A SPONTANEOUS RHEUMATOID ARTHRITIS-LIKE DISEASE IN MRL/l MICE*

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One of the difficulties in defining the etiology and pathogenesis of rheumatoid arthritis has been the lack of a spontaneous animal model. A number of contrived, experimentally induced arthritides—type II collagen (1), adjuvant (2), mycoplasma agents (3), and intra-articular antigen antibody reactions (4), which display one or more of the features of rheumatoid arthritis—have been developed. However, although they may shed some light on the phlogogenic processes within the joint, they can be of little help in elucidating the etiology and perhaps even the pathogenesis of spontaneous human rheumatoid disease, because these models lack the morphological and serological characteristics associated with the human disease.

The MRL/l mouse strain, developed by Murphy and Roths (5), has been a very useful model for study of spontaneous systemic lupus erythematosus (SLE).[1] Similar to the other SLE mice (NZB, NZB × W, and BXSB males), the MRL/l mice have autoantibodies and immune complex-mediated glomerulonephritis. In addition, our initial studies (6) revealed that they possess four unique characteristics, one being a genetically determined excessive proliferation of T lymphocytes with enhanced helper activity. The other three features relate to their arthritis; they are (a) rheumatoid factors (RF) of both the IgM and IgG varieties, (b) polyarteritis, and (c) clinically evident polyarthritis involving primarily the hindlegs. In the present experiment, a detailed analysis was undertaken to study more completely the characteristics of this arthritis and its relationship to rheumatoid factors and other serological manifestations of autoimmunity. We found that ~75% of the 5–6-mo-old female MRL/1 mice had histological evidence of synovial and/or joint inflammation, with 54% of these arthritic mice demonstrating significant articular erosion by pannus formation and frequent periarticular inflammation with coexisting vasculitic and/or arteritic processes. Subcutaneous inflammatory nodules containing fibrinoid centers, not unlike human rheumatoid nodules, were present in 38% of the affected mice. Periductal mononuclear infiltrates involving salivary glands occurred in ~60% of both the arthritic and nonarthritic mice.

[1] *Abbreviations used in this paper:* dsDNA, double-stranded DNA; HE, hematoxylin-eosin; RA, rheumatoid arthritis; RF, rheumatoid factor; SLE, systemic lupus erythematosus; ssDNA, single-stranded DNA.

Materials and Methods

Mice. MRL/Mp *lpr/lpr* (MRL/l) mice were bred and maintained at the Scripps Mouse Colony. The mice examined consisted of randomly selected MRL/l females, 66 at 5–6 mo of age, 20 at 3–4 mo of age, and 20 at 1 mo of age. For comparative purposes, mice of other autoimmune and normal strains were also examined for presence of joint pathology. They consisted of (*a*) (NZB × W)F_1 (*b*) BXSB, (*c*) MRL/n, and (*d*) C57Bl/6. These were also bred and maintained at the Scripps Mouse Colony.

Histologic Studies. Complete autopsies were done on all mice. Sections of major organs were fixed in Bouin's fluid and processed for paraffin embedding. Hindlegs were removed and decalcified for 24 h in Decal (Scientific Products Div., American Hospital Supply Corp., McGraw Park, IL) before processing for embedding. 5-μm-thick sections were stained with periodic acid-Schiff and hematoxylin-eosin (HE).

Histologic Grading. Individual joints and salivary glands, as well as all major organs, were examined histologically. The joints were evaluated for the presence of the following features: (*a*) subsynovial mononuclear inflammatory infiltrates; (*b*) synovial proliferation and hyperplasia with or without inflammatory exudates; (*c*) pannus formation and articular cartilage destruction; (*d*) vasculitis and/or arteritis in subsynovial or periarticular regions; (*e*) periarticular inflammation, i.e., tendonitis, myositis, and perineuritis; and (*f*) subcutaneous fibrinoid inflammatory nodules without apparent epidermal trauma. Mice with (*a*) plus any additional features of (*b*) to (*f*) were considered as having histological evidence of arthropathy. Salivary glands from individual mice with or without arthropathy were examined for periductal mononuclear inflammatory infiltrates with or without acinar destruction.

Electron Microscopy. Samples of synovial tissue were obtained from ankle or knee joints and fixed immediately in a modified Karnovsky's fixative (2% paraformaldehyde, 1.5% glutaraldehyde in 0.1 M cacodylate buffer, pH 7.2), post-fixed in 1% OSO_4 in the same buffer, and embedded in epon. Thin sections were mounted on grids and stained with uranyl and lead acetate for examination with a Hitachi 12A electron microscope (Hitachi Ltd., Tokyo, Japan).

Serologic Studies. Anti-single stranded DNA (ssDNA) and anti-double stranded DNA (dsDNA) antibodies were measured by a modified Farr radioimmunoassay (7). IgMRF assay used a solid-phase radioimmunoassay. Mouse IgG-coated microtiter wells were reacted with the sera to be tested. After washing, the bound IgMRF was quantitated by a radio-iodinated I^{125}-goat anti-mouse-specific affinity-purified antibody as described (8). The modified Raji cell assay was used to detect immune complexes in sera (6, 9). Serum levels of Ig-bound retroviral gp70 complexes were determined by absorption of sera with staphylococcal protein A (Calbiochem-Behring Corp., American Hoechst Corp., San Diego, CA). Values from absorbed serum were subtracted from the total serum gp70, and the differences were considered to be Ig-bound gp70 expressed as percent total (10).

Cellular Analysis. Spleen cells bearing Ig or Thy-1.2 alloantigen were enumerated as previously described (11).

Results

Table I displays the incidence of joint pathology and associated features of periarticular/subsynovial and subcutaneous abnormalities in relation to age. 1-mo-old mice had no evidence of either synovial or periarticular abnormalities. About 45% of 3–4-mo-old mice had evidence of early synovial pathology characterized by synovial thickening and subsynovial mononuclear inflammatory infiltration. Coexisting periarticular vasculitis and/or arteritis could often be demonstrated. Pannus formation with early articular erosion was also evident. By 5–6 mo of age, 75% of the mice had significant joint pathology; 60% of the arthritic mice contained two or more of the features listed in criteria (*a* to *f*) (see Materials and Methods). In the inflamed joints, the synovia were thickened by synovial cell proliferation and subsynovial infiltration of lymphocytes and plasma cells. Exudates consisting of sloughed synovial cells, lymphocytes, polys, and fibrin could be seen in 34% of the affected joints (Fig. 1). The

TABLE I

Synovial and Periarticular Pathology

Age	Number of mice examined	Significant arthropathy	Subsynovial or periarticular perivascular inflammation	Pannus and articