

## SYNOVIAL PATHOLOGIC CHANGES IN SPONTANEOUS CANINE RHEUMATOID-LIKE ARTHRITIS

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The synovial fluid and membrane were studied in 10 dogs meeting the American Rheumatism Association criteria for classic human rheumatoid arthritis (RA). Light microscopic pathologic features were consistent with those found in the human disease. Neutrophilic infiltration of synovium was somewhat more prominent than in chronic human RA, and activated lymphocytes in fluid or membrane were less frequent. The proliferative and plasma cell reaction seemed identical. Electron microscopy (EM) suggested microvascular injury with findings which included electron dense deposits in the vessel walls of 2 dogs. Seven dogs had meshworks of 20–25 nm tubules in tubuloreticular structures (TRS) similar to those seen in human systemic lupus erythematosus and only occasionally in human RA. There were also crystalline arrays of tubules, a configuration previously reported in tumors and virus infections and possibly suggestive of a cellular reaction to virus infection. To date no initiating agent has been identified, but this spontaneous canine disease which is very similar to human RA can provide a valuable model in which to examine pathogenesis of chronic arthritis.

A spontaneous, chronic, erosive polyarthritis similar to human rheumatoid arthritis (RA) occurs in dogs (1–3). This arthritis is of importance to rheumatologists because it may provide the first spontaneously occurring model for the human disease. A preliminary study suggests that canine RA can be responsive to gold salt therapy (4). It is also intriguing that epidemiologic studies (5,6) have shown a greater exposure of human RA patients to dogs and other pets during the 5 years prior to onset of disease than for osteoarthritis and patients with other miscellaneous minor musculoskeletal problems. Examples of coincidental arthritis in pets and owners have been found. Household dogs of patients with systemic lupus erythematosus (7) have also recently been suggested to be clinically and serologically involved. This report describes the gross and the light and electron microscopic (EM) synovial changes in 10 dogs with canine arthritis that fulfilled the American Rheumatism Association (ARA) criteria for classic RA (8).

### MATERIALS AND METHODS

All dogs presented to the University of Pennsylvania Veterinary Hospital (UPVH) were screened for symptoms of arthritis. After eliminating from the study dogs with degenerative joint disease, septic arthritis, and polyarthritis associated with systemic lupus, 10 dogs were further studied by x-ray, Rose-Waaler tests for rheumatoid factor, clinical examination, and biopsies to identify those with a definite diagnosis of rheumatoid arthritis.

All dogs diagnosed as having canine rheumatoid-like arthritis met at least 7 of the ARA criteria for a diagnosis of human rheumatoid arthritis (8). Canine RA-like arthritis affected both pure and mixed breeds. The age range at initial presentation was from 13 months to 8 years, and age at onset was from 5 months to 7 years, with 1 male and 9 females affected. Seven dogs had rheumatoid factor titers according to

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**Table 1.** Clinical features and synovial fluid finding in rheumatoid-like disease in dogs

Dog no.	Sex*	Arthritis duration, months	Drugs†	WBC/mm <sup>3</sup> ‡	% PMN§	% small lymphs	% activated lymphs	% mono-cytes	% large macrophages	% SLC¶	% eosinophils
1	F	18	Gold		10	44	0	3	0	43	
2	M	6		6,500	15	15	0	40	10	10	
3	F	18	0		2	62	6	5	0	25	
4	F	12	ASA	54,000	94	2	0	0	4	0	
5	F	18	ASA		40	31	7	13	6	4	2
6	FS	2	0	5,800	81	7	2	4	2	3	
7	F	6	0		85	9	0	1	1	4	
8	FS	24	ASA		38	42	0	10	0	0	
9	F	18	ASA								
10	F	8	0								

\* F = female; M = male; FS = spayed female.  
 † Dog no. 1 received 12 injections of gold. ASA = aspirin.  
 ‡ WBC = leukocyte count.  
 § PMN = polymorphonuclear neutrophils.  
 ¶ SLC = synovial lining cells

No fluid studied  
 No fluid studied

the standard Rose-Waaler technique (1,9) ranging from 1:18 to 1:256. Of 100 normal control dogs and 25 dogs with other inflammatory diseases, only 5% of each group had rheumatoid factor titers, none higher than 1:16. No animals had positive LE cell preparations, Coombs tests, or antinuclear antibodies.

The joints primarily affected with the disease were the large peripheral joints, i.e., carpus, tarsus, knee, and elbow. The metacarpophalangeal, metatarsophalangeal, and interphalangeal joints were less prominently affected. Erosions of multiple joints were seen in all 10 dogs reported here.

Gross changes in synovial membrane of rheumatoid-like joints were noted at surgical synovial biopsy in 7 animals or on gross pathologic examination at necropsy in the remaining 3 animals.

Histopathologic examination was performed on multiple specimens from the affected joints of the 10 rheumatoid dogs. Specimens were collected in 10% formalin or Bouin's solution and processed through routine paraffin embedding and sectioning. Hematoxylin and eosin staining was performed on all synovial membranes.

Electron microscopy was performed on specimens obtained simultaneously with those collected for light microscopy and immediately placed in 1/4 strength Karnovsky's paraformaldehyde-glutaraldehyde fixative (10).

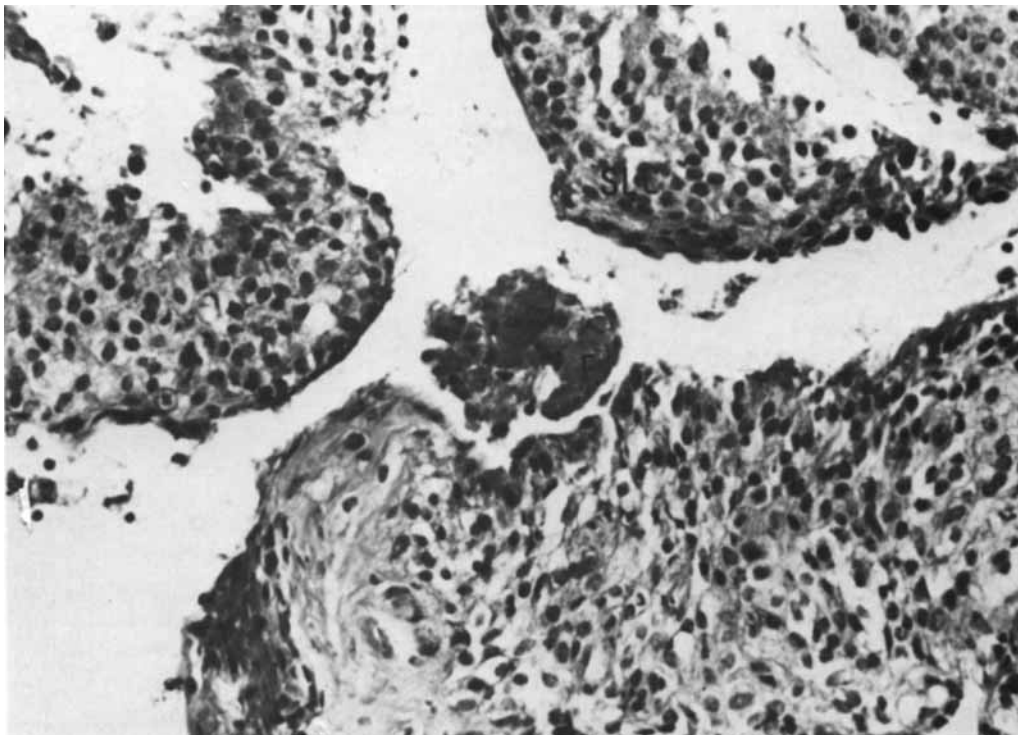
Specimens were diced into 1 x 1 mm pieces, fixed for a total of 4 hours at room temperature, washed in 0.1M sodium cacodylate buffer at 4°C, post fixed in cold Palade's osmium-veronal for 2 hours, and then dehydrated in alcohol. They were then placed in 50% propylene oxide and Epon mixtures over 2 hours and embedded in Epon 812. Thick sections (1µ) were cut on an LKB-2 ultramicrotome with a glass knife and stained with toluidine blue for orientation. Thin sections were cut with a diamond knife, stained with uranyl acetate and lead citrate, and then examined on a Zeiss EM-10 electron microscope with a 60 KV beam. In 2 dogs, EM histochemical staining for acid phosphatase was performed by using a modified Gomori technique (11).

