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Cat scratch disease

An epidemiological and ultrastructural study of lymphadenitis caused by Warthin-Starry positive bacteria

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Summary. The aetiological agent of cat scratch disease (CSD) has been unknown for more than 30 years. Recently, a micro-organism clearly shown with Warthin-Starry silver (W-S) stain was found and thought to be a possible cause of the disease. In this study, 32 cases of regional lymphadenopathy histologically compatible with CSD and 20 contrasting cases of lymphadenopathy were examined retrospectively with W-S stain. W-S positive pleomorphic organisms were clearly demonstrated in 20 of the 32 suspected cases of CSD, but in none of the other cases. The onset of disease in these 20 cases with W-S positive organisms occurred between July and January. This seasonal variation in the onset of disease was highly significant ($P<0.005$) and was not due to a single epidemic. Moreover, some characteristic morphological features of the organism were found by electron microscopic observations. Ultrastructurally, the organism was a bacterium showing a chain-like arrangement, septal formation, branching and clubbed ends.

Key words: Cat scratch disease – Epidemiology – Ultrastructure – Bacterial morphology – Warthin-Starry stain

Introduction

Cat scratch disease (CSD), first recognized by Debré et al. in 1950 (Debré 1950; Debré et al. 1950a and b; Carithers 1970), is an infectious disease characterized by regional lymphadenopathy and a history of a scratch or bite by animals, or other skin puncture from various causes (Daniels and MacMurray 1954).

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Several organisms have been proposed as possible aetiological agents of CSD, including the virus of Petzetakis' disease (Fox 1952), Herpes simplex virus (Turner et al. 1960; Kalter et al. 1969), atypical mycobacteria (Boyd et al. 1961) and Chlamydia belonging to the Psittacosis-lymphogranuloma venereum group (Mollaret et al. 1951a and b; Gifford 1955; Kalter et al. 1955; Fowler and Bailey 1961). The actual causative agent is unknown. Therefore, three of the following four criteria are required for clinical diagnosis of CSD (Warwick 1967): (i) a positive skin reaction to Hanger-Rose antigen, (ii) negative laboratory findings for other causes of lymphadenopathy, (iii) a history of contact with animals and the presence of a scratch or primary dermal or eye lesion, and (iv) a characteristic histopathological appearance of a biopsied lymph node. In 1983, Wear et al. identified a bacterium that appeared pleomorphic with Warthin-Starry silver (W-S) stain, gram-negative with Brown-Hopps' (B-H) gram stain and was not acid-fast in 34 of 39 excised lymph nodes from 39 patients with CSD (Wear et al. 1983). Subsequently, Gerber et al. (1985) reported culture of a bacterium from an excised lymph node of a patient with CSD, which contained a pleomorphic W-S stained organism. This cultured bacterium seemed to be *Rothia dentocariosa*. More recent reports confirmed the observations of Wear et al. (Margileth et al. 1984; Kitchell et al. 1985; Cotter et al. 1986; Korbi et al. 1986; Miller-Catchpole et al. 1986). To our knowledge, there has been no study of cases of lymphadenitis with a W-S stain-positive organism from an epidemiological point of view, and discrepancies in former electron microscopic observations on this organism (Gerber et al. 1985; Hadfield et al. 1985; Wear et al. 1985; Osborne et al. 1987) have not yet been resolved.

Fig. 1. Case of abscess-forming reticulohistiocytic lymphadenitis containing Warthin-Starry positive bacteria. The belt-like abscess along the marginal zone is characteristic of the early stage in group 1. H&E, × 50

In the present study, we examined 32 cases of abscess-forming reticulohistiocytic lymphadenitis (ARHL) showing the histological features of CSD. For comparison, 20 cases of other kinds of regional lymphadenopathies were also examined. The difference in bacterium-positive and -negative cases of these diseases were studied, and the ultrastructural features of the bacteria in two cases were examined.

Materials and methods

Lymph node biopsy specimens from 52 patients with regional lymphadenopathy selected from the file of the Department of Pathology, Tokushima University for 1970 through 1987 were examined. All excised lymph nodes were fixed in 10% formalin and embedded in paraffin.

All sections stained with H&E were reexamined histologically, and the presence of abscess was confirmed by the Naphthol AS-D chloroacetate method (Katayama et al. 1983). The cases reevaluated were as follows: 32 cases of ARHL, 15 cases of histiocytic necrotizing lymphadenitis (HNL), three cases of mesenteric lymphadenitis, one case of lymphadenitis with rheumatoid arthritis and one case of lymhadenitis with systemic lupus erythematosus.

All specimens were stained with W-S stain (Bridges and Luna 1957) and B-H gram stain (Brown and Hopps 1973; Wear et al. 1983) and specimens in all 32 cases of ARHL were stained with Ziehl-Neelsen stain. Specimens from two cases in which bacilli were demonstrated with W-S stain were also stained with PAS stain and Grocott's stain.

The bacilli in specimens from two cases could be examined by electron microscopy. Portions of the 10% formalin-fixed lymph node of one case were excised and washed with water. Portions of the paraffin-embedded lymph node of the other case in which bacilli were demonstrated with W-S stain were excised and deparaffinized. Then each specimen was cut into small blocks, postfixed with 1% osmium tetraoxide and embedded in Epon 812. Ultrathin sections were stained with uranyl acetate and lead citrate, and observed with a Hitachi H-300 electron microscope.

