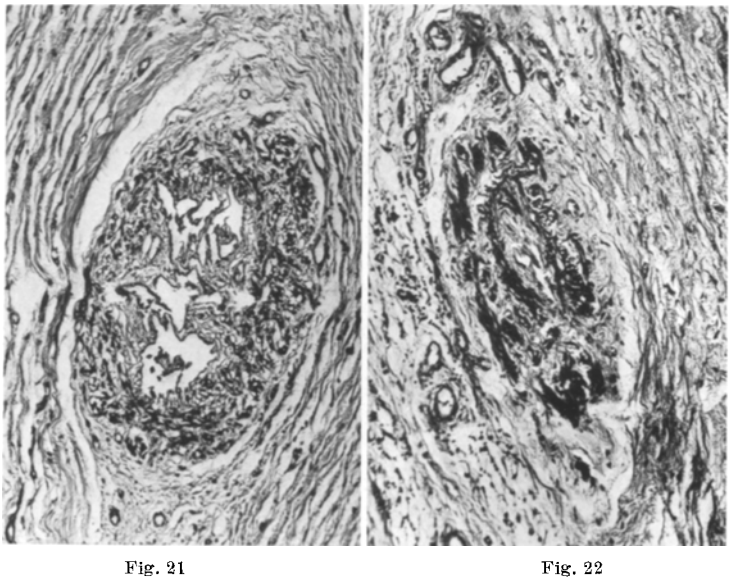

Fig. 21 Fig. 22

Fig. 21. Mesenteric lacteal. Subendothelial fibrous cribriform structure in place of lumen. AFIP Neg. No. 59-1583. MASSON'S trichrome stain. ×85

Fig. 22. Mesenteric lacteal. Fibrous obliteration of lumen. AFIP Neg. No. 59-1583. MASSON'S trichrome stain. ×85

were incorporated in these hyaline bodies, it seemed likely that the PAS-positive material acted as a stimulant to their formation. This process is probably related to that seen in the lymph nodes. In all of the cases the splenic capsule was thickened

and in some instances was covered by partly organized fibrinous material. Vascular hyalinization was prominent in 4 patients. Extramedullary hematopoiesis was occasionally seen.

In the liver, PAS-positive material was present in 10 of our cases. Most commonly it was seen in the portal triads within macrophages, and occasionally as distinct PAS-positive particles in Kupffer cells (Fig. 19). In the latter the material was sometimes associated with small basophilic vacuoles. The capsular changes resembled those described in the spleen but were usually less severe.

Miscellaneous. In the adrenal gland characteristic PAS-positive macrophages occurred in 10 patients but only in or around the thickened capsule (Fig. 18). Sometimes PAS-positive material was located in the smooth muscle of the adrenal vein.

In the posterior pituitary of 1 patient (515813) groups of specific macrophages were present. These changes were probably stimulated by an inflammatory reaction secondary to systemic nocardiosis.

In the pancreas, ductal stasis with occasional strongly acidophilic casts was noted in 6 of our patients, but the parenchyma and islets were apparently not involved. PAS-positive macrophages were seen only in the interstitial and capsular connective tissue.

In brain and spinal cord small deposits of specific PAS-positive material were seen along blood vessels and in occasional isolated glial cells. These changes were found in the cortex, midbrain, and spinal cord. Involvement of the meninges was not observed.

In 2 patients relatively large glial deposits of particulate PAS-positive material were noted in areas of reactive gliosis. In 1 the changes were found about a metastatic abscess; in the other they occurred about a focus of *Nocardia asteroides* infection (Fig. 20).

Etiology

Nature and source of the deposited material. In WHIPPLE's disease, unlike other storage diseases, the abnormal deposits are stored primarily in the intestinal tract. Systemic deposits, although present in all our cases, are less conspicuous and may represent only excess material from the primary intestinal site.

Abnormal substances are stored in two basic forms: 1. as a solid strongly PAS-positive, particulate matter in macrophages; and 2. as a liquid that resembles chyle but differs by some of its staining reactions and by its presence outside of lymphatic spaces. The liquid substance not only fills numerous extravascular spaces, often bestowing a cribriform pattern to intestinal villi of lymph nodes, but occurs also in close association with the solid deposits within macrophages (Fig. 13). In fact, it seems that many of these spaces are created by dissolution and vacuolation of the solid material (Fig. 15).

While it is entirely possible that both substances are basically different, it is conceivable that one basic substance is stored in two forms: in a solid state conjugated with intracellular protein and as a liquid substance intermixed with chyle.