Synovial fluid was collected from affected joints of 8 dogs and smeared and stained with Wright's and Sudan stains (Table 1). In most instances there was insufficient fluid to pro-

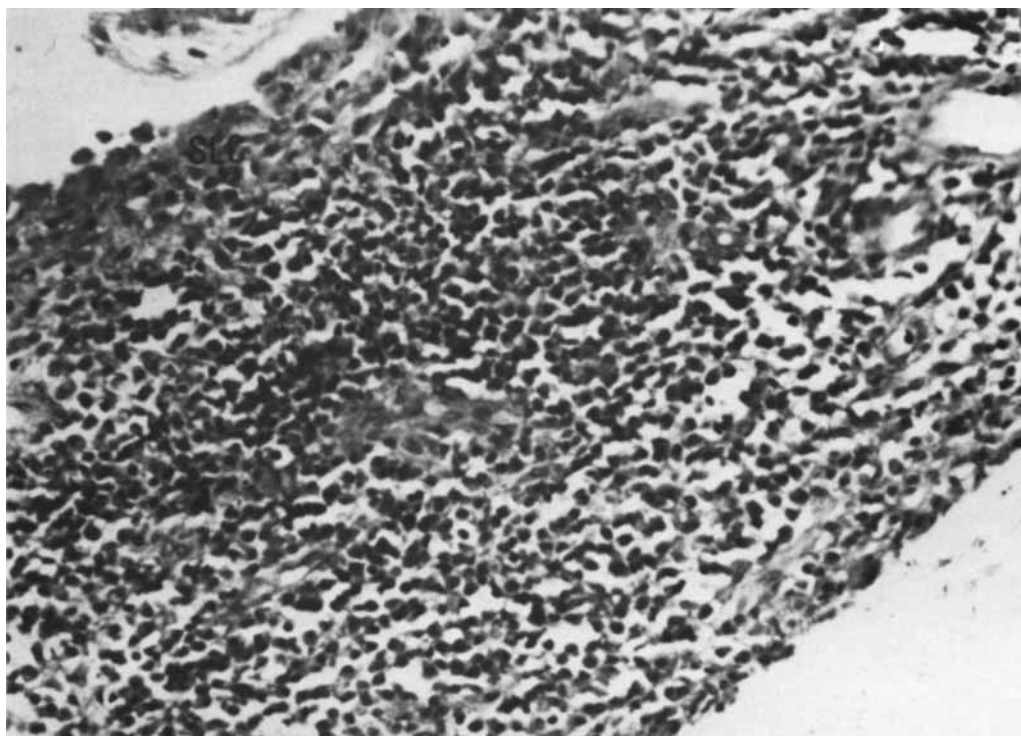
**Table 2.** Light microscopic synovial membrane findings in rheumatoid-like disease in dogs\*

Dog no.	Superficial fibrin	Polymorpho-nuclear neutrophils	Lymphocytes	Plasma cells	Congested vessels	Synovial lining cell proliferation	Hemosiderin in deep macrophages	Edema
1			+	+++		+		
2	+	+		++			+	
3	+			+++	+	+	+	
4	++			++	+	+	+	
5	++	+	+	++				
6	+		+	++		+		+
7	+	+		++		++		+
8		+	+	++	+	+		
9	++	++	+	++		+	+	+
10				++		++		+

\* + = occasional; ++ = intermediate; +++ = extreme amount.



**Figure 1.** Superficial fibrin (F) and hyperplastic lining cells (SLC) in dog no. 3. (Hematoxylin and eosin; magnification  $\times 200$ .)



**Figure 2.** Synovial villus from dog no. 8 showing hyperplastic lining cells (SLC) and moderate chronic inflammatory cell infiltration which includes some plasma cells. (Hematoxylin and eosin; magnification  $\times 200$ .)

Table 3. Electron microscopic synovial membrane findings in rheumatoid-like disease in dogs\*

Dog no.	Superficial fibrin	Superficial granular material	SLC types†			PMN‡	Lymphocytes	Plasma cells	Deep phagocytic cells	Interstitial debris	Gaps between endothelial cells	Increased layers of vascular basement membrane	Extra-vasated RBC or iron in macrophages	TRSS§	Crystalline arrays
			A	B	C										
1		+						++							+
2		+					+	++	++		++				+
3	+							++	++		++				+++
4	+++							++	++		++				+++
5	+++							+++	++		++				+++
6	+							+++	++		++				+++
7	+						+	+++	++		++				+
8	+++							+	++		++				+++
9	+++							+	++		++				+++
10		++						+	++		++				+++

\* + = occasional; ++ = intermediate; +++ = extreme numbers.  
 † SLC = synovial lining cells.  
 ‡ PMN = polymorphonuclear leukocytes.  
 § TRS = tubuloreticular structures.

vide accurate cell counts or cells for EM examination. All synovial biopsies were obtained before any treatments, other than aspirin, were given to the animals. One joint fluid was obtained after initiation of gold salt therapy (Table 1). Synovial fluid cells were classified by Wright's and Sudan stains as described by Traycoff et al (12).