Clinical histories were obtained from the application forms for pathological diagnosis.

Results

The cases of ARHL were classified into three stages according to the following criteria.

Stage 1: The presence of small histiocytic granulomas or early micro-abscesses throughout the node. Some narrow micro-abscesses may also be present in the marginal zone of the lymph node (Fig. 1). Follicular hyperplasia and paracortical hyperplasia are also seen.

Stage 2: The presence of definite round micro-abscesses randomly distributed throughout the node, but not extending to form "stellate abscesses".

Stage 3: The presence of one or more large, irregular abscess, a so-called "stellate abscess". (Features of the earlier stages may also be seen in this stage.)

Of the cases, 11 were classified as stage 1, nine as stage 2 and 12 as stage 3.

In the specimens from the cases of HNL, irregular focal lesions containing many transformed lymphocytes and histiocytes and a small amount of nuclear debris were seen. The border of the lesions was clear, but no palisade structure of histiocytes around the lesions was seen. Few neutrophils were found in the lesions on staining by the AS-D chloroacetate method.

Specimens from the cases of mesenteric lymphadenitis showed marked sinus histiocytosis and follicular hyperplasia. In addition, scattered small

histiocytic granulomas and definite abscesses were seen in two of three cases. In these two cases, histological findings were similar to those in stage 2 of ARHL except for the presence of sinus histiocytosis.

In the specimen from the case of lymphadenitis with SLE, similar necrotic lesions to those of HNL extended throughout the entire lymph node. In this case, clinical symptoms and laboratory findings were compatible with those of SLE.

In the specimen from the case of lymphadenitis with rheumatoid arthritis, folicular hyperplasia with a distinct germinal center and plasmacytosis in the residual parts of the node were seen.

Bacteria that stained black with W-S stain were seen in 20 of 32 cases (67%) of ARHL. These 20 cases were classified as group 1, while the other 12 cases in which no bacteria were detected with W-S stain were classified as group 2. No bacteria were detected with W-S stain in any cases of HNL, which were classified as group 3. All the cases of mesenteric lymphadenitis and two cases of lymphadenitis with collagen disease, where no bacteria were detected with W-S stain, were classified as group 4.

In seven cases in group 1, bacteria staining very faintly with basic fuchsin in B-H gram stain could be seen to correspond to bacteria staining black with W-S stain (Fig. 2). In other 45 cases, no bacteria could be detected with B-H gram stain. With Ziehl-Neelsen stain, acid-fast bacteria were not detected in any case of ARHL. The bacteria were not stained with PAS stain or Grocott's stain.

The bacteria had the same morphology in all cases and were seen only in the foci. The bacteria showed pleomorphism; that is, they were rod-shaped or coccoid or of transition forms between rod and coccoid forms. In small histiocytic granulomas and early micro-abscesses, the bacteria were mostly rod-shaped and about 2–4 by 0.5 μm in size and were seen in clumps that could easily be detected at low magnification (Figs. 3 and 4). Some chains of rod-shaped bacteria were also seen (Fig. 5a). The bacteria were mostly in extracellular sites, but a few seemed to be in the wall of capillaries and in macrophages lining the sinuses, as reported by Wear et al. (1983) (Fig. 6). However, in micro-abscesses at later stages, the bacteria were more pleomorphic and fewer in number (Fig. 5b).

Electron microscopy of specimens from the first case, which were obtained from a formalin-fixed lymph node, revealed some clumps of bacteria wrapped in highly electron-dense material, resembling fibrin. The bacteria were mostly uniform in width, but varied in length, the largest bacterium being about 2.5 by 0.5 μm. Some bacteria seemed to have septa. Chain-like arrangements of somewhat irregular bacteria were also seen (Fig. 7). The cell wall-like structure and plasma membrane of a bacterium could be observed at the site where it was attached to a cell (Fig. 8).

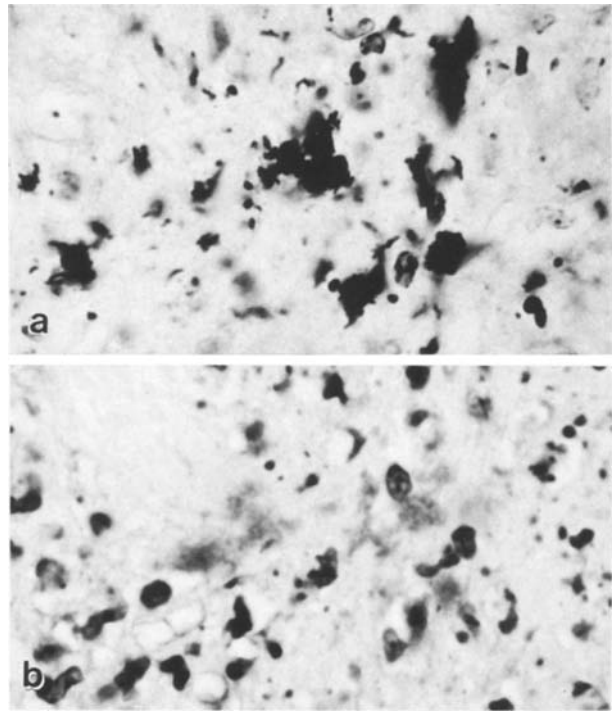

Fig. 2. (**a**) Bacteria stained strongly with Warthin-Starry stain. (**b**) Bacteria stained weakly with basic fuchsin in Brown-Hopps' gram stain, so that they appeared gram-negative in sections. Serial sections. × 500

In the specimens from the second case, which were obtained from a paraffin-embedded lymph node, the morphology of the bacteria seemed identical to that in the first case except for artifacts due to paraffin-embedding. The subpopulation of rods was slightly higher than in the first case. Chain-like arrangements and branchings of rods, and rods with swollen ends, like "clavate cells" were observed (Figs. 9 and 10).

Unlike in some former studies (Hadfield et al. 1985; Wear et al. 1985) no evidence was obtained for the existence of bacteria within cells in either case. These findings were consistent with those of Osborne et al. (1987). The bacteria in semithin sections did not stain with 2% toluidine blue.

Clinically, the patients ranged from 9 to 67 years old (mean, 32 years) in group 1, from 10 to 68 years old (mean, 29 years) in group 2, and from 16 to 39 years old (mean, 27 years) in group 3. There were 11 females and 9 males in group

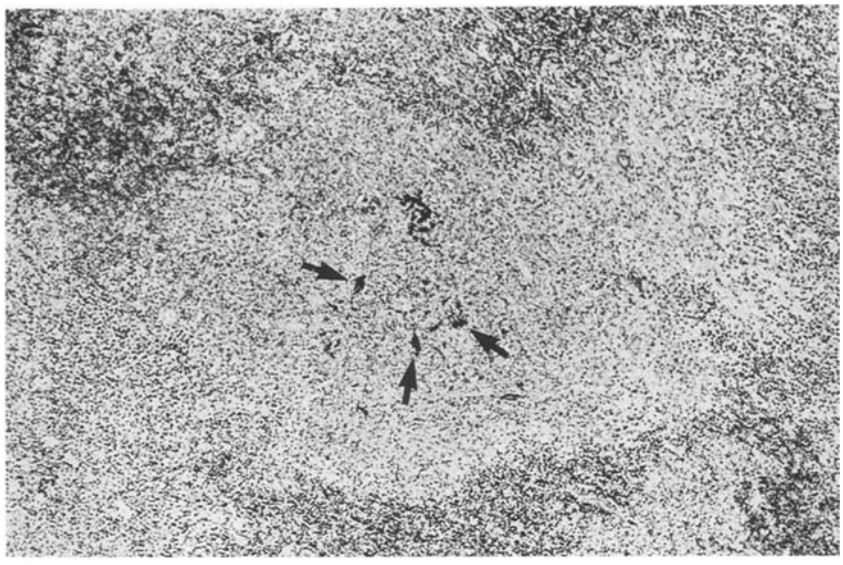

Fig. 3. Three clumps of bacteria (*arrows*) in the center of an early micro-abscess. Warthin-Starry, ×75

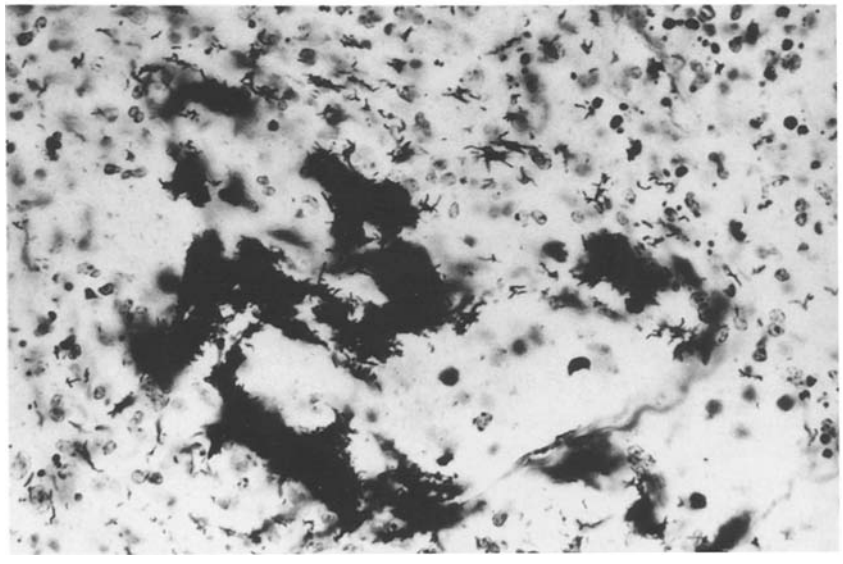

Fig. 4. High power view of a clump of bacteria. The clump consists of numerous rod-shaped bacteria. Warthin-Starry, ×450

1, 5 females and 6 males in group 2, and 10 females and 5 males in group 3. The age and sex of one case in group 2 were not recorded. The common sites of lymphadenopathy were cervical, axillary and inguinal in group 1, and cervical and axillary in group 2. In group 3, all cases had cervical lymphadenopathy, and this tendency was consistent with that reported by others (Kikuchi et al. 1977; Turner et al. 1983) (Fig. 11).

In all cases in group 1, the disease occurred between July and January, and this seasonal variation in onset was highly significant ($P<0.005$), though it was not due to a single epidemic (Figs. 12 and 13). In the other groups, there was no significant seasonal variation in onset (Fig. 12). No regional clustering of the location of the patients' homes was seen in any group, and no patient in group 1 was an inhabitant of the endemic area of Tularemia.

No patient was recorded to have had any scratch, and only one patient in group 2 was recorded to have contact with cats. As regards systemic symptoms, fever was recorded in one case in group 1, none in group 2, and six in group 3. In five of the six cases in group 3, the fever was moderate to high. General fatigue was recorded in one case in group 3, and systemic lymphadenopathy in another case in group 3. Leukocytopenia was recorded in three cases in group 3, but in none in group 1 or 2.

Discussion

In the present study, we found bacteria in 20 of 32 cases (67%) of ARHL, and observed that their form and distribution were as reported by Wear et al. (1983). But these cases were diagnosed clinically as cases of regional lymphadenopathy and their recorded histories were insufficient to allow a diagnosis of CSD. In Japan, clinicians have paid little attention to CSD, and the Hanger-Rose skin test is rarely given. Therefore, a history of a scratch, bite or other skin puncture is probably overlooked in many instances. Judging from the findings in the present study, we consider that there are many unnoticed cases of regional lymphadenitis caused by this bacteria in Japan.

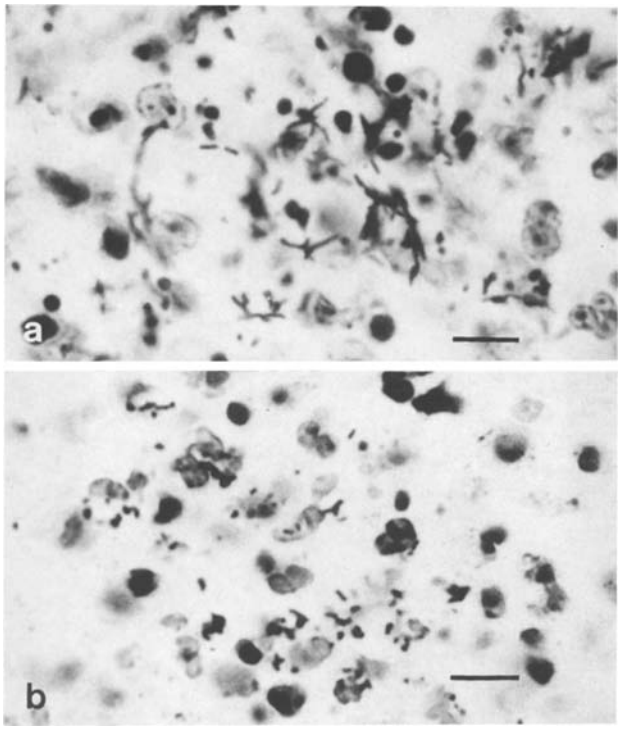

Fig. 5. (**a**) A small histiocytic granuloma or early micro-abscess. The bacteria are mostly rod-shaped, and some of them show chain-like arrangements and branchings. (**b**) Micro-abscess at a later stage. The bacteria are more pleomorphic. The features shown in (**a**) and (**b**) were seen in the same lymph node in some cases in group 1. Warthin-Starry, ×1000. Bar = 10 μm

It is especially noteworthy that the seasonal occurrence of disease was striking in group 1. Since 1957 (Merten 1957), many studies have confirmed the high incidence of CSD in the fall and winter months (Spaulding and Hennessy 1960; Fowler and Bailey 1961; Warwick 1967). However, in six cases (30%) in group 1, the disease occurred in the summer, and the seasonal incidence in group 1 showed a significant difference ($P<0.01$) from that of 421 cases of CSD recorded in North America and Europe and summarized by Warwick (1967). This difference might have been due to the regional variation in the seasonal incidence, or simply to differences in numbers of cases examined. Therefore, it does not necessarily indicate that the causative agents of CSD was not W-S positive bacteria. Further study of more cases and regional variation of cases are needed to clarify this point. As regards the cause of the seasonal variation in the occurrence of CSD, Warwick and Good (1960) observed that an epidemic of CSD was associated with kittens born during the late summer or fall and guessed that they were responsible for the inoculation of the disease. However, it seems difficult to explain other seasonal epidemics with their theory alone.

