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Pathological Evaluation of Paratuberculosis in Naturally Infected Cattle

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Abstract. Thirty-two of 51 cattle infected with *Mycobacterium paratuberculosis* had chronic enteritis, chronic lymphangitis or mesenteric lymphadenopathy, or all three, at slaughter. Granulomatous inflammatory lesions were mild to advanced and predominantly involved the distal small intestine. Rectal involvement was seen only in five cattle. Fourteen had microgranulomas in the liver. There were three cytological forms of macrophages: histiocytic, polygonal and epithelioid. The latter two types had engulfed moderate numbers of acid-fast bacilli. The histiocytic macrophages usually were packed with acid-fast bacilli. Except in the liver and occasionally its nodes, remote lesions of paratuberculosis were not found in other organs. One animal had endocardial and aortic calcifications. Most cattle with signs of diarrhea had globule leukocytes in or around myenteric ganglion cells. The thymus of 3- to 8-year-old cattle with clinical signs frequently had mild to advanced involution. The thymus of similarly aged infected animals without clinical signs, and of paratuberculosis-negative animals, had not involuted.

Paratuberculosis (Johne's disease), a chronic infectious disease of domesticated and wild ruminants, has been recognized throughout the world since it first was described in 1895. Its causative agent is *Mycobacterium paratuberculosis,* a facultative intracellular acid-fast bacterium. The macroscopic and histologic lesions of paratuberculosis basically remain confined to the intestine, mesenteric and ileocaecal lymph nodes [7]. Although *M. paratuberculosis* has been cultured from a variety of other organs, microscopic lesions have been found only in the liver [12]. *M. paratuberculosis* is assumed to spread primarily via circulating macrophages. In the liver these macrophages may become focally trapped in sinusoids and with lymphocytes may give rise to microgranulomas.

Early investigators of paratuberculosis emphasized its similarity to leprosy [3, 5, 10]. Both diseases are caused by acid-fast bacteria that are difficult to culture and have long growth periods. The inflammatory response in both diseases is similar. Despite involvement of different organ systems, the microscopic lesions are dominated by macrophages and Langhans' giant cells.

Leprosy has been classified into two polar forms—tuberculoid and lepromatous

leprosy – with marked histological differences [11]. In tuberculoid leprosy, the dermal granuloma is composed of a well developed population of epithelioid macrophages surrounded by dense collections of small lymphocytes. M. leprae organisms are seldom found by standard methods of examination. This is in contrast to the situation in lepromatous leprosy in which small lymphocytes are absent or scanty and immature macrophages are packed with leprosy bacilli. In accordance with the morphologic findings are the observations of immunologic impairment in these patients [14].

We have classified paratuberculous lesions in the intestinal tract and associated lymph nodes, using as a model the morphologic scale of leprosy proposed by Ridley and Jopling [11].

Materials and Methods

Tissues from 32 Holstein cows (herd A) and from 19 Angus cattle (herd B), all infected with *M. paratuberculosis,* were collected at slaughter. Tissue specimens taken were from the duodenum, jejunum, ileum, ileocaecal valve, caecum, convoluted colon, terminal colon-rectum (last 30 centimeters anterior to the anus), mesenteric nodes, ileocaecal node, pharyngeal tonsil, heart, lung, kidney, liver, liver node, mammary gland, supramammary node, thymus, spleen, bronchial node, adrenal and uterus. Major fetal organs and placental tissues were collected from infected pregnant cows. Tissues were fixed in 10% buffered formalin, embedded in paraffin and sectioned at 6 micrometers. Selected sections were stained with hematoxylin and eosin (HE) and an acid-fast Ziehl-Neelsen stain.

Results

The necropsy and microscopic findings of Johne's disease, the relative numbers of acid-fast bacilli and degree of thymic involution were as shown in tables I, II and V.

Twenty-two of the 32 cows in herd A had gross changes characteristic of Johne's disease (table I). There were corrugations of the mucosa of the distal small intestine and prominent mesenteric and subserosal lymphatics in 17 cows. Twelve had large mesenteric and ileocaecal lymph nodes. Six cows had loss of skeletal muscle substance or atrophy of body fat or both.

Ten cattle in herd B had gross lesions with mucosal thickening. Of these, three had prominent subserosal lymphatics and two had mesenteric lymphadenopathy. The body condition of two cattle was poor. Extensive alopecia was diagnosed in two other cattle. One 5-year-old cow (no. 2) had endocardial and aortic calcifications (table II).