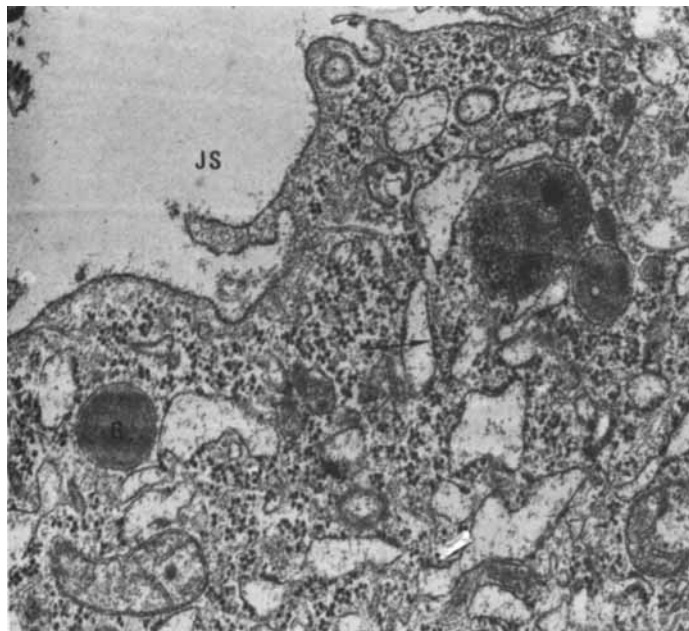
RESULTS

**Gross findings.** Gross changes included striking synovial proliferation with bony and cartilaginous destruction. All 10 dogs demonstrated proliferative, brown, discolored synovium that in most instances was markedly thickened 1-3 mm. There were large papillae of synovium and long fingers of fibrin present in 4 animals. Mild invasion of synovial tissue into subchondral bone was present in 3 dogs, and massive invading pannus was present in the other 7.

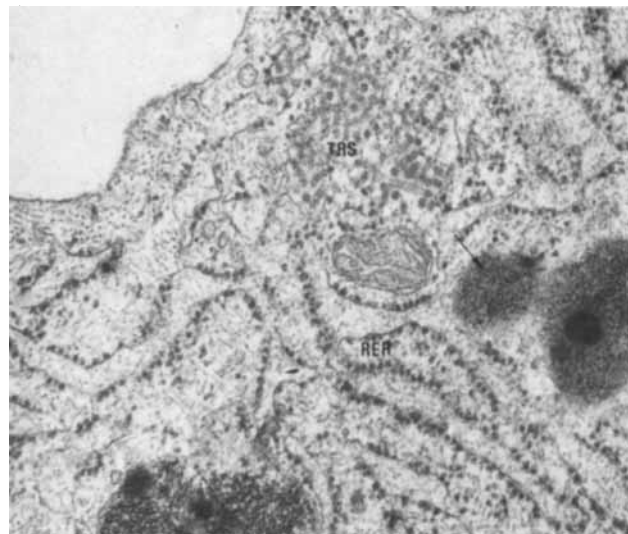
**Light microscopy.** Table 2 delineates the light microscopy findings. Histologically, synovium demonstrated marked lining cell proliferation in 8 of the dogs examined (Figures 1 and 2). In most instances the underlying connective tissue was equally proliferative with increased numbers of fixed tissue cells. Infiltration of the underlying connective tissue with plasma cells occurred in all 10 dogs (Figure 2). The plasma cells were found to be scattered diffusely in most dogs, although focal aggregations were found as well. More than rare lymphocytes were also found in the synovium of 5 dogs. The lymphocytes were diffusely scattered throughout two of the synovial membranes and were present in more focal aggregates in two. Infiltration with polymorphonuclear neutrophils (PMN) was seen in 5 dogs; in these tissues, the PMN were diffuse in 3 dogs and focal in the other 2.

Deposits of acellular fibrin were easily demonstrated on the synovial surface in 7 dogs (Figure 1). Hemosiderin was recognizable in deep macrophages in 6 dogs. Congested capillaries were seen in 3 tissues and edema in 2.

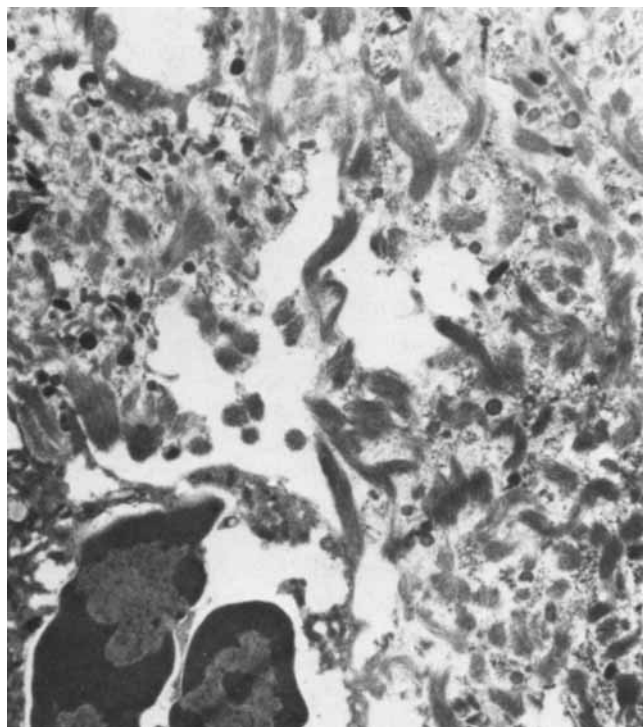
**Electron microscopy.** Table 3 shows the EM results. Ultrastructural studies allowed some extension of the light microscopic findings. Finely granular material was frequently mixed in with the prominent surface fibrin. Lining cells could be characterized as including types A (phagocytic), B (synthetic), and C (intermediate) cells (13) with B and C cells (Figure 3) predominating only slightly. Finely granular material and cell debris were phagocytized by some type A lining cells and by prominent deep phagocytic cells. Considerable deep interstitial necrotic debris and fibrin (Figure 4) were found in 3 synovial membranes, as in human RA. The pattern of inflammatory cell infiltration with



**Figure 3A.** Synovial lining cell from dog 4. Intermediate or C type lining cell with vacuoles containing finely granular material (G) and primarily cross sections of 20–25 nm tubules (T) closely packed in one vacuole. Note moderate amount of rough endoplasmic reticulum (arrow): JS = joint space. (Electron micrograph,  $\times 15,000$ .)



**Figure 3B.** Synovial lining cell from dog no. 10. Type B or intermediate lining cell with tubuloreticular structures (TRS), rough endoplasmic reticulum (RER), and some membrane bound bodies containing dense ferritin granules (arrows). (Electron micrograph,  $\times 48,000$ .)



**Figure 4.** Interstitial fibrin, apparent cell debris including unidentified round particles of various sizes, and degenerating polymorphonuclear cell at the bottom. (Magnification  $\times 18,000$ .)

predominant plasma cells (Figure 5) was similar to that seen by light microscopy. Note that despite examining multiple blocks by EM, sampling still was limited so that inflammatory cells, for example, were not seen by EM in all dogs. Interstitial polymorphonuclear cells were degenerating (Figure 4) or degranulating in 3 synovia. Plasma cells often had dramatically dilated rough endoplasmic reticulum. Activated lymphocytes with polyribosomes were not identified.

Vessels showed occasional gaps (Figure 6) between endothelial cells and multilaminated basement membranes, but no vessel wall necrosis, fibrinoid, or evidence of virus-like particles was observed. Electron-dense deposits were seen in vessel walls of 2 dogs (Figures 6 and 7), and degranulating polymorphonuclear cells and platelet clumps (Figure 6) were present in vessel lumens of 2 dogs each.

Occasional extravasated erythrocytes and iron in deep macrophages were consistent with the light microscopic finding of hemosiderin deposits in some dogs. Seven synovia had prominent lipid droplets in deep synovial cells or lining cells. No identifiable bacterial or other organisms were found.

