# SYNOVITIS IN SECONDARY SYPHILIS

## Clinical, Light, and Electron Microscopic Studies

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**Polyarthritis and tenosynovitis were seen as the presenting complaints in 7 patients with secondary syphilis. Synovial needle biopsy was obtained in 3 cases and showed mild synovitis with infiltration by lymphocytes, plasma cells, and polymorphonuclear leukocytes; vascular congestion; and slightly increased synovial lining cells. In addition, electron microscopy in these synovial membranes showed many necrotic polymorphonuclear leukocytes, much interstitial debris and fibrin, and in 2 patients, bodies suggestive of *Treponema pallidum* in the interstitium and in vessel lumens.**

Articular and bone diseases have only occasionally been described as prominent manifestations of secondary syphilis (1–3). Since no modern studies attempting to identify spirochetes in synovial fluid or membrane have been performed and biologic false positive serologic reactions for syphilis can be seen with rheumatic diseases such as systemic lupus erythematosus, the existence of synovitis in secondary syphilis has been seriously questioned (4).

This study reports the clinical features and light and electron microscopic findings of synovial fluid and synovial membrane in 7 patients with synovitis associated with secondary syphilis. The presence of bodies with electron microscopic appearance of spirochetes in 2 synovial biopsies and the rapid response to penicillin tend to favor infection in the joint as the cause of synovitis.

## PATIENTS AND METHODS

Five female and 2 male patients (Table 1), ages 20–44, were studied. These cases were accumulated over 12 years. Five of these patients were seen in the University Hospital in Santiago, Chile, and 2 in the Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania. All patients except 1 denied a primary lesion, but all 7 had generalized lymph node enlargement and characteristic nonpruritic maculopapular rash. Five patients also had oral or perigenital mucous plaques. Dark field examinations of perigenital mucous plaques (condyloma lata) performed in 5 patients were positive for spirochetes. A small persistent primary lesion in 1 additional patient showed spirochetes. Serologic tests for syphilis were positive in the sera of all 7 patients (RPR or VDRL in all patients, fluorescent treponemal antibody absorption test in 4).

Synovial fluid was available for study in 4 patients and knee synovial needle biopsy was performed in 3 of these patients. Half of each biopsy was fixed in buffered formalin for light microscopy, then stained with hematoxylin and eosin and Van Gieson's stain.

For electron microscopy specimens of synovium and synovial fluid buttons were immediately placed in Karnovsky's formaldehyde glutaraldehyde fixative diluted 1:1 with 0.1*M* cacodylate buffer at pH 7.4. After 30 minutes fixation the specimens were sliced into pieces 1 mm in diameter

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Table 1. Musculoskeletal manifestations in seven patients with secondary syphilis

| Case | Age | Sex | VDRL | Lymph node enlargement | Rash | Mucous plaques | | Tenosynovitis | Arthritis |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Throat | Genital | | |
| 1 | 20 | F | 1 : 64 | + | + | + | +* | Wrists, ankles | MCP† |
| 2 | 44 | F | 1 : 126 | + | + | + | +* | Wrists | Knees,‡ ankles |
| 3 | 35 | F | 1 : 64 | + | + | + | +* | 0 | Knees |
| 4 | 26 | F | 1 : 1512 | + | + | 0 | 0 | 0 | PIP,§ ankles |
| 5 | 40 | M | 1 : 256 | + | + | 0 | 0 | 0 | Knees,‡ ankles |
| 6 | 25 | F | 1 : 64 | + | + | 0 | +* | 0 | Sternoclaviculars |
| 7 | 35 | M | 1 : 126 | + | + | 0 | +* | 0 | Sternoclaviculars |

* Positive for spirochetes by dark field examination.
† Metacarpophalangeal joints.
‡ Positive for bodies with appearance of spirochetes on synovial biopsy under electron microscope.
§ Proximal interphlangeal joints.

and replaced for a total of 4 hours at room temperature in the fixative solution. Specimens were washed in 0.1*M* sodium cacodylate buffer at 4°C overnight. They were postfixed in cold Palade's osmium-Veronal for 2 hours, dehydrated in alcohol, placed in 50% propylene oxide and Epon-812 mixture for 2 hours, then embedded in Epon 812. Sections 1$\mu$ thick were cut on a LBK-2 ultramicrotome with a glass knife, stained with toluidine blue, and examined for orientation. Thin sections were cut with a diamond knife, stained with uranyl acetate and lead citrate, and examined on a Zeiss EM-10 electron microscope with a 60 kV beam.

## RESULTS

**Clinical findings.** The main complaints of 5 patients were nonmigratory symmetrical polyarthritis involving metacarpophalangeal joints in 1 patient, proximal interphalangeal joints in 1, wrists in 1, knees in 4, and ankles in 2 (Table 1). The involved joints showed mild tenderness, synovial thickness, and effusion without redness or increased local heat. The arthritis had persisted 3 to 12 weeks (with an average of 4 weeks) before diagnosis and treatment. In addition, 2 of these patients presented with tenosynovitis involving the dorsum of wrists and ankles (Figure 1). The tendon sheaths appeared swollen with fluctuation but without tenderness, redness, or local increased heat, and followed a subacute course much like the arthritis.

Two other cases were seen because of polyarthralgias and acute onset of severe bilateral sternoclavicular joint pain associated with slight periarticular swelling and erythema. No aspiration of these joints was performed.

A generalized nonpruritic papulosquamous rash and generalized lymphadenopathy were present in all 7 patients. Lesions were fading and less obvious on 1 patient with only faint residual rash. Only 1 had a persistent primary penile lesion along with secondary manifestations. Mucous plaques in the throat or mouth were present in 3 patients with mild but persistent sore throat which paralleled the joint or bone manifestations. Easier to recognize were the perigenital lesions or condyloma lata present in 5 patients. Two had a history of fever but none had temperatures over 99.6°F when examined.

Sedimentation rates (Westergren) were elevated in 5 patients, ranging from 20–101 mm/hour with a mean of 52 mm/hour. A serum cryoglobulin was detected during active disease in 1 patient. Radial immunodiffusion assay of serum immunoglobulins performed in 3 patients showed mild elevation of IgG and IgM. Serum latex fixation tests for rheumatoid factor and fluorescent tests for anti-nuclear antibodies performed in 4 patients with arthritis were all negative. Total serum hemolytic complement studies in 3 patients were within normal limits. White blood cell counts, differentials, hematocrits, and urinalyses were normal.

Articular roentgenograms of patients with synovitis showed only soft tissue swelling of involved joints.

Patients with synovitis received 1,000,000 units

Table 2. Synovial fluid in four patients with secondary syphilis

| Case | White cell count/mm$^3$ | Polymorphonuclear leukocytes, % | Mononuclear cells | CH50, mg% | Cultures | Dark field |
|---|---|---|---|---|---|---|
| 2 | 10,500 | 46 | 54 | | – | |
| 3 | 13,000 | 48 | 52 | 170 | – | |
| 4 | 4,000 | 56 | 44 | | – | – |
| 5 | 4,150 | 83 | 17 | | – | – |

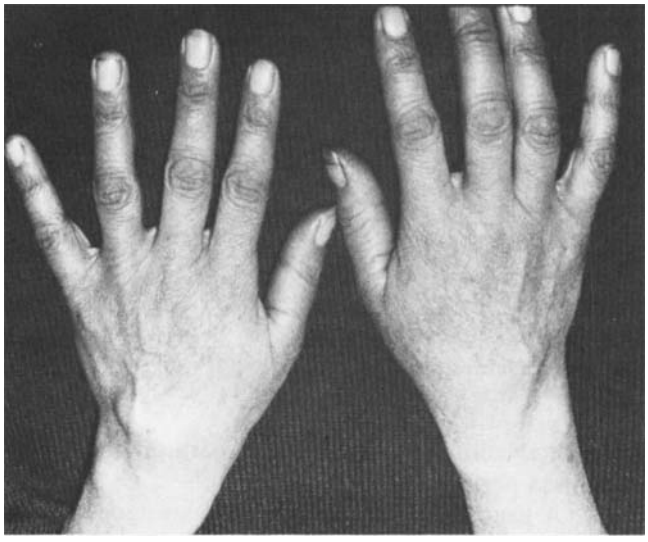

**Figure 1.** Hands of patient (Case 4) showing symmetrical swelling of wrist extensor tendon sheaths.

of penicillin G intramuscularly daily for 10 days or a single intramuscular dose of benzathine penicillin 2,400,000 units. All patients showed a rapid decrease in their symptoms and by the fourth day the synovitis,