Herd A

Histologic lesions compatible with those of paratuberculosis were graded as mild in nine cows, moderate in 11 and marked in 12.

In cows with mild lesions (class 1), individual Langhans' giant cells usually were detected in the lamina propria of intestinal villi (fig. 1) or scattered within the paracortical zone of mesenteric nodes. Specific epithelioid macrophages were

difficult to identify. Acid-fast bacilli indicative of *M. paratuberculosis* were seen in only one cow.

Cows with moderate histologic lesions (class 2) had several small groups of macrophages or several individual Langhans' giant cells or both in the lamina propria of intestinal villi, in the intestinal submucosa, in the subcapsular sinus, or in the paracortical zone of regional mesenteric nodes. Small aggregates of macrophages were seen in the livers of two cows.

In three cows of class 2 the number of macrophages to giant cells was equal; in four cows, macrophages exceeded giant cells; in four other cows giant cells were the predominant cell type. Cow 3 had small foci of mineralisation in some giant cells.

Many macrophages and giant cells had infiltrated the lamina propria and the submucosa of various segments of the small intestine in cows with advanced lesions (class 3). These macrophages and giant cells also were in the stromal tissue of the tunica muscularis and in the serosa. They filled the submucosal, subserosal and mesenteric lymphatics and partially occluded the lumen. A substantial number of macrophages, giant cells and lymphocytes surrounded these lymphatics.

The intestinal villi were short and distorted. Cryptal glands were distended and filled with neutrophils and mucoid substances. Villous lacteals were prominent because of dilation and some contained a few inflammatory cells. Some lacteals had ruptured and fistulation into the gut lumen had occurred.

Peyer's patches were surrounded by inflammatory cells, but usually were not infiltrated by them. The submucosa was widened either by infiltrating inflammatory cells or transudate. In 11 cows, the myenteric ganglion cells of Meissner's plexus either were surrounded or infiltrated by a few globule leukocytes (fig. 2).

The granulomatous inflammatory response tended to extend to the adjacent mesenteric nodes. Afferent lymphatics were distended and infiltrated by macrophages and giant cells. The subcapsular sinuses were filled with similar cells. The lymphoid cells within the paracortical zone largely were replaced by macrophages and giant cells. Lymphoid nodules were spared.

The infiltrating process usually stopped abruptly distally to the ileal part of the ileocaecal valve. The lamina propria of the mucosa of the large intestine, if involved, was only slightly infiltrated by a few macrophages or by Langhans' giant cells. The glands of Lieberkuehn remained uninvolved.

In three cows of class 3, the dominant cell type was Langhans' giant cell; in four cows, the number of macrophages and giant cells was equal; and in five cows, macrophages mostly were seen.

Three types of macrophages could be distinguished morphologically. The granulomatous inflammatory infiltrates of three cows were composed of elongated, spindle-shaped macrophages, and they were arranged in syncytial-like formations within the intestinal mucosa as well within mesenteric nodes (fig. 3). They also were packed with acid-fast bacilli. Macrophages of eight cows were polygonal with prominent, foamy or vacuolated cytoplasm (fig. 4). Ten cows had macrophages that had formed well developed epithelioid cells with deep eosinophilic