Tubuloreticular structures (TRS) as typically seen in human SLE (14–16) were seen in 7 dogs (Figures 3, 8, and 9). These were seen in endoplasmic reticu-

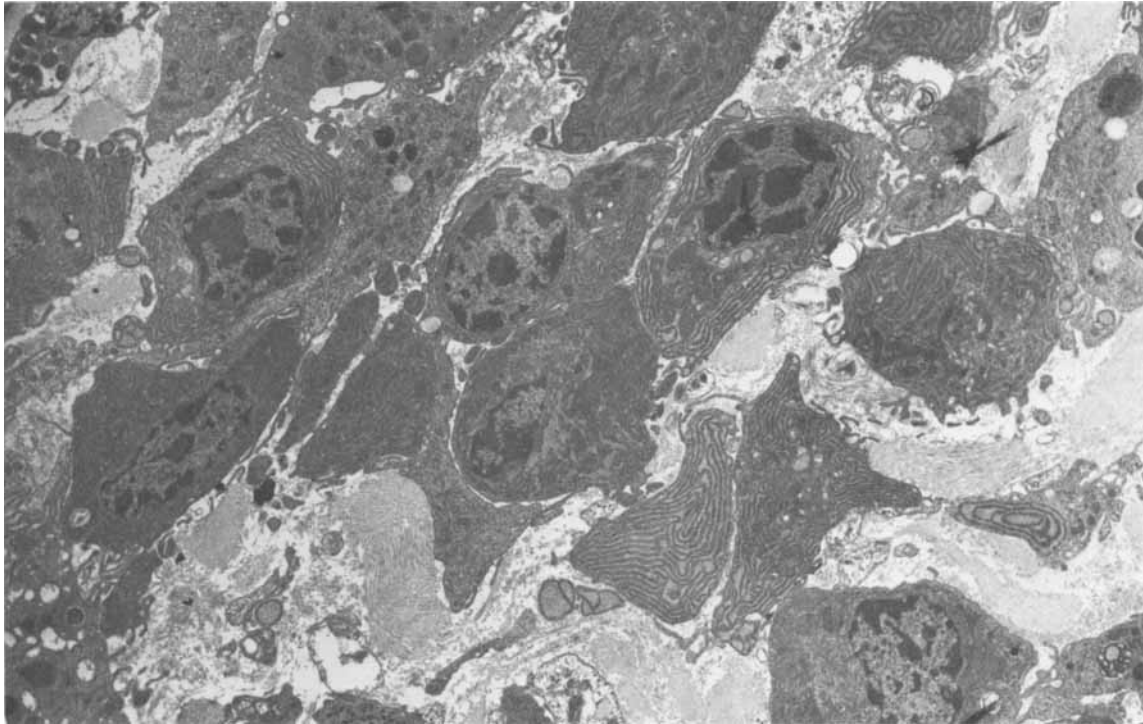


Figure 5. Deep synovial plasma cell infiltrate from dog no. 4. (Electron micrograph,  $\times 4,000$ .)

lum (ER) or adjacent to ER in the cytoplasm of lining cells and deep synovial cells with prominent rough ER. Some TRS-containing cells appeared to be plasma cells. Tubules 20–25 nm in diameter were arranged in a loose (or occasionally tightly packed) random meshwork.

Tubules of similar 20–25 nm diameter were also seen in crystalline arrays (Figure 10) in 9 dogs including all 7 who had identifiable TRS. Crystalline arrays were documented in cross and longitudinal sections. Some were in the ER, but others were in the cytoplasm or in membrane-bound dense bodies. Acid phosphatase EM histochemistry confirmed the lysosomal nature of these dense bodies with crystalline arrays of tubules in 2 dogs (Figure 11). TRS were never seen associated with acid phosphatase positive areas. Cells with the crystal-like arrangement of tubules in dense bodies also frequently contained other unidentified, highly dense, lipid-like or finely granular material or ferritin granules.

In 3 dogs some round vesicle-like bodies mixed with various types of cell debris were seen in occasional vacuoles or in interstitium (Figure 5). None strongly suggested any specific virus or other organism.

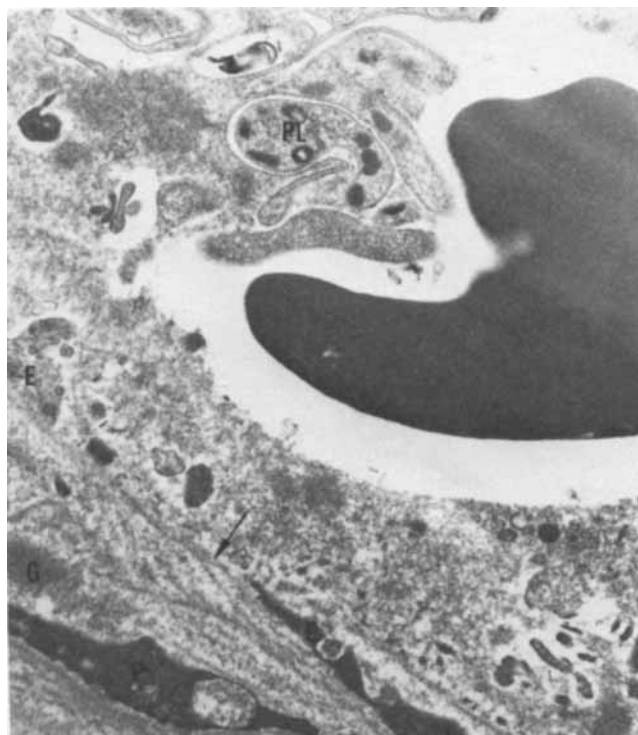
Twenty control dog synovial membranes were reviewed. No TRS were found in 7 normal mongrels used for experimental injection of urates (17), 10 normal mongrels used in study of joint trauma, or 3 osteo-

arthritic dogs. In two of the supposedly normal mongrels, small crystal-like arrays of membrane bound tubules were found in lining cells.

**Synovial fluid analysis (Table 1).** Total cell counts on the 3 synovial fluids with sufficient volume for leukocyte counts ranged from 5,800 to 54,000/mm<sup>3</sup>. The widely varying differential counts found are shown in Table 1. PMN predominated in 3 fluids. There were no large mononuclear cells that had phagocytized PMN ("Reiters cells"), LE cells, or other unusual features.