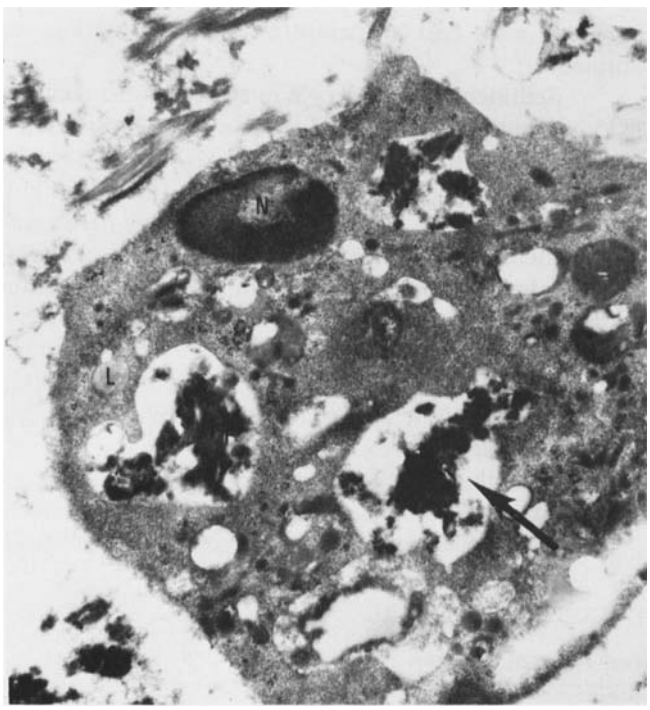


**Figure 2.** Synovial effusion from patient (Case 2). Fibrin-like material (**F**) and osmiophilic unidentified material (**arrow**) are seen in vacuoles. **L** = lipid droplets, **N** = nucleus. (Electron micrograph × 28,000)

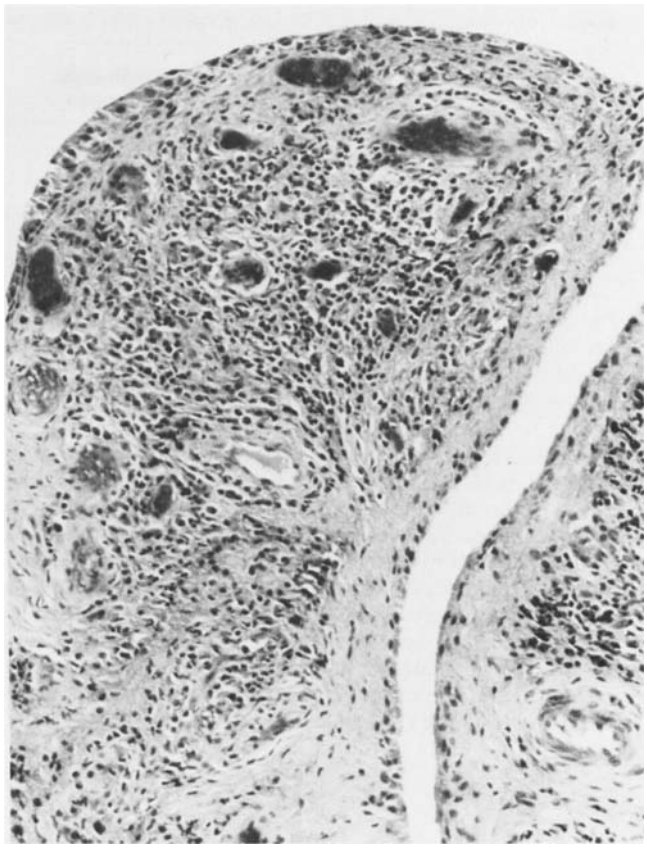

**Figure 3.** Synovial biopsy in patient (Case 4) showing minimal increase in synovial lining cells, mild vascular congestion, and deep lymphocyte, plasma cell, and polymorphonuclear leukocyte exudate. (Hematoxylin and eosin × 178.)

skin, and mucous membrane manifestations had disappeared. Two patients developed a Jarish Herxheimer reaction. Patients were followed for variable periods of time ranging from 1 to 5 years; serologic tests for syphilis became negative in all of them within 2 years after penicillin therapy. None have presented further musculoskeletal complaints.

**Synovial fluid studies.** Knee joint effusions were examined in 4 patients (Table 2). Synovial fluid white cell counts ranged from 4,000 to 13,000/mm$^3$. Polymorphonuclear neutrophils predominated in 2 patients (Cases 4 and 5) while the other 2 had mononuclear cells (Cases 2 and 3). Viscosity was poor on all patients. Routine and gonococcal cultures were negative in all 4 cases. Dark field examination in 2 patients (Cases 4 and 5) and antitreponemal fluorescent antibody stain and silver stain to identify spirochetes in a button of synovial fluid from 1 other patient (Case 3) did not show spirochetes.

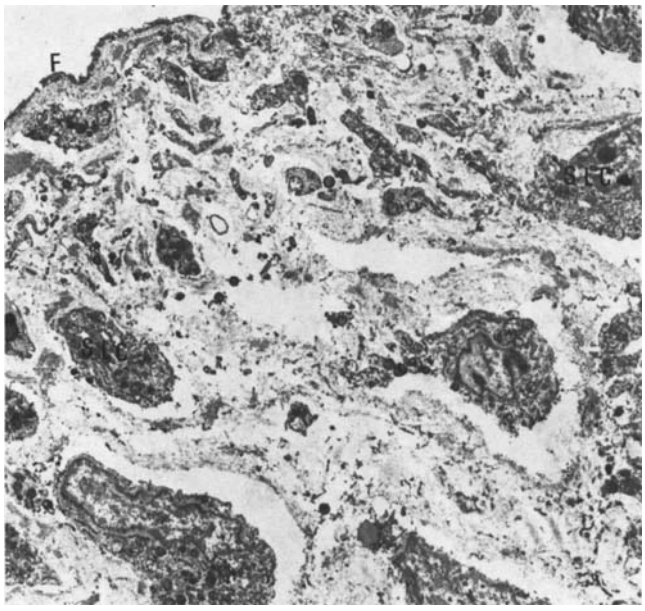


**Figure 4.** Synovial surface of patient (Case 2) with small amount of surface fibrin-like material (**F**), lining cells (**SLC**), and large amounts of interstitial debris. (Electron micrograph × 7,000.)

Examination of the synovial fluid of 3 patients (Cases 3, 4, and 5) by electron microscopy revealed polymorphonuclear neutrophils and phagocytic mononuclear cells with large vacuoles containing unidentifiable debris (Figure 2). No definite spirochetes or finely granular deposits that might specifically suggest immune complexes were seen. Many polymorphonuclear leukocytes contained lipid droplets. There were also small lymphocytes with scattered ribosomes but no activated lymphocytes with polyribosomes.

**Synovial membranes.** Synovial biopsy findings by light microscopy were similar in the 3 patients studied (Cases 3, 4, and 5). Synovial lining cells were only minimally increased in most areas. Lymphocytes, plasma cells, and polymorphonuclear leukocytes infiltrated the deeper synovium. Some vessels were congested but there was no vasculitis (Figure 3).

Electron microscopic studies of these 3 synovial membranes supported the above findings and, in addition, identified considerable necrotic debris among the superficial synovial cells (Figure 4). Glycogen was prominent in some synovial cells. In the interstitial de-