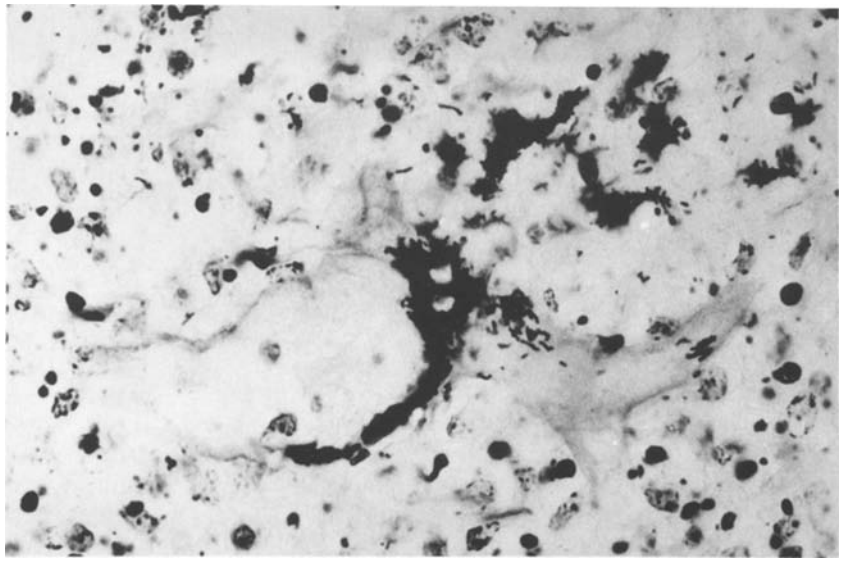

Fig. 6. Bacteria in the wall of a capillary. These were seen occasionally. Warthin-Starry, ×500

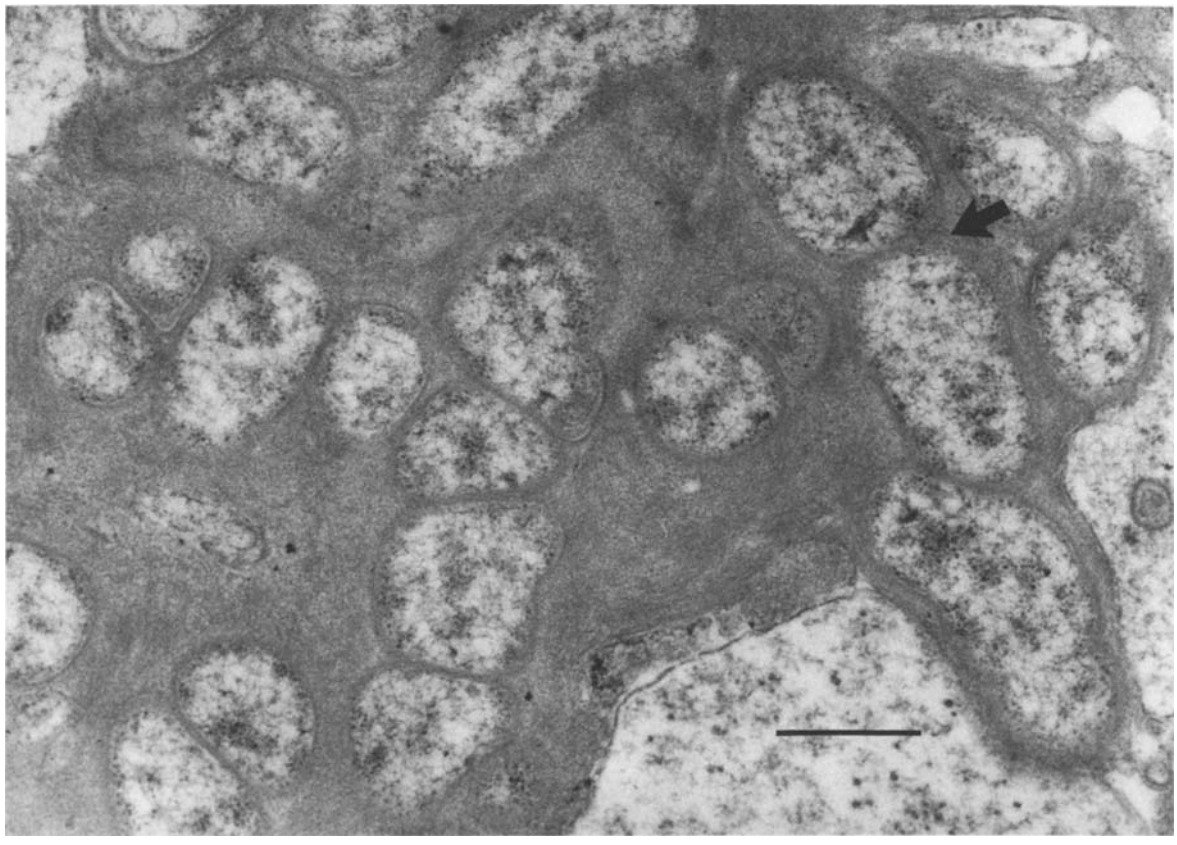

Fig. 7. Bacteria wrapped in fibrin-like material and showing a chain-like arrangement in the first case. Transverse septation (*arrow*) is also observed. From formalin-fixed material. × 38 500. Bar = 0.5 μm

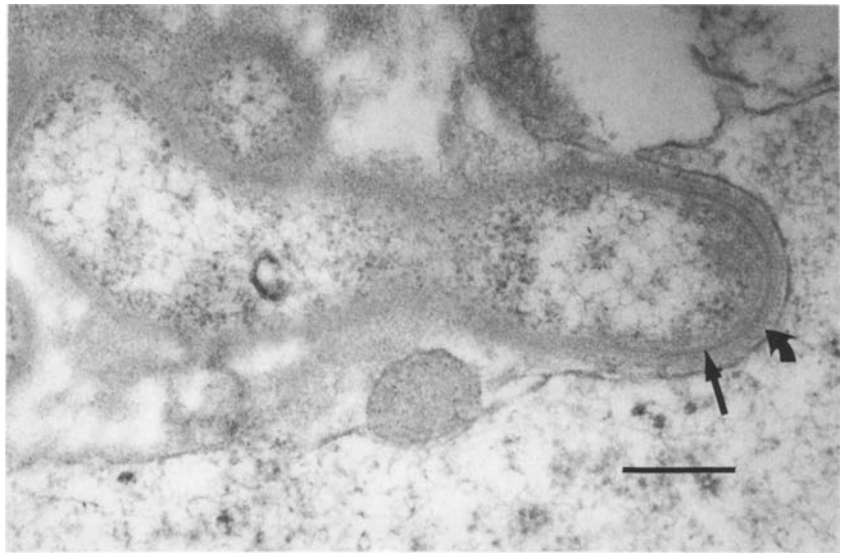

Fig. 8. Cell wall-like structure (*curved arrow*) and plasma membrane (*straight arrow*) of a bacterium in the first case. × 66 500. Bar = 0.25 μm

Miller-Catchpole et al. (1986) reported that *Francisella tularensis* and *Hemophilus ducreyi* also seem to be pleomorphic on W-S staining, and appear almost as large on B-H gram staining as on W-S staining, whereas the CSD organism can barely be judged as gram-negative on B-H gram staining. Therefore, they stated that confirmation of CSD requires the use of B-H gram staining to exclude other organisms. However, marked differences in the positivity rates of B-H gram staining

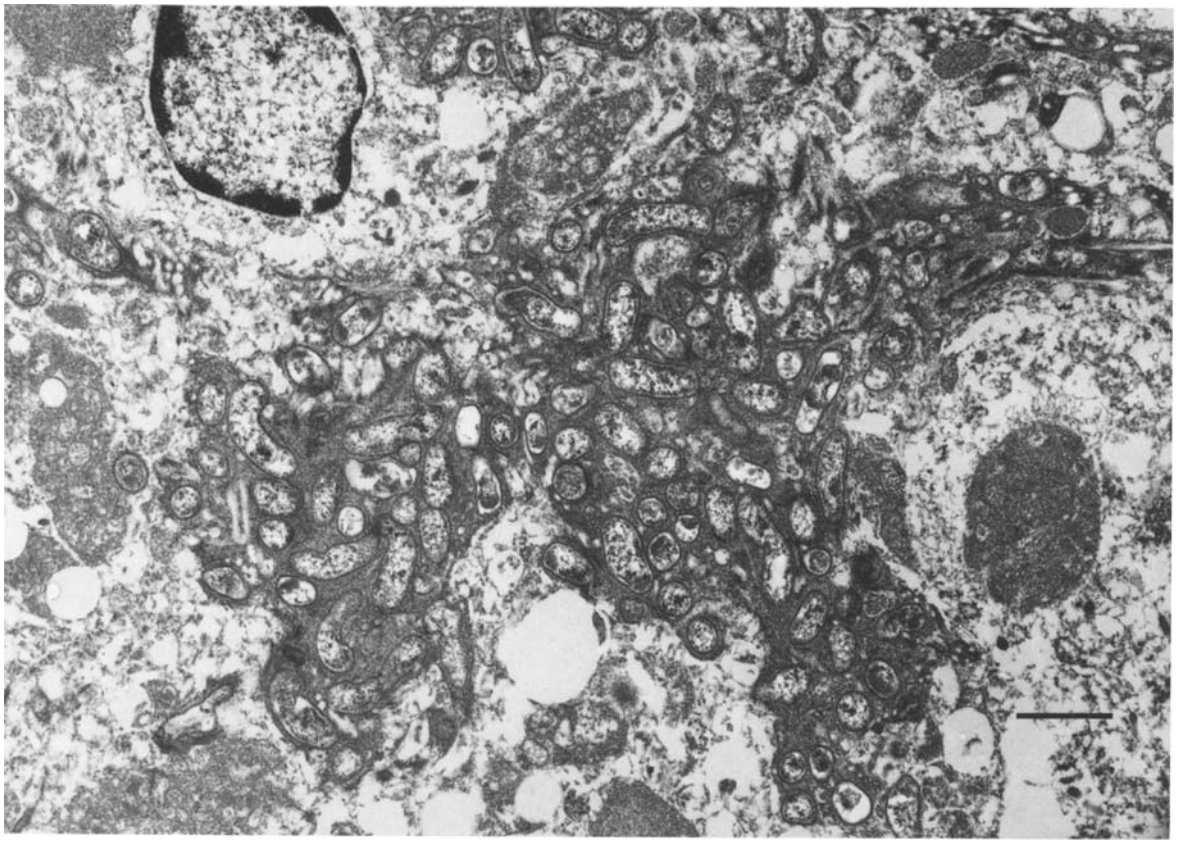

Fig. 9. A clump of bacteria in the second case. This section was from the same case as for Fig. 3, and was prepared from deparaffinized material. ×12500. Bar = 1 μm

have been found; that is, 28 of 29 (Wear et al. 1983) 0 of 40 (Korbi et al. 1986) 7 of 7 (Miller-Catchpole et al. 1986) 2 of 2 (Osborne et al. 1987) and 7 of 20 (present study). These discrepancies were probably due to the very weak staining of the bacteria with B-H gram stain and the different degrees of strictness of criteria used to identify the bacteria on this staining. Our criteria were strict, and only clumps of bacteria that were more than a certain size were scored. The difficulty in detecting this bacterium by gram staining is probably the reason why it was found only recently.