Relatively little attention has been paid by earlier investigators to the material accumulated in macrophages. WHIPPLE, using osmic acid, found small "jet black" deposits in some but not in all of the macrophages and mentioned also the presence of "fat grains" in giant cells, wandering cells, endothelial cells, and muscularis mucosa. BLACK-SCHAFFER was the first to demonstrate the strong affinity of the deposited material to the periodic acid-Schiff reagent. From his studies he concluded that the material probably represented glycoprotein. More

recently UPTON and CASSELMAN et al. came to similar conclusions as a result of more detailed histochemical studies. Our findings (Tables 6, 7 and 8) support in the main BLACK-SCHAFFER's and CASSELMAN's interpretation. The intracellular material stained in all cases as a complex mucopolysaccharide conjugated to protein. It is notable, however, that a large number of macrophages in our material contained in addition small amounts of lipid material, which could be demonstrated by a variety of stains (Table 7).

Table 6. WHIPPLE'S *Disease — Histochemical Characteristics of Macrophages in Small Intestines and Mesenteric Lymph Nodes*[1]

Staining method	Results	Staining method	Results
Carbohydrates		*Carbohydrates*	
Hematoxylin-eosin	basophilic-acidophilic	Crystal violet	orthochromatic
Periodic acid-Schiff[3] (PAS)	3+	Congo red	0
Schiff, without oxidation	0	Giemsa	1+
PAS, with diastase[3]	3+	*Protein*	
PAS, with hyaluronidase	3+	Millon's (tyrosine)	0
PAS, with acetylation	0—1+	Schmorl	0
PAS, with bromination	2+	Ninhydrin-Schiff	0—1+
Performic acid-Schiff	0	Danielli	1—2+
Performic acid-Schiff, bromination	0	*Miscellaneous*	
Acid mucopolysaccharides	1—2+	Acid-fast	0
Sulfonated mucopolysaccharides	0—1+	Iron	0
AMP, with hyaluronidase	1—2+	Brown-Brenn	1+
AMP, with diastase	1+	Acid fuchsin	1+
Alcian blue	1+	Gomori methenamine silver	1+
Alcian blue, with hyaluronidase	1+	Gridley	1+
Mucicarmine (MAYER)	1+	Plasmal	0
Best's carmine	0	Phosphomolybdic acid	0
Toluidine blue, aqueous[4]	orthochromatic	Oil red 0 (24 hr.)	0
Toluidine blue, sulfation[4]	weakly metachromatic	Myelin (WEIL)	0
		Luxol blue	0
		Polarization	isotropic
		Fluorescence, primary[2]	0

[1] = Formalin-fixed tissue; [2] = Frozen section embedded in glycerin; [3] = Paraffin and frozen section; [4] = Frozen section.

From the foregoing it is suggested that the accumulated material is not solely a mucopolysaccharide-protein complex but represents rather a lipopolysaccharide bound to protein in the phagocytizing macrophages. As in every storage disease, the composition of the deposits may vary slightly from patient to patient, and this may cause some variation in tissue response and consequently in the individual clinical course.

The site of origin of the material is not clear. It may be formed in situ but it appears more likely that the abnormal metabolites originate primarily in the intestinal tract and enter the systemic circulation from there via lymphatics. From the observations on our patients it is suggested that most of the material enters the lymph stream in a liquid phase rather than in macrophages, since most macrophages seem to be bound to the surrounding stroma and are encountered only rarely within intestinal and mesenteric lymphatics.

The role of lymphatic obstruction. Lymphatic obstruction, its site, and its extent, have been the subject of considerable discussion. Earlier investigators considered partial or complete obstruction of the thoracic duct as a possible cause; others emphasized fibrotic changes at the mesenteric root as responsible for most of the lesions (CHAPNICK, CLEMMESEN, CRANE and AQUILAR, HILL, JARCHO, REVENO, ROSEN and ROSEN). From our study we believe that the role of obstruction is insignificant in the early phase of the disease but is of considerable importance in its late phases and is, as in other mesenteric obstructions, the prime cause of the steatorrhea and the concomitant malabsorption syndrome.

Table 7. WHIPPLE's *Disease — Lipid Stains: Foamy Macrophages and Substance in Cystic Spaces of Small Intestines and Mesenteric Lymph Nodes*[1]

Lipid stains	Macrophages	Cystic spaces
Oil red 0	0—2+	3+
Sudan IV	0—1+	3+
Sudan black	0—2+	3+
Nile blue sulfate	Lavender-blue	Blue
Cholesterol (SCHULTZ)	0—1+	2+
Smith-Dietrich	0—1+	1+
Osmium tetroxide	0—1+	2+
Acid hematin (BAKER)	0—1+	2+

[1] Frozen sections of formalin-fixed material.