## DISCUSSION

Since first being reported in the last 10 years (1–3), canine rheumatoid-like arthritis has begun to receive attention as a potential animal model of human disease. Major studies of the disease have been reported from the University of California at Davis (2) and the University of Pennsylvania (1,4,9). Case reports account for an additional 15 cases present in the literature (3,18). All reports agree on the major gross and histopathologic findings. These are described as villous proliferation, hyperplastic synovium, fibrin deposition over the proliferative synovium, bony erosions, and infiltration with mononuclear cells including plasma cells. Pederson (2) did not mention the PMN which were also seen in some



**Figure 6.** Electron-dense, finely granular deposits (G) between venular endothelium (E) and pericyte (P) in synovium of dog no. 3. Note the large gap (arrow) between the endothelial cells and considerable cellular or other debris that is present in the vessel lumen but not in dense deposits. Erythrocyte and platelets (PL) are also present in the lumen. (Electron micrographs, magnification  $\times 19,000$ .)

of our dogs, but Scott did (18). Otherwise, our light microscopic findings differ little from previous reports. These findings meet the ARA criteria as characteristic of human RA synovium (8). Necrosis also mentioned in the ARA criteria was not usually appreciated by light microscopy but was seen prominently by EM in 3 dogs. Polymorphonuclear cell infiltration in synovium in our series and in the dog studied by Scott (18) appeared to be slightly more common than in human RA. However, PMN can be seen in some chronic human RA synovial membranes and are even more common in early RA (19). The prominence of hemosiderin deposits was more marked than in most reports of human RA, possibly because dogs abused actively inflamed joints more than humans. Iron was localized, as it is in human RA synovial membranes, predominantly in deep phagocytic cells (20).

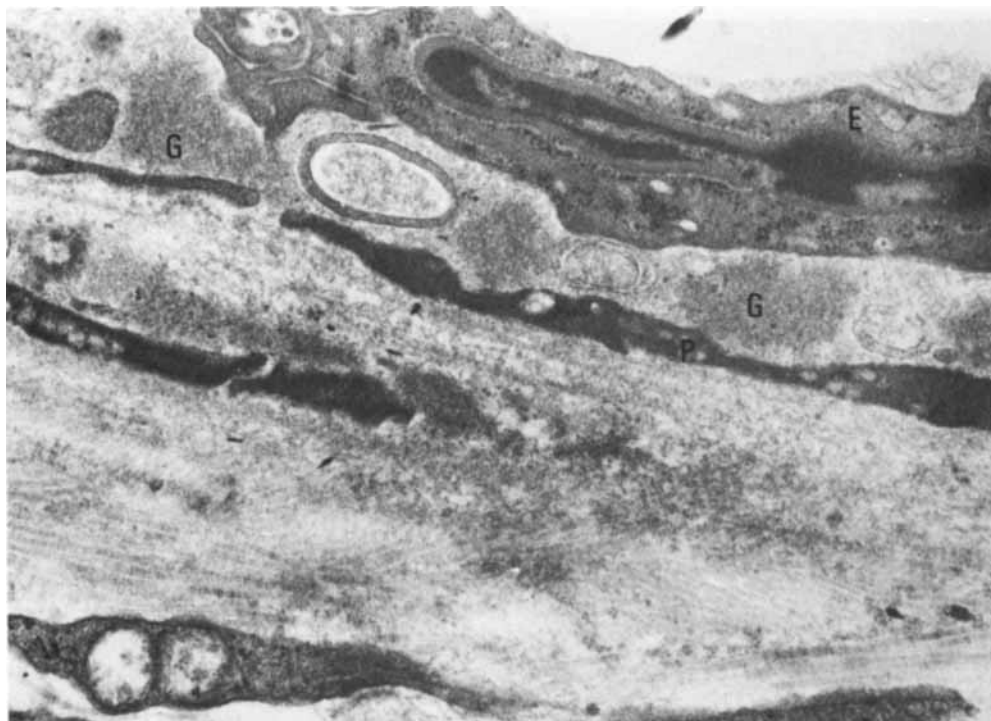
We previously reported a single case of only limited EM findings in canine rheumatoid-like arthritis (9);

no other report appears in the literature. The absence of activated lymphoblasts in our synovial biopsies appears to be different from human RA (21), but this may represent in part a sampling problem since activated lymphocytes were seen in some synovial fluids.

Microvascular changes have not been as prominent in human RA of chronic duration as in these dogs, but these changes have been emphasized in early human RA of up to 6 weeks duration (19,22). The presence of large electron-dense deposits in vessel walls of 2 dogs resembled findings in some early human RA (19) which suggests the possibility of deposition of immune complexes in these vessels. These dense deposits in the dogs have not yet been further characterized. Platelet plugging, degranulating intraluminal cells, gaps between endothelial cells, and multilaminated vascular basement membranes were also evidences of some microvascular injury.

The tubuloreticular structures found in synovial membranes in 7 of our rheumatoid dogs are familiar to rheumatologists because of their frequent occurrence in human systemic lupus erythematosus (14–16). They have also occasionally been described in human RA (14,23). To our knowledge, EM studies to search for TRS in synovial membrane or other tissues in canine SLE have not been performed. Tubuloreticular structures have also been identified in various other tissues (in addition to synovium) of patients with systemic lupus erythematosus (14–16), in muscle tissue of patients with dermatomyositis (14,29,30), and in a variety of sites in other diseases. They have been found in infectious mononucleosis (31), human lymphoma cell lines growing herpes simplex (32), human herpes encephalitis cerebral tissue (33), dog intestine in coronavirus infection (34), and a variety of tumors (35). Thus there seems to be a suggestion of association of TRS with rheumatic disease, virus infection, and neoplasm. The nature and cause of TRS are not known. Tubuloreticular structures differ from paramyxoviruses, including canine distemper virus, by the regular association of TRS with the endoplasmic reticulum and the smaller (15–17 nm) diameter fibrillar nucleocapsids of the virus (24,25). Although nucleic acid is apparently not demonstrable in TRS (36), Pincus et al (37) have suggested that they might be a cellular reaction to virus infection.

The crystalline arrays of tubules seen in 9 rheumatoid-like dogs have not been reported in human RA. These inclusions appear virtually identical to clumps of cytoplasmic tubular arrays without binding membranes found in the cytoplasm of endothelial cells in placentas



**Figure 7.** Electron-dense, finely granular deposits (G) between venular endothelium (E) and pericyte (P) in synovium of dog no. 8. (Electron micrograph, magnification  $\times 34,000$ .)