The ultrastructural features of the bacteria were consistent with those reported by others (Hadfield et al. 1985; Wear et al. 1985; Osborne et al. 1987). Moreover, in the present study, a plasma membrane, cell wall, chain-like arrangement, septation and branching of the bacteria were observed. These features suggest that this bacteria is not *Fransicella tularensis* or *Hemophilus ducreyi*, but resembles *Rothia dentocariosa* (Roth et al. 1976; Gerber et al. 1985). Especially in formalin-fixed material (first case), this bacteria seemed to have the structure of a gram-positive organism, in spite of results by B-H gram staining. Osborne et al. (1987) suggested that this discrepancy could be explained by supposing that the degenerated or old gram-positive bacteria become gram-negative. Another possibility is that paraffin-embedding may change the gram-stainability.

In general, cases in groups 1 and 3 differed clinically and in histopathological features, including those with special stains. However, one case in group 1 showed very similar histopathological features to those in the early stage of HNL. Therefore, especially in early stages, some cases of lymphadenitis caused by this bacteria may have been diagnosed as HNL. The naphthol AS-D chloroacetate method is useful for detecting early micro-abscesses and distinguishing ARHL from HNL.

Cases in group 2 were histologically indistinguishable from cases in group 1 except that the bacteria could not be detected in those with W-S stain. The cases in group 2 in this work correspond to some of those reported previously (Wear et al. 1983; Cotter et al. 1986; Korbi et al. 1986). We think that group 2 may consist of three different populations of cases. One population may be cases with the histopathological appearance of ARHL, but caused by another micro-organism. For exam-

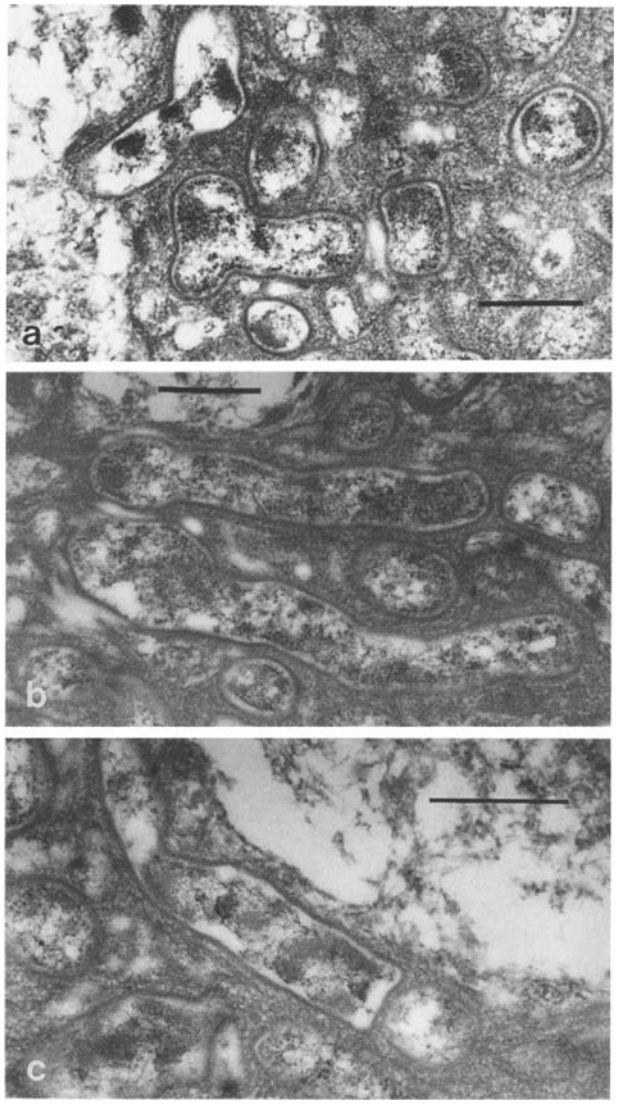

Fig. 10. Sections from the second case. (**a**) A bacterium seems to branch and form a "Y" shape. ×30000. Bar=0.5 μm. (**b**) Bacteria have swollen ends and look like "clavate cells". ×30000. Bar=0.5 μm. (**c**) A bacterium with a square end that seems to be due to a septum. ×40000. Bar=0.5 μm

ple, lymphogranuloma venereum, caused by *Chlamydia trachomatis*, shows histopathological features that are indistinguishable from those of CSD (Robb-Smith and Taylor 1981).