Occlusion at the level of the thoracic duct can be excluded as a possible cause of WHIPPLE's disease. Careful inspection in 16 cases never demonstrated such changes. Moreover, it appears quite doubtful whether chronic obstruction of the thoracic duct is capable of producing accumulations of chyle in mesenteric nodes. FAIRLEY and MACKIE were unable to demonstrate such lesions in a patient with obstruction of the thoracic duct, and KLOOS reported a patient in whom complete blockage of the duct by a squamous carcinoma of the esophagus was without effect on the mesenteric lymph nodes. Experimentally, BLALOCK et al. were unable to impede or block mesenteric lymph drainage in dogs by ligation of the thoracic duct alone. In all their animals, collaterals bypassed the point of obstruction shortly after ligation.

Table 8.

WHIPPLE's *Disease — Solubility of Deposited Substance in Macrophages in Small Intestines and Lymph Nodes*[1]

Type of solvent	Time hours	Solubility
H_2O, ethanol, xylene, chloroform	—	nonsoluble
Methanol — chloroform 1:1, hot	24	nonsoluble
Alcoholic picric acid, saturated	24	nonsoluble
Carbon tetrachloride	24	nonsoluble
Pyridine, hot, anhydrous	6	nonsoluble
KOH, 1%	6	nonsoluble
Alcohol — acetone, cold, 1:1	24	nonsoluble

[1] Frozen sections of formalin-fixed material.

In contrast, severe impediment of lymph flow and consequent intestinal symptoms can be induced readily by obstructing lesions at the level of the mesenteric root (BLALOCK et al.). Examples are the steatorrhea and absorption defect produced by some neoplasms, granulomatous inflammations (tabes mesaraica) and, rarely, by parasitic infections.

In WHIPPLE's disease, in the autopsy material at least, partial obstruction appears to be present at two levels: 1. in the membrana propria, due to compression of lacteals by the accumulated macrophages and cystic spaces; 2. in the mesentery and mesenteric root, by an obliterating fibrosing process in lymphatics, and lymph nodes.

The obstruction of the mesenteric lacteals by subintimal and muscular proliferation was emphasized by CLEMMESEN, REVENO, and STAEMMLER and more recently by CRANE and AQUILAR, who believe these changes play an important if not primary role in the pathogenesis of the disease. Earlier, narrowing and subintimal proliferation of para-aortic lymphatics were described by KLOOS. In our material proliferative and obstructive changes in mesenteric lacteals were conspicuous only at autopsy and were always accompanied by similar fibrosing changes of the regional lymph nodes. In sharp contrast to the autopsy material, these changes were absent or much less prominent in the biopsy material.

As mentioned above, another barrier to normal lymph flow probably exists in the membrana propria. At this site lymphatics are rarely seen on histologic examination, and necrosis and rupture of villi are frequent. No doubt the numerous large macrophages that distend some villi to several times their original volume lead to compression of lymphatics and capillaries alike. The fact that the lymphatics of the submucosa, muscularis, and mesentery are not distended in most cases of WHIPPLE's disease suggests that normal chyle formation is already impaired at the intestinal level.

Systemic lesions. While most of the intracellular PAS-positive material is found in intestines and mesenteric lymph nodes, small amounts can be found almost anywhere in the body (Table 5). The process of dissemination is not known. Most probably it reaches the general circulation via the thoracic duct after having by-passed the mesenteric lymph node barrier.

The question arises whether the systemic lesions are due directly to chronic irritation by the deposited abnormal material, or whether there is a chronic hypersensitivity state and the deposits represent a locally formed antigen-antibody complex. Except for polyserositis, however, the usual morphologic substrate of a hypersensitivity state, vascular necrosis, fibrinoid degeneration, extensive proliferation of eosinophiles, plasma cells, and hyperglobulinemia are absent in WHIPPLE's disease. Clinically, no evidence of an allergic background was present in any of the patients. Yet, the extensive amyloidosis in an otherwise uncomplicated case of WHIPPLE's disease in one of our patients (854481) seems to support the concept of a chronic low-grade antigenic stimulation.

Conclusions

The clinical and pathological observations made in a series of 15 necropsied cases of WHIPPLE's disease are presented and compared with the literature.

1. WHIPPLE's disease is a chronic progressive illness of long duration and often fatal outcome. It is most prevalent in the fifth and sixth decades and is more common in males than in females. The duration of the disease varies, but more that one-half of the patients live at least 5 years after onset of symptoms.