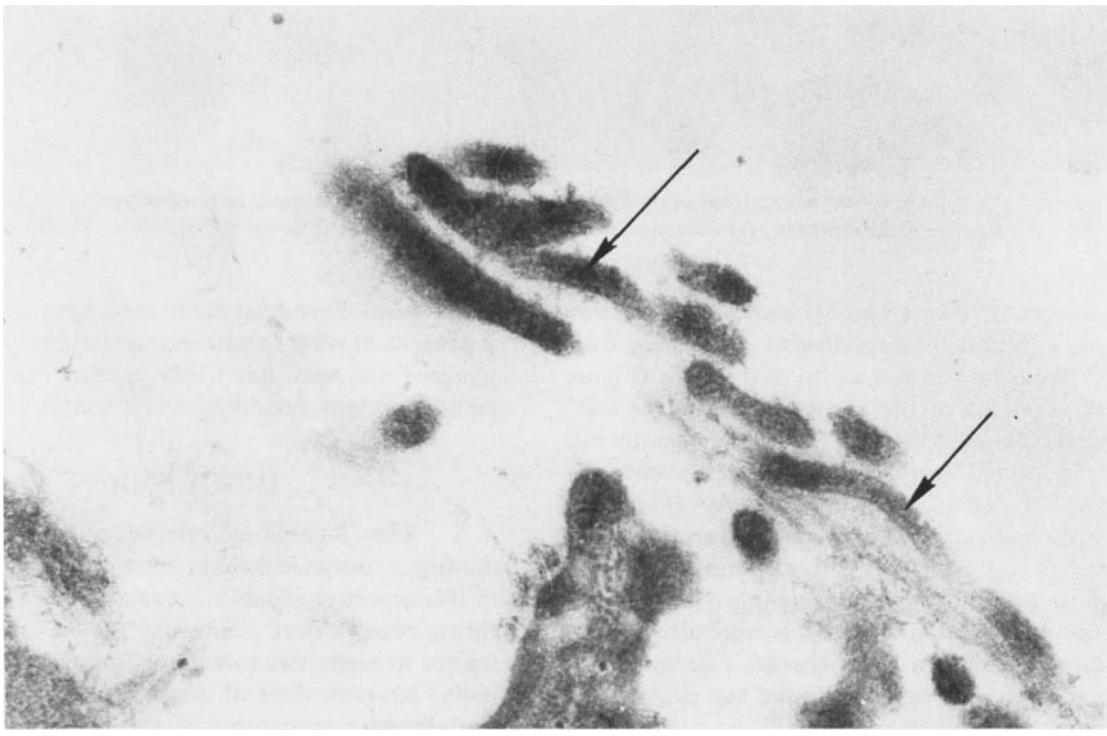

**Figure 5.** Interstitial treponema-like bodies in synovium of patient (Case 2). Note faintly visible longitudinal filaments (**arrow**) in body with two spirals. (Electron micrograph × 50,000.)