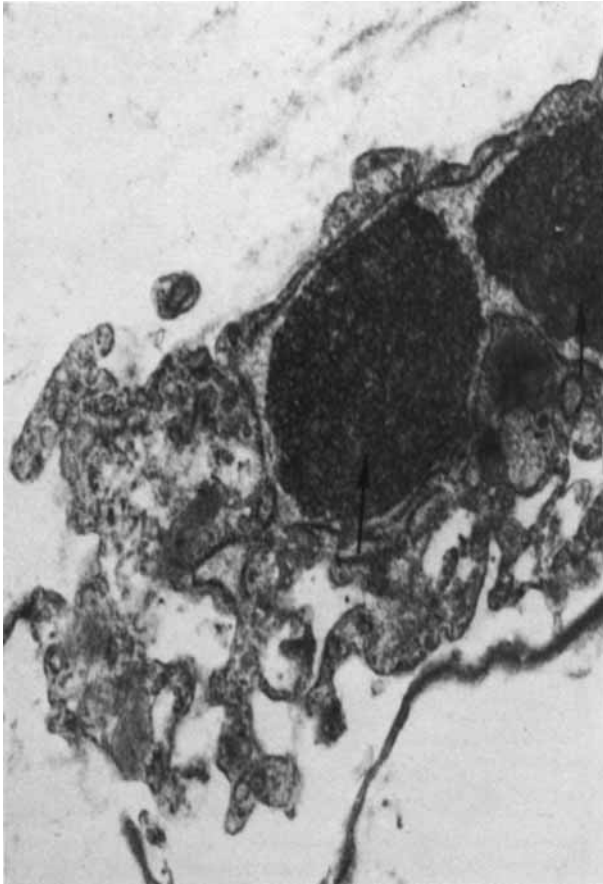
from patients with SLE; such inclusions are not found in normal placentas (26). Those in the human material were believed to be protein of unknown type and could be distinguished morphologically from the membrane-bound Weibel-Palade bodies (27) which earlier had been confused with viruses (28). The significance of the crystalline arrays, as with the TRS, is unknown, but they have also been suggested to possibly be a result of virus-cell interaction because of the other diseases in which they are seen. Crystalline arrays have been reported in ER and dense bodies of dogs with meningeal tumors induced by Rous sarcoma virus; they are not found in normal dog meninges (38). Similar arrays have also been seen in a wide variety of other virus infections including monkey kidney cell cultures infected with rubella virus (39), rabbit experimental herpes encephalitis (40), and Aleutian disease of mink (41). Schaff et al (42) have found crystalline arrays of similar tubules with light cores that are an estimated 25 nm (22–28 nm) in diameter in ER of rabbit myxosarcomas. There were also identical size tubules in ER arranged more like the typical tubuloreticular structures in the same tumors. Schaff (36) and others (43) have suggested that there

may be a relationship between the two types of tubules. Some relationship is also supported by our studies showing the 2 kinds of structures together in 7 of the RA dogs and some densely packed, but not crystalline, TRS (Figure 8) that might suggest a transition phase between these and crystalline arrays seen in rough endoplasmic reticulum.

No type C particles or coronavirus-like particles have been found in our dogs. They have occasionally been noted in human rheumatoid synovial membrane only with very early disease (19) or with cocultivation (44). The wide variety of types of debris in the dog synovium as well as human RA could certainly harbor material from an infectious agent that is no longer morphologically identifiable.

There have been a few light microscopic studies of dog synovial membrane in other states that should be compared with our rheumatoid-like dog findings. Dog synovial membrane in culture-positive chlamydia arthritis has been described by Young et al (45) as showing large amounts of superficial fibrin, hyperplastic lining cells, and infiltration of neutrophils and plasma cells. A group of culture-negative dogs (46) with non-





**Figure 8.** Tubuloreticular structures packed densely in cisterns of rough endoplasmic reticulum (arrows) in deep synovial cell of dog no. 3. (Electron micrograph, magnification  $\times 31,000$ .)

erosive arthritis, including some with SLE and some undiagnosed, were reported to show superficial fibrin, a paucity of synovial lining cells, and predominantly neutrophilic infiltration with mononuclear cells. There was no villous hyperplasia or pannus. Dogs whose knees were experimentally injected with cartilage homogenate (47) developed synovial round cell infiltration after several months. As with human disease, most synovial membrane findings are not diagnostic. RA findings can be mimicked by other diseases, but synovial findings in conjunction with other features can be helpful in diagnosis (8).

Previous electron microscopic studies on dog synovium in other diseases include those of Huxtable and Davis (48) who studied synovia of 17 young greyhounds with erosive inflammatory polyarthritis and negative tests for rheumatoid factor. Electron microscopic find-

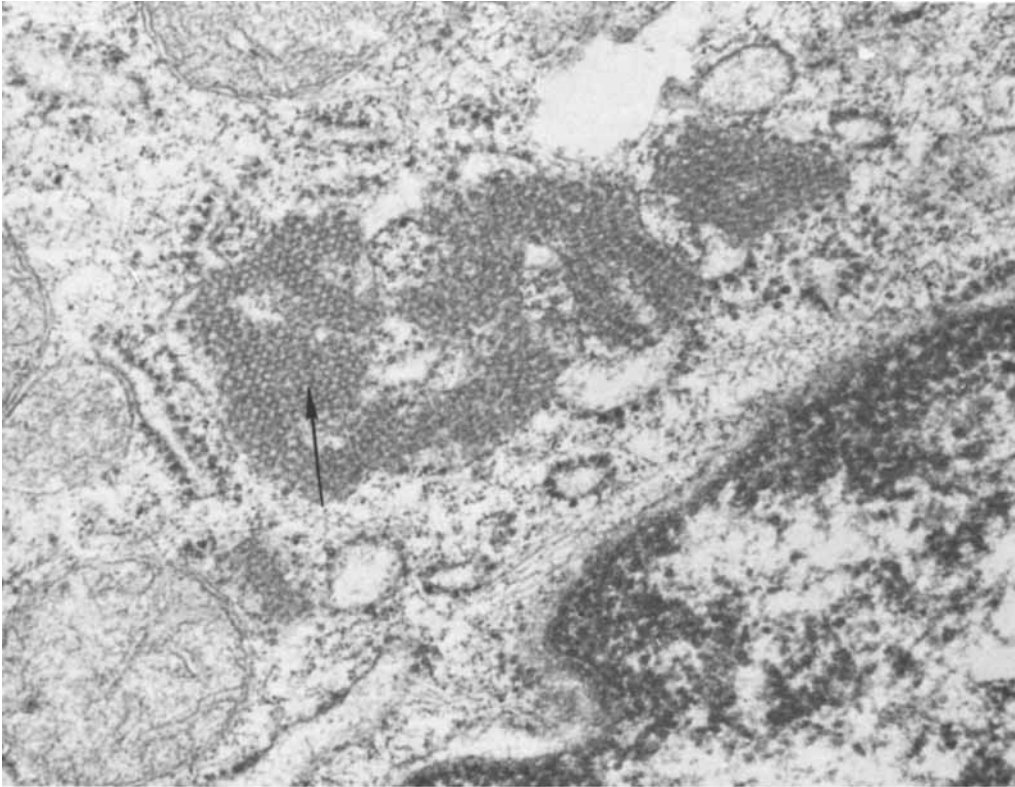
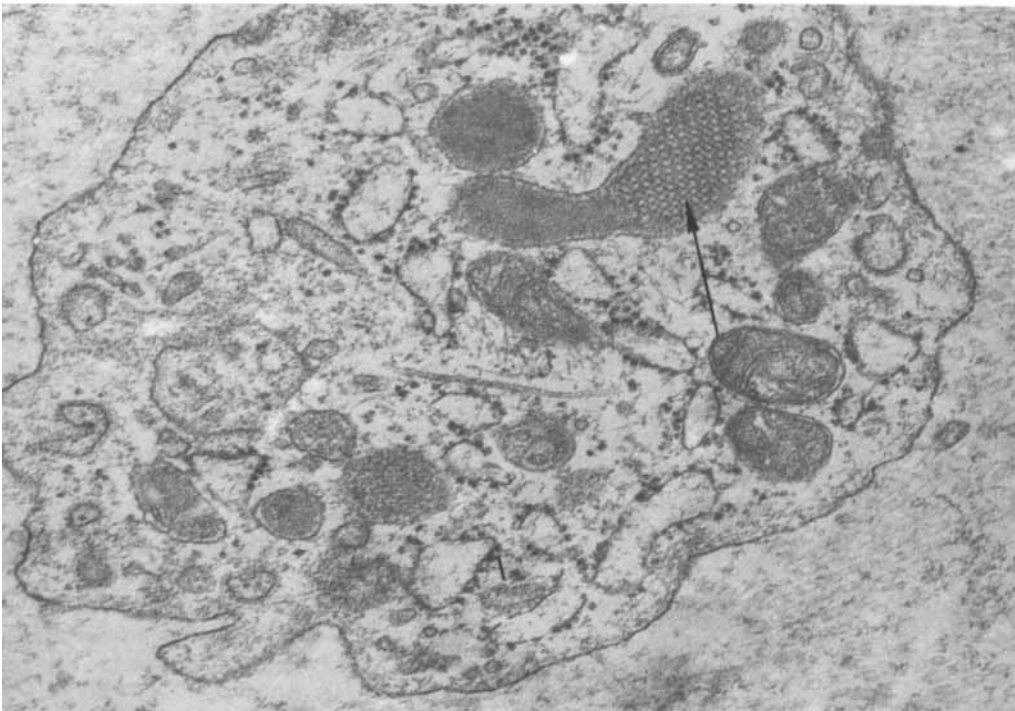
ings reported included increased numbers of intermediate type (13) synovial lining cells, some of which included large vacuoles containing particles of various sizes and electron density. They did not report TRS or crystalline arrays or evidence of infectious agents. As noted above, we have observed occasional crystalline arrays but not TRS in apparently normal dog synovium.