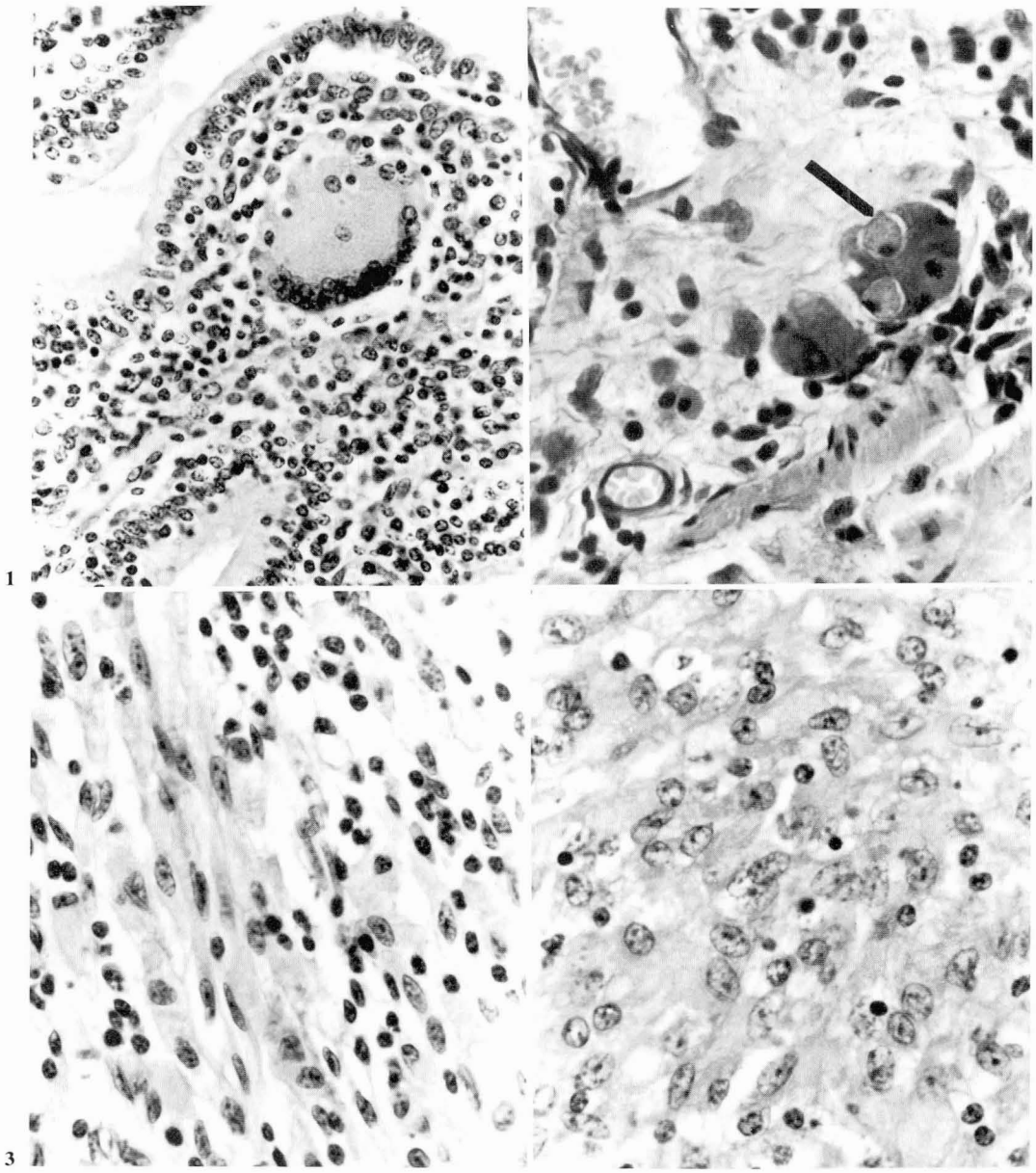

Fig. 1: Small intestine from cow with paratuberculosis. Langhans' giant cell in lamina propria of mucosa (class 1 lesion). HE.

Fig. 2: Small intestine from cow with paratuberculosis. Globule leukocytes (arrow) in Meissner's plexus. HE.

Fig. 3: Mesenteric node from cow with paratuberculosis. Spindle-shaped histiocytic macrophages in bundle-like formations. HE.

Fig. 4: Small intestine from cow with paratuberculosis. Polygonal macrophages with vacuolic cytoplasm. HE.

cytoplasm, distinct cell boundaries, eccentric, oval hypochromatic nuclei, and several nucleoli of various sizes (fig. 5).

Of the 32 cows with histologic changes in the upper small intestinal tract, six had lesions of paratuberculosis in the caecum; three had lesions in the convoluted colon; only two had lesions in the rectum.

The duodenum was free from granulomatous infiltrations in all cows.

Nine cows had small granulomas in the liver (fig. 6). Two of them had slight infiltration of the hepatic nodes with Langhans' giant cells. Acid-fast stains were negative for *M. paratuberculosis*. All other examined organs, including fetal tissues, were free from histologic evidence of paratuberculosis.

In cows with gross lesions in the small intestine, more hepatic than rectal granulomas were seen histologically (table III). Similarly, more hepatic granulomas than rectal lesions occurred in cows with such clinical signs of Johne's disease as persistent diarrhea and weight loss. Hepatic granulomas also occurred more frequently in subclinical cases of paratuberculosis (table IV).

Of the 12 cows with advanced histologic lesions, eight had clinical signs of Johne's disease. Six of 11 cows with moderate histologic involvement were reported to have shown clinical signs, as were three of nine cows with mild lesions (table I).