Clinically three different stages become manifest as the disease evolves: a) an early and indeterminate stage, with insidious onset marked by arthralgia, weight loss, fatigue, and anemia; b) a second stage, with abdominal pain and distention followed by diarrhea and steatorrhea, and c) a short terminal stage dominated by various manifestations of malnutrition, disturbed electrolyte balance, cachexia, and often cardiac failure. Migratory arthralgia occurs in most of the patients, and in about two-thirds it is the initial symptom. Diarrhea and

steatorrhea occur late and are almost always heralded by episodes of abdominal pain and distention; absence of diarrhea or steatorrhea does not preclude a diagnosis of WHIPPLE's disease.

2. Most clinical manifestations of the disease are the result of three basic tissue alterations:

a) Deposition of a strongly PAS-positive substance in macrophages of the small intestines, regional lymph nodes, and — to a lesser degree — extra-mesenteric visceral and peripheral lymph nodes, valvular endocardium, spleen, and other organs. Histochemical studies of the deposited material suggest a complex mucopolysaccharide with a protein and lipid component.

b) Accumulation of a lymphlike lipid-containing liquid substance within lymphatics and in extralymphatic cystic spaces of the intestinal mucosa and regional lymph nodes.

c) Fibrosis in the regional lymph nodes, spleen, and mesenteric lymphatics, probably incited by the deposited material.

Comparison between the biopsy and autopsy material indicates that fibrous obstruction of mesenteric lymphatics (chronic endolymphangitis), nodular and capsular fibrosis of lymph nodes, and the formation of cystic spaces occur late and always follow the appearance of macrophages. Fibrosis and cystic spaces are not prominent in lymph nodes obtained during the first stage of the disease.

It is suggested that intestinal and systemic deposition of PAS-positive material is responsible for most of the earlier symptoms, while the late manifestations are the result of progressive impairment of intestinal lymph drainage by a relentless fibrosing process of lymph nodes and lacteals. The degree of impairment of lymph drainage is clinically reflected in the severity of abdominal symptoms.

3. Early diagnosis is best accomplished by transoral small bowel biopsy or by the examination of peripheral lymph nodes. Diagnosis, however, must always be based upon demonstration of distinctly particulate and strongly PAS-positive intracellular deposits of variable size and shape. Weakly PAS-positive amorphous and finely granular material in macrophages is not rare in various nonspecific inflammatory conditions and is, therefore, neither diagnostic nor indicative of WHIPPLE's disease.

Summary

15 necropsied cases of WHIPPLE's disease are presented and compared with the literature. Most clinical manifestations of the disease are the result of three basic tissue alterations: a) Deposition of a strongly PAS-positive substance in macrophages of the small intestines, regional lymph nodes, and, to a lesser degree, extramesenteric visceral and peripheral lymph nodes, valvular endocardium, spleen, and other organs. Histochemical studies of the deposited material suggest a complex mucopolysaccharide with a protein and lipid component. b) Accumulation of a lymph-like lipid-containing substance within lymphatics and in extralymphatic cystic spaces of the intestinal mucosa and regional lymph nodes. c) Fibrosis in the regional lymph nodes, spleen, and mesenteric lymphatics as late phenomenon, probably incited by the deposited material. The degree of impairment of lymph drainage is clinically reflected in the severity of abdominal symptoms. Early diagnosis is best accomplished by transoral small bowel biopsy or by the examination of peripheral lymph nodes.

Whipplesche Krankheit
Literaturübersicht und Mitteilung von 15 Fällen

Zusammenfassung

Die makroskopischen und histologischen Untersuchungsbefunde von 15 Fällen von Whipplescher Krankheit werden mitgeteilt und mit den Literaturbefunden verglichen. Die klinischen Erscheinungen lassen sich auf drei Grundprozesse zurückführen: 1. Speicherung einer stark PAS-positiven Substanz in den Makrophagen des Dünndarms, den regionalen Lymphknoten und, in geringerem Grade, in den übrigen visceralen und peripheren Lymphknoten, im Endokard, in der Milz und anderen Organen; histochemische Untersuchungen machen es wahrscheinlich, daß das gespeicherte Material ein komplexes Mucopolysaccharid darstellt mit einer Eiweiß- und einer Lipoidkomponente. 2. Anreicherung einer lymphähnlichen, Lipoide enthaltenden Substanz in den Lymphbahnen und extralymphatischen Spalträumen der Dünndarmschleimhaut und der regionalen Lymphknoten. 3. Fibrose der regionalen Lymphknoten, der Milz und mesenterialen Lymphbahnen, wahrscheinlich ausgelöst durch die Speicherung der Mucopolysaccharide; die dadurch verursachte Störung des Lymphabflusses spiegelt sich in der Schwere der Bauchsymptome wider. Die Frühdiagnose kann am zuverlässigsten durch die histologische Untersuchung einer transoralen Dünndarmbiopsie oder eines peripheren Lymphknotens gestellt werden.

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