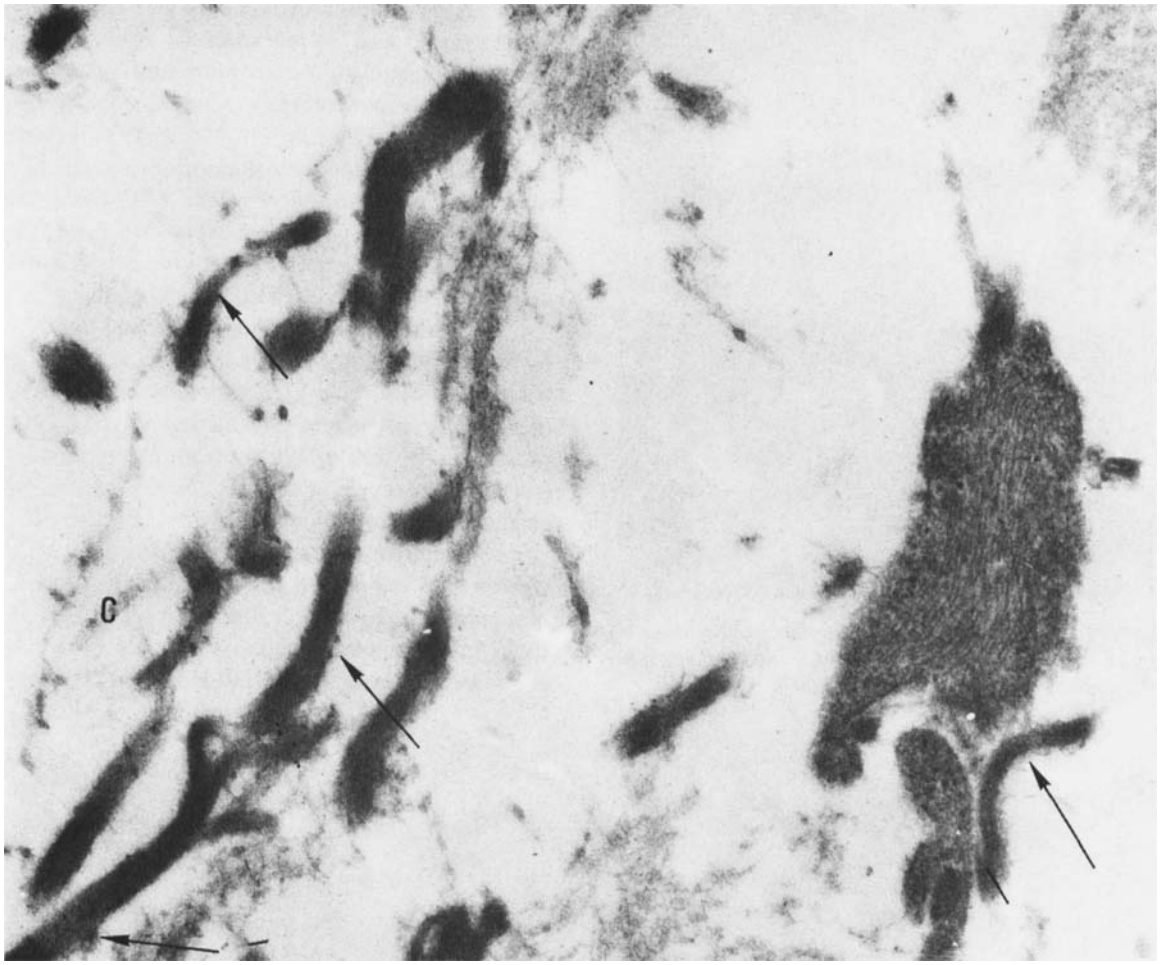


**Figure 6.** Dark staining structures with longitudinal filaments best seen where cut is tangential (**arrows**) suggestive of degenerating treponemes in necrotic area of synovium in secondary syphilis. **C** = collagen. (Electron micrograph × 39,000.)

bris of 2 patients (Cases 4 and 5), bodies with electron microscopic appearance suggestive of spirochetes were identified. These bodies had up to two spirals (Figure 5). Longer segments of the suspected organisms were not seen in the plane of the thin sections of electron microscopy. Suspected spirochetes were often intensely osmiophilic because of their lipid content (Figure 6) and were seen especially well in unstained sections. The deep filaments characteristic of treponemes (5–8) were seen only in fortuitous sections (Figure 5). Similar osmiophilic spirochete-like structures were also seen in a vessel lumen and in a gap between vascular endothelial cells. Synovial vessels showed no evidence of electron-dense deposits in vessel walls, as might be expected in immune complex injury of the vessel.

Fluorescent antitreponemal antibody study and silver stain of synovial membrane were not done on the 2 patients in whom electron microscopic evidence of organisms was seen, but 1 other patient tested with these techniques was negative for spirochetes (Case 3).

## DISCUSSION

The 7 cases of secondary syphilis with predominant musculoskeletal manifestations documented in this report represent the experience of two active arthritis centers over a 12 year period and are not intended to suggest an increasing frequency of these problems. Musculoskeletal manifestations of secondary syphilis were recognized in the United States in 1916 when Wile and Sonnear performed a clinical study on 165 patients with infectious syphilis (9). Of sixty pa-

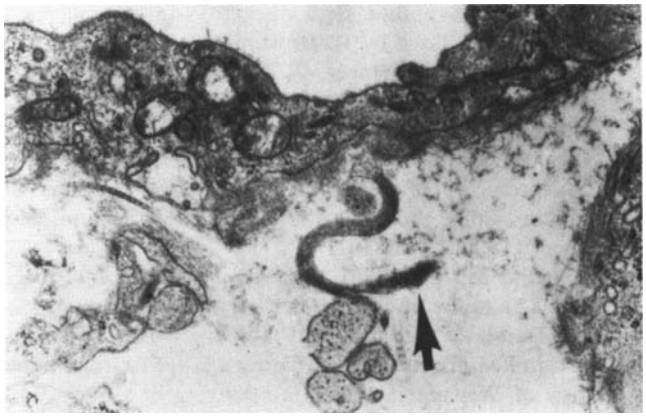

**Figure 7.** Experimentally induced rabbit syphilitic orchitis. A treponeme (**arrow**) is seen coiling in the extracellular space, but the typical spirals are absent. [Electron micrograph × 25,000 from Lauderdale et al (6), courtesy of the British Journal of Venereal Diseases.]

tients with musculoskeletal complaints, 27 had clinical bone involvement, 21 had joint symptoms, and in 12, bone and joints were involved together. Seventeen patients were considered to have only arthralgias while 5 had actual arthritis of knees, hips, and shoulders (9). Recent reports from Europe (2,3) have also shown prominent involvement of knees but also occasional synovitis of fingers and shoulders, ranging from subacute to chronic duration of symptoms. The patients in the present study, as noted in Table 1, had subacute disease with prominent involvement of knees, but often had ankle arthritis, as well. Symmetrical arthritis seemed more frequent in the present series than in the others. The nonmigratory character of the arthritis and the invariable association with characteristic mucocutaneous manifestations of secondary syphilis helped in diagnosis.