In 15 noninfected cows from the same herd, and in all infected cows, the thymus was examined histologically for evidence of involution. The population of lymphocytes in the cortex and medulla as well as the size and number of the thymic lobules were evaluated. When correlating the histologic findings of the thymus with the age of the cow and these with the stage of infection of *M. paratuberculosis* we found the following: 1) 11 of 16 cows from 3 to 8 years old with clinical signs had moderate to marked thymic involution; 2) 12 of 16 3- to 8-year-old cows that were infected but free from clinical signs had a fully developed thymus; 3) 11 of 15 cows between 3 and 12 years old that were histologically and culturally negative for *M. paratuberculosis* had a well developed thymus (table V).

Herd B

Of the 19 infected cattle, nine had mild histological lesions of paratuberculosis, four had moderate changes, and six had severe lesions (table II).

Of the cattle with mild lesions (class 1), five only had individual scattered Langhans' giant cells. The other four had a few macrophages in addition to giant cells. Acid-fast organisms could not be demonstrated.

Two cattle with moderate changes (class 2) had predominantly giant cells and a few acid-fast bacilli; in two cattle of this group, the number of macrophages and giant cells was equal and each cell type had a moderate number of acid-fast bacilli.

Two cattle with severe changes (class 3) had mainly macrophages that were packed with numerous acid-fast organisms. Three cows had equal numbers of

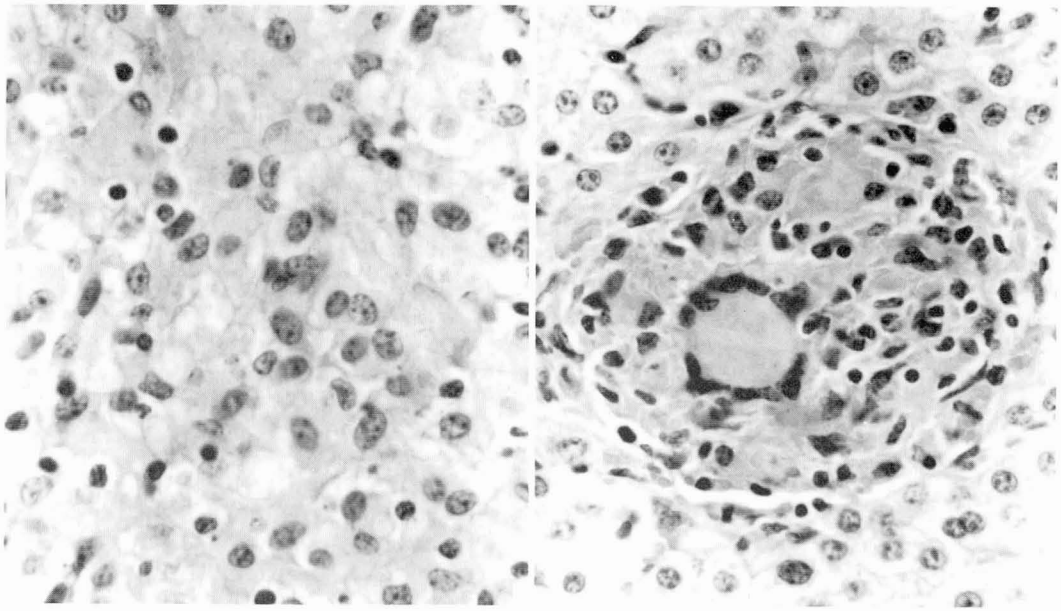

Fig. 5: Small intestine from cow with paratuberculosis. Epithelioid macrophages. HE.
Fig. 6: Liver from cow with paratuberculosis. Microgranuloma in hepatic lobule. HE.

macrophages and giant cells, with a moderate number of ingested acid-fast bacilli; one had mainly giant cells with a moderate number of bacilli.

The macrophages of three cattle were spindle-shaped, histiocytic cells; they frequently formed whorls or bundles and were packed with acid-fast bacilli. The granulomatous infiltrate of three cattle was composed of pleomorphic macrophages with foamy cytoplasm. Six cattle had well developed epithelioid cells with or without Langhans' giant cells. In the remaining seven cattle, giant cells predominated.

In three cattle globule leukocytes were prominent in or around myenteric plexus ganglionic cells; two had clinical signs of Johne's disease.