The synovial fluid findings in our dogs with RA-like disease are quite consistent with the generally accepted findings in human RA (49). Polymorphonuclear neutrophils or mononuclear cells predominated in different fluids. Prominence of activated lymphocytes, which we recently reported in human RA effusions (12), was seen in only 2 dogs.

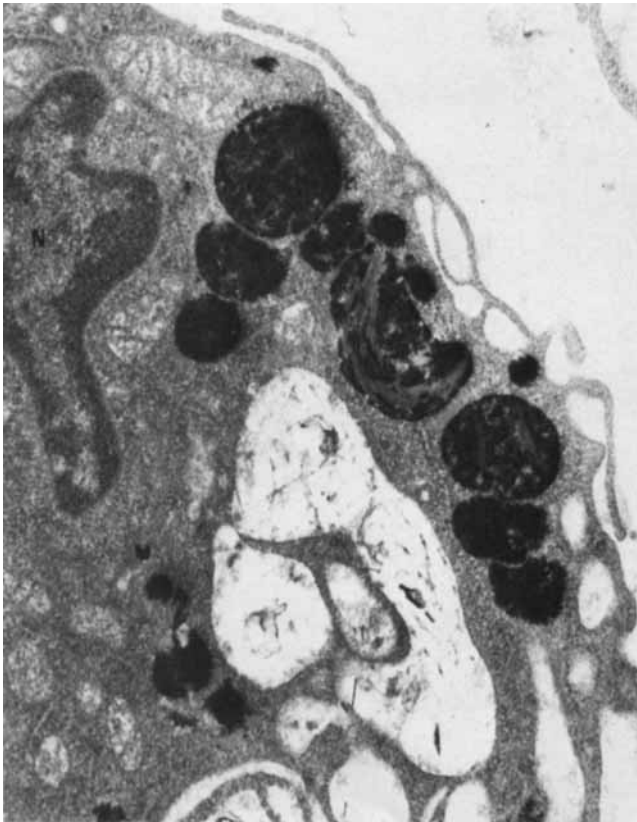
We recognize that dogs with systemic lupus erythematosus can also have polyarthritis (50,51). Systemic lupus was excluded in our dogs by absence of any of the characteristic clinical or laboratory findings. We are not aware of EM studies on lupus synovium in dogs. A light microscopy study (50) on synovium of a dog with fea-



**Figure 9.** Loosely packed tubuloreticular structures at the rough endoplasmic reticulum of dog no. 6. (Electron micrograph, magnification  $\times 38,000$ .)

**A****B**

**Figure 10. A**, Crystalline arrays of 20–24 nm tubules in cross section (**arrow**) were closely associated with the rough endoplasmic reticulum in dog no. 10. (Electron micrograph, magnification  $\times 40,000$ .) **B**, Crystalline arrays, as described in A, found in dense bodies in dog no. 3. (Electron micrograph, magnification  $\times 31,000$ .)



**Figure 11.** Acid phosphatase histochemistry clearly identifies some light crystalline longitudinally cut parallel tubular arrays lying with the dark enzyme in lysosomes. N = nucleus. (Electron micrograph, magnification  $\times 36,000$ .)

tures of systemic lupus, as well as a destructive arthritis, demonstrated surface fibrin, increased villi, clumps of infiltrating lymphocytes, plasma cells, and perivascular neutrophils.

This model, which we consider to very closely mimic human RA, nevertheless does have some differences as documented above. We believe that rheumatoid-like dogs are potentially useful for studies of therapy. We are studying pathogenetic mechanisms in hopes that they will provide clues to mechanisms in human disease.

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### REFERENCES

1. Newton CD, Lipowitz AJ, Halliwell RE, Allen HL, Biery DN, Schumacher HR: Rheumatoid arthritis in dogs. *J Am Vet Med Assoc* 168:113-121, 1976
2. Pedersen NC, Pool RC, Castles JJ, Weisner K: Non-infectious canine arthritis. *J Am Vet Med Assoc* 169:295-303, 1976
3. Liu S, Suter PR, Fischer CA, Dorfman HD: Rheumatoid arthritis in a dog. *J Am Vet Med Assoc* 154:495-502, 1969
4. Newton CD, Schumacher HR, Halliwell RE: Effectiveness of gold therapy in canine rheumatoid arthritis. *J Am Vet Med Assoc* 174:1308-1309, 1979
5. Gottlieb NL, Ditchek N, Polley J, Liem IM: Pets and rheumatoid arthritis: an epidemiologic survey. *Arthritis Rheum* 17:229-234, 1974
6. Schumacher HR: Unpublished studies, 1978
7. Beaucher WN, Garman RH, Condemi JJ: Familial lupus erythematosus: antibodies to DNA in household dogs. *N Engl J Med* 296:982-984, 1977
8. Ropes MW, Bennet GA, Cobb S, et al: Revision of diagnostic criteria for rheumatoid arthritis. *Bull Rheum Dis* 9:175-176, 1958
9. Newton CD, Allen HL, Halliwell RE, Schumacher HR: Clinicopathologic conference. *J Am Vet Med Assoc* 165:459-464, 1974
10. Karnovsky MJ: A formaldehyde glutaraldehyde fixative of high osmolality for use in electron microscopy (abstract). *J Cell Biol* 27:441, 1965
11. Miller F, Palade G: Lytic activities in protein absorption droplets. *J Cell Biol* 23:513-519, 1964
12. Traycoff RB, Pascual E, Schumacher HR: Mononuclear cells in human synovial fluid: identification of lymphoblasts in rheumatoid arthritis. *Arthritis Rheum* 19:743-748, 1976
13. Barland P, Novikoff A, Hamerman D: Fine structure and cytochemistry of the rheumatoid synovial membrane with special reference to lysosomes. *Am J Pathol* 44:853-866, 1964
14. Gyorkey FC, Sinkovics JG, Min KW, Gyorkey P: A morphologic study on the occurrence and distribution of structures resembling viral nucleocapsids in collagen diseases. *Am J Med* 53:148-158, 1972
15. Schumacher HR: Tubular paramyxovirus-like structures in synovial vascular endothelium. *Ann Rheum Dis* 29:445-447, 1970
16. Haas JE, Yunis EJ: Tubular inclusions of systemic lupus erythematosus. *Exp Mol Pathol* 12:257-263, 1970
17. Schumacher HR, Phelps P, Agudelo C: Urate crystal induced inflammation in dog joints: sequence of synovial changes. *J Rheumatol* 1:102-113, 1975
18. Scott DW: Rheumatoid arthritis in a dog. *Cornell Vet* 65:100-111, 1975
19. Schumacher HR: Synovial membrane and fluid morpho-