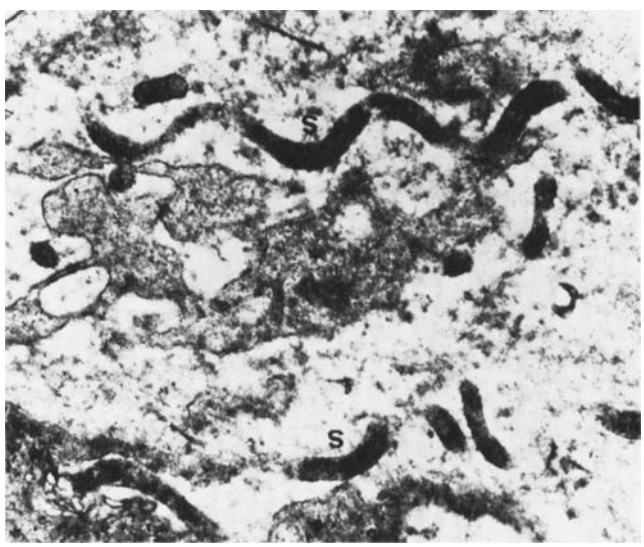


**Figure 8.** Penile syphilitic chancre. Spirochetes (**S**) in interstitial spaces of perivascular area are seen. [Electron micrograph × 24,000 from Azar et al (5), courtesy of Archives of Pathology.]

Two of 7 of these patients with arthritis also had nontender swelling of the extensor tendon sheaths of both hands while 1 had tenosynovitis of the ankles. Since there was no increase in local heat or redness, it resembled more the tenosynovitis frequently seen in rheumatoid arthritis than that of gonorrhea (Figure 1). No needle aspiration of these areas was performed. Although tenosynovitis is also commonly seen in gonococcemia, this form is characteristically very painful and associated with signs of acute inflammation (10). None of these patients had urethral or vaginal discharge and all synovial fluid cultures were negative for gonococci. Two of the patients with arthritis had pain and mild swelling of both sternoclavicular joints. Roentgenograms showed these joints were normal and no articular aspiration was performed. Whether low grade osteitis was present is unknown. Recently $^{99m}$technetium bone scans were reported to detect areas of osteitis despite normal bone roentgenograms in one patient with secondary syphilis and sternoclavicular involvement (11).

In most of the published cases of secondary syphilis with synovitis, diagnosis has been based on clinical and serologic findings, without identification of spirochetes in the synovial membrane or synovial fluid (1–3,12,13). Early this century, Chesney was able to recover spirochetes in 3 cases after synovial fluid inoculation into rabbit testicles (14). Dark field examinations of synovial fluid in 2 of our patients (Cases 4 and 5) and in other studies of joint effusions in congenital and secondary syphilis have been negative (2,13,14), however. Identification of treponeme-like bodies in two joints by electron microscopy in the present study supplies renewed support for direct invasion of the joints. Spirochete-like bodies in these two synovial biopsies have some coiling typical of spirochetes and the characteristic longitudinal filaments even though cell membrane structure is not well defined. Loss of cell membrane has also been described in other studies including one of rabbit syphilitic orchitis, where the authors noted that phagocytized treponemes were also shorter and more dense (6) (Figure 7). The treponemes were found in areas of the synovial membrane that showed considerable necrosis and were almost certainly altered by the

inflammatory process. The rapid resolution of arthritis after treatment with penicillin also supports the infectious etiology.

It seems possible that spirochetes might also be easily identified in joints in secondary syphilis by using more modern methods such as the immunofluorescent antitreponemal antibody technique. With this method spirochetes have been identified in aqueous humor and in spinal and synovial fluid of a patient with latent syphilis (15); spirochete antigens have been identified in the kidney of a patient with acquired syphilitic glomerulonephritis (16). This technique is not generally available and dark field examination in experienced hands is still the most reliable method for identification of *Treponema pallidum* on promptly examined fresh preparations (17). No electron-dense deposits like those described in the glomeruli of patients with syphilitic glomerulonephritis were seen in the synovial membrane vessels (16). The extracellular localization of the spirochete-like bodies in our electron microscopic studies is similar to electron microscopic studies performed in other primary or secondary syphilic lesions (Figure 8) and provided little information about the mechanisms by which spirochetes might induce inflammation (5–8).

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