In all *M. paratuberculosis*-infected cattle, the duodenum was free of granulomatous infiltrates. In six cattle, the caecum was minimally infiltrated; in four of these the convoluted colon was infiltrated; and in three the terminal colon and rectum also were affected.

The livers of five cattle had microgranulomas; two hepatic lymph nodes were infiltrated by Langhans' giant cells. Acid-fast bacilli were not seen on special stains. The pattern was similar to that of herd A. Microscopic hepatic lesions were more frequent than rectal mucosal infiltrations in cattle with gross findings and in cattle without clinical signs of Johne's disease (tables III and IV).

Most cattle infected with *M. paratuberculosis,* but without clinical signs, and most cattle without infection had a fully developed thymus (table V). Two infected cattle from 3 to 6 years old that had clinical signs had an involuted thymus.

Discussion

More than half of our cattle had gross lesions of paratuberculosis. These were mucosal thickening of the distal small intestine and dilated subserosal and mesenteric lymphatics. Enlargement of mesenteric nodes, cachexia and alopecia were less frequent findings.

Histologically, granulomatous inflammatory responses in intestinal and associated mesenteric tissues were from mild to advanced. The inflammatory responses did not extend beyond the ileocaecal valve in most cattle. Large intestine segments were infiltrated only in a few cattle and then only mildly. This may be important in attempting to diagnose paratuberculosis with the help of rectal scrapings or rectal tissue taken for biopsy. The chances of confirming a clinical diagnosis of Johne's disease with this method are considered low. We found infiltration of rectal mucosa by macrophages in only a few cattle with clinical signs and with gross findings of paratuberculosis.

In contrast, the liver of infected cattle more frequently had microgranulomas. Therefore, liver tissue for biopsy might be more useful than rectal tissue in verifying Johne's disease. The finding of liver granulomas in paratuberculosis is paralleled by similar findings in leprosy [4]. In leprosy, the liver was the most frequently affected organ other than the neurocutaneous system and lymph nodes. Hepatic granulomas were reported in 90% of patients with lepromatous leprosy and in 20% of patients with tuberculoid leprosy [4]. As with paratuberculosis, there were no signs of liver dysfunction.

Many of the paratuberculous granulomas were composed of macrophages as well as giant cells, the ratio fluctuating from animal to animal. Many cattle had either macrophages or giant cells as the dominant cell type. The giant cell was frequently the only cell type in minimal lesions of paratuberculosis. In these cases, it usually was not possible to demonstrate acid-fast organisms with special stains. In more severe cases, giant cells had phagocytized acid-fast bacteria, but to a considerably lesser degree than adjacent macrophages. Where macrophages were the dominant cell type, they tended to have many bacilli.

Various cytological features and arrangements of individual macrophages were seen. Many cattle had macrophages that varied either in size and shape or that looked uniform and differentiated and resembled epithelial cells. The bacterial index for both cell types was roughly the same. A few cattle had elongated histiocytic macrophages, arranged in bundles or whorls, that had a comparatively higher number of acid-fast bacteria.

When the histologic changes of paratuberculosis were compared with those of leprosy, the severely affected draining mesenteric nodes looked similar to those of lepromatous leprosy [15]. The entire paracortical zone was replaced by macrophages and giant cells, sparing lymphoid follicles. There were various cytologic forms, from a histiocytic macrophage to an epithelioid cell. Giant cells were numerous.

The identification of variations of the granulomatous response in the intestinal tract of paratuberculous cattle was less successful than in the skin of leprosy

patients, in whom nodular lesions are easier to evaluate. Well defined granulomas with central macrophages and peripheral lymphocytes as seen in the skin of tuberculoid leprosy patients were not found in the intestinal tract of infected animals [10, 11, 13, 14]. Individual macrophages, however, varied in their cytological appearance. Many were polygonal with vacuolated cytoplasm, but without a tendency to evolve to epithelioid cells. Langhans' giant cells were or were not present. Eosinophils, plasma cells and lymphocytes were intermingled in varying numbers. The formation of epithelioid cells was recognizable in other instances. Contrary to tuberculoid leprosy, many of the epithelioid cells could be shown to have ingested various numbers of acid-fast bacteria. Similar to their appearance in lepromatous leprosy, the macrophages in a few cattle with paratuberculosis were undifferentiated. They also were filled with acid-fast bacilli.