- logic alterations in early rheumatoid arthritis: microvascular injury and virus-like particles. *Ann NY Acad Sci* 256:39-64, 1975
20. Muirden K, Senator GB: Iron in the synovial membrane in rheumatoid arthritis and other joint disease. *Ann Rheum Dis* 27:38-48, 1968
  21. Ishikawa H, Ziff M: Electron microscopic observations of immunoreactive cells in the rheumatoid synovial membrane. *Arthritis Rheum* 19:1-14, 1976
  22. Kulka JP, Bocking D, Ropes MW, Bauer W: Early joint lesions of rheumatoid arthritis. *Arch Pathol* 59:129-150, 1955
  23. Dryll A, Cazalais P, Ryckewaert A: Lymphocyte tubular structures in rheumatoid arthritis. *J Clin Pathol* 30:822-826, 1977
  24. Cornwell HJC, Laird HM, Wright NG, et al: Ultrastructural features of canine distemper virus infection in a dog kidney cell line. *J Gen Virol* 12:281-292, 1971
  25. Confer AW, Kahn DE, Koestner A, et al: Comparison of canine distemper viral strains: an electron microscopic study. *Am J Vet Res* 36:741-748, 1975
  26. Imamura M, Phillips PE, Mellors RC: The occurrence and frequency of type C virus-like particles in placentas from patients with systemic lupus erythematosus and from normal subjects. *Am J Pathol* 83:383-389, 1976
  27. Weibel ER, Palade GE: New cytoplasmic components in vascular endothelia. *J Cell Biol* 23:101-112, 1964
  28. Highton TC, Caughey DE, Rayns DG: A new inclusion body in rheumatoid synovia. *Ann Rheum Dis* 25:149-155, 1966
  29. Norton WL, Velayos E, Robison L: Endothelial inclusions in dermatomyositis. *Ann Rheum Dis* 29:67-72, 1970
  30. Hashimoto K, Robison L, Velayos E, Niizuma K: Dermatomyositis: electron microscopic, immunologic and tissue culture studies of paramyxovirus-like inclusions. *Arch Dermatol* 103:120-135, 1971
  31. Moses HL, Glade PR, Kasel JA, et al: Infectious mononucleosis: detection of herpes-like virus and reticular aggregates of small cytoplasmic particles in continuous lymphoid cell lines derived from peripheral blood. *Proc Nat Acad Sci* 60:489-496, 1968
  32. Bedoya V, Rabson AS, Grimley PM: Growth in vitro of herpes simplex in human lymphoma cell lines. *J Natl Cancer Inst* 41:635-652, 1968
  33. Baringer JR: Tubular aggregates in endoplasmic reticulum in herpes simplex encephalitis. *N Engl J Med* 285:943-945, 1971
  34. Takeuchi A, Binn LN, Jervis HR, et al: Electron microscopic study of experimental enteric infection in neonatal dogs with a canine coronavirus. *Lab Invest* 34:539-549, 1976
  35. Uzman BG, Saito H, Kasac M: Tubular arrays in the endoplasmic reticulum in human tumor cells. *Lab Invest* 24:492-498, 1971
  36. Schaff Z, Heine U, Dalton AJ: Ultramorphological and ultracytochemical studies on tubuloreticular structures in lymphoid cells. *Cancer Res* 32:2696-2706, 1972
  37. Pincus T, Blacklow NR, Grimley PM, et al: Glomerular microtubules of systemic lupus erythematosus. *Lancet* 2:1058-1061, 1970
  38. Bucciarelli E, Rabotti GF, Dalton AJ: Ultrastructure of meningeal tumors induced in dogs with Rous sarcoma virus. *J Natl Cancer Inst* 38:359-382, 1967
  39. Kim KS, Boatman ES: Electron microscopy of monkey kidney cell cultures infected with rubella virus. *J Virol* 1:205-214, 1967
  40. Baringer JR, Griffith JF: Experimental herpes encephalitis: crystalline arrays in endoplasmic reticulum. *Science* 165:1381, 1969
  41. Tsai K, Grinyer I, Pan I, Karstad L: Electron microscopic observations of crystalline arrays of virus-like particles in tissues of mink with Aleutian disease. *Can J Microbiol* 15:138-140, 1969
  42. Schaff Z, Grimley PM, Michelitch HJ, et al: Brief communication: spontaneous myxosarcoma in a cottontail rabbit (*Sulilogus floridanus*): observation of tubular structures in the endoplasmic reticulum of tumor cells. *J Natl Cancer Inst* 51:293-297, 1973
  43. Blinzinger K, Simon J, Magrath D, et al: Poliovirus crystals within the endoplasmic reticulum of endothelial and mononuclear cells in the monkey spinal cord. *Science* 163:1336-1337, 1969
  44. Godzeski C, Boyd R, Smith C, Hamerman D: Viral-like particles in co-cultivated rheumatoid synovial cells (abstract). *Arthritis Rheum* 21:559, 1978
  45. Young S, Storz J, Malerhofer CA: Pathologic features of experimentally induced chlamydial infection in dogs. *Am J Vet Res* 33:378-383, 1972
  46. Pedersen NC, Weisner K, Castles JJ, et al: Non-infectious canine arthritis: the inflammatory, nonerosive arthritides. *J Am Vet Med Assoc* 169:304-310, 1976
  47. Chrisman OD, Fessl JM, Southwick WO: Production of synovitis and marginal articular exostoses in knee joints of dogs. *Yale J Biol Med* 37:409-412, 1965
  48. Huxtable CR, Davis PE: The pathology of polyarthritis in young greyhounds. *J Comp Pathol* 86:11-21, 1976
  49. Ropes MW, Bauer W: *Synovial Fluid Changes in Joint Disease*. Cambridge, Harvard University Press, 1953, p 150
  50. Lewis RM, Hathaway JE: Canine systemic lupus erythematosus: presenting with symmetrical polyarthritis. *J Small Anim Pract* 8:273-284, 1967
  51. Lewis RM, Schwartz RS: Canine systemic lupus erythematosus. *J Exp Med* 134:417-438, 1971