A second population might be cases caused by W-S positive bacteria that could not be detected. The following reasons for inability to detect bacteria have been suggested in former reports (Cotter et al. 1986; Miller-Catchpole et al. 1986): (a) At advanced stages when the abscess becomes larger, the bacteria are removed by neutrophils and macrophages, and decrease in number. (b) The distribution of the bacteria in an abscess is not uniform,

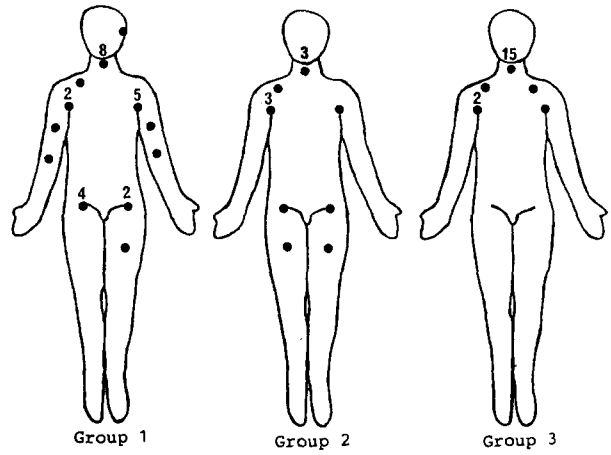

Fig. 11. Sites of lymphadenopathy. Numbers above dots indicate numbers of cases. Dots without a number represent one case. In group 1, the common sites of lymphadenopathy are cervical, axillary, and inguinal. In group 2, the sites are similar to those in group 1. In group 3, which are the cases of histiocytic necrotizing lymphadenitis, the sites of lymphadenopathy are focused around the neck

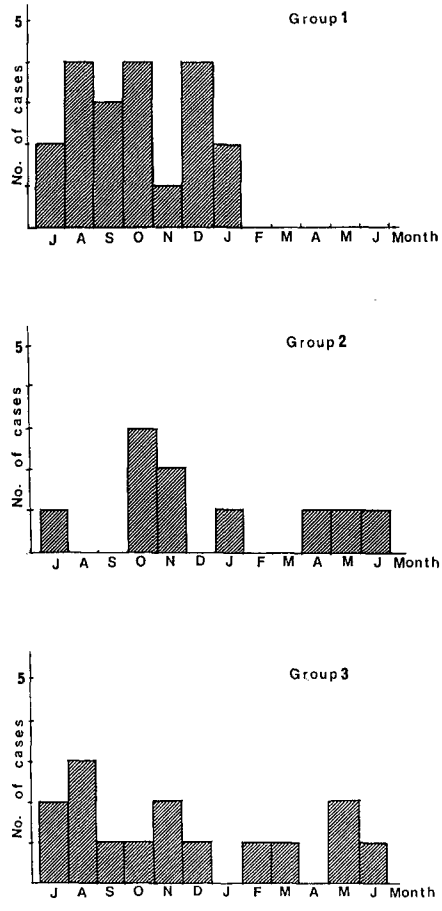

Fig. 12. Month of onset. Cases in group 1 show a significant seasonal variation in onset ($P<0.005$). Cases in groups 2 and 3 show no significant seasonal variation of onset

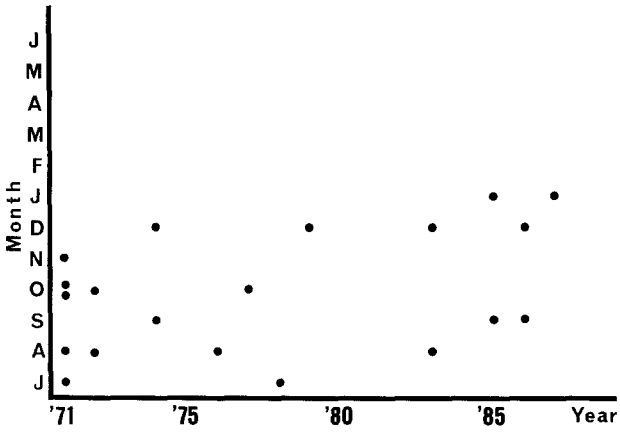

Fig. 13. Month of onset in cases in group 1 in successive years. A dot represent one case. The sporadic occurrences of disease show that the seasonal variation in onset is not due to a single epidemic

and so bacteria may not be present in some sections stained with W-S stain. (c) Antibiotic therapy may have decreased the number of bacteria. These explanations may apply in some cases in group 2. In fact, the number of cases classified into stage 1 was less in group 2 than in group 1 (9/20 cases in group 1, 2/12 cases in group 2), though there was no recorded case of antibiotic therapy in group 2.

A third population, which seems to have been missed in previous studies, might also have been present. Warwick (1967) suggested in his comprehensive review about "the cat-scratch syndrome" that many cases of cat-scratch syndrome are probably due to one or several closely related causative agents, but that some cases may be caused by agents that differ significantly from the central agent or group of related agents, because patients with CSD vary in reactivity with the Hanger-Rose antigen. Therefore, a third population in group 2 may be cases of CSD due to some other aetiological agents that are not stained with W-S stain.

Moreover, there may be several subpopulations of W-S positive bacteria corresponding to several closely related causative agents, because W-S stain is not specific for a certain genus of bacterium and also because it may be impossible to identify a bacterium by its morphology alone. As Emmons (1984) pointed out, the bacteria from a suitable number of excised lymph nodes of different patients with CSD must be cultured and identified in further studies.

In conclusion, it is obvious that a significant number of cases of ARHL are caused by the bacteria reported by Wear et al., and that the W-S stain is very useful for diagnosis of these cases and demonstration of the causative agent.

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