The epithelioid cell has been described as the end stage of stimulated, phagocytic macrophages [1, 9]. These macrophages are derived from circulating monocytes of bone marrow origin. Macrophages turn into epithelioid cells when they become immobilized at the site of inflammation [9]. Epithelioid cells are active in phagocytosis, degradation of ingested substances and destruction of microbes. They have secretory functions as well.

Multinucleated giant cells arise by fusion of mature macrophages. The giant cells initially formed are of the foreign body type and convert later to Langhans' type [1].

The globule leukocyte is considered a mast cell that is in the process of discharging its contents of pharmacologically active amines [6]. Globule leukocytes in our investigation were detected in many cases with clinical signs of Johne's disease and in the absence of infestation with helminths. Their close association with myenteric ganglionic cells may be morphologic evidence of an immunologic mechanism by which diarrhea is mediated. It has been suggested that diarrhea in the initial phase of Johne's disease is precipitated by immediate hypersensitivity [8]. It is elicited by histamines released from mast cells and is responsive to antihistamines.

The histology of paratuberculosis did not differ between breeds. Necrosis, caseation and ulceration as they occur in tuberculosis were always absent. This observation can be helpful in distinguishing paratuberculosis from tuberculosis in cattle. With rare exceptions (one animal each) intestinal and cardiovascular mineralisation were also absent, the latter being in contrast to the reported high incidence of arteriosclerosis in cattle with Johne's disease [2, 5].

The histologic evaluation of the thymus with regard to its possible role in the pathogenesis of paratuberculosis led to the observation that in age-matched animals with clinical signs, there is a tendency to lymphocytic depletion. Cattle without clinical signs and paratuberculosis-negative animals, behaved similarly in that only a few of them had signs of thymic involution. Age-dependent involution could not be demonstrated. The occurence of thymic depletion in clinically ill cattle can be interpreted as contributing to the cause, or as being a consequence of the clinical condition. It could be an additional morphologic correlate of the

immunologic unresponsiveness seen in clinical cases such as failure to manifest delayed type of hypersensitivity. The examination of the number and immunologic function of thymus-dependent lymphocytes should be helpful in identifying the significance of this thymic involution.

Table I. Herd A. Cattle positive for paratuberculosis on histologic examination

Animal	Age, years	Clinical signs[1]	Gross[2]	Histology						
				Small intestine[3]	Large intestine[4]	Liver[1]	Bacterial index[3]	Granuloma type[5]	Macrophage type[6]	Globule leukocytes[3]
1	5	+	1-4	2+	Cae,Co	−	2+	G-M	P	1+
2	3	+	1-4	1+	−	−	1+	G-M	P	1+
3	6	+	1,3,4	2+	Cae,Re	+	2+	G	−	−
4	5	+	1,2	3+	Cae	+	1+	G	−	1+
5	5	+	1	2+	−	−	−	G-M	P	1+
6	4	−	−	2+	−	−	−	M	E	1+
7	4	−	1,2	1+	−	−	−	G-M	P	−
8	4	−	1,2	3+	−	+	3+	M	H	−
9	5	+	1-4	3+	−	+	2+	M	P	1+
10	3	−	3	2+	−	+	−	M	E	−
11	7	−	−	1+	−	−	−	M	E	−
12	4	+	1,2,4	3+	−	+	2+	M	E	−
13	7	+	1,2	2+	−	−	3+	M	E	−
14	3	+	1,2,4	2+	Cae Co,Re	−	1+	G-M	P	1+
15	5	+	−	2+	−	−	1+	M	E	−
16	3	−	−	2+	−	−	−	G	−	−
17	3	−	1	3+	Cae	+	1+	G-M	E	−
18	4	+	−	1+	−	−	−	M	E	−
19	3	−	2	1+	−	−	−	G	−	−
20	4	−	2,3	1+	−	−	−	G	−	−
21	3	+	1-3	3+	−	+	3+	G-M	E	1+
22	6	+	2	3+	−	−	1+	G	−	−
23	4	+	1-3	3+	−	+	3+	G-M	H	−
24	3	−	−	2+	−	−	−	G	−	−
25	3	−	−	1+	−	−	−	G	−	−
26	5	+	−	1+	−	−	−	G	−	−
27	3	−	1,3	3+	Co	−	2+	M	H	2+
28	4	−	2,3	3+	−	−	2+	G	E	−
29	4	−	−	2+	−	−	−	G	−	−
30	5	+	1-3	3+	−	−	3+	M	P	1+
31	3	+	1-3	3+	Cae	−	2+	G-M	P	2+
32	3	−	−	1+	−	−	−	G	−	−

[1] + = positive finding; − = negative finding.

[2] Gross findings. 1= mucosal corrugation; 2 = prominent lymphatics; 3 = lymphadenopathy; 4 = weight loss.

[3] Severity of findings. 1+ = mild; 2+ = moderate; 3+ = marked.

[4] Cae = caecum; Co = colon; Re = rectum.

[5] Granuloma type. G = Langhans' giant cell; M = macrophage.

[6] Type of macrophage. H = histiocytic; P = polygonal; E = epithelioid.

Table II. Herd B. Cattle positive for paratuberculosis on histological examination

Animal	Age, years	Clinical signs[1]	Gross[2]	Histology						
				Small intestine[3]	Large intestine[4]	Liver[1]	Bacterial index[3]	Granuloma type[5]	Macrophage type[6]	Globule leukocytes[3]
1	2	+	1–4	3+	Cae, Co,Re	+	3+	M	H	–
2	5	+	1,2	2+	Cae	–	2+	G-M	H	–
3	2	–	–	1+	–	–	–	G	–	–
4	8	–	1	1+	–	–	–	G-M	E	–
5	2	–	1	2+	–	–	1+	G	–	–
6	2	–	–	1+	–	–	–	G-M	E	–
7	2	–	–	1+	–	–	–	G	–	–
8	4	–	1	3+	Cae, Co,Re	+	2+	G-M	E	–
9	3	–	1	3+	Cae,Co	+	2+	G	–	–
10	4	+	1	3+	Cae, Co,Re	–	3+	M	P	1+
11	4	–	1-3	2+	–	+	1+	G	E	1+
12	9	–	–	1+	–	–	–	M	E	–
13	2	–	–	1+	–	–	–	G	–	–
14	2	–	–	1+	–	–	–	G	–	–
15	4	–	–	1+	–	–	–	G	–	–
16	2	–	–	1+	–	–	–	G-M	E	–
17	6	–	1	3+	–	–	2+	G-M	P	–
18	5	+	1,4	3+	Cae	+	2+	G-M	P	1+
19	5	–	–	2+	–	–	2+	G-M	H	–

[1] + = positive finding; – = negative finding.

[2] Gross findings. 1 = mucosal corrugation; 2 =prominent lymphatics; 3 = lymphadenopathy; 4 = weight loss.

[3] Severity of findings. 1+ = mild; 2+ = moderate; 3+ = marked.

[4] Cae = caecum; Co = colon; Re = rectum.

[5] Granuloma type. G = Langhans' giant cell; M = macrophage.

[6] Type of macrophage. H = histiocytic; P = polygonal; E = epithelioid.

Table III. Comparison between gross changes of paratuberculosis and histologic lesions in the rectum and liver, herds A and B

	Gross Changes		No Gross Changes	
	Herd A	Herd B	Herd A	Herd B
Rectal lesions	2	3	0	0
Hepatic lesions	9	5	0	0

Table IV. Comparison between clinical signs of Johne's disease and histologic lesions in the rectum and liver, herds A and B

	Clinical Signs		No Clinical Signs	
	Herd A	Herd B	Herd A	Herd B
Rectal lesions	2	2	0	1
Hepatic lesions	6	2	3	3

Table V. Herds A and B. Comparison between thymic status, presence of *M. paratuberculosis*, with and without clinical disease, and age of cattle

Age, years	Infected cattle with clinical signs				Infected cattle without clinical signs				Uninfected cattle				Number of cattle
	4+	3+	2+	1+[1, 2]	4+	3+	2+	1+	4+	3+	2+	1+	
0–2					(10)			(1)	(10)				(21)
3–4	2	2		3(1)	10 (1)	1(1)	1		4	1			24 (3)
5–6	3	2	1	2(1)	1				2 (1)				11 (2)
7–8		1			1		1	(1)	1				4 (1)
9–10						(1)		(1)				(1)	(3)
11–12						1			2		1	1	5
Over 12									2			1	3
Total	5	5	1	5(2)	12(11)	2(2)	2	(3)	11(11)	1	1	2(1)	47(30)

[1] Histologic thymic involution. 4+ = normal; 3+ = mild involution; 2+ = moderate involution; 1+ = marked involution.

[2] Numbers in parentheses represent cattle from herd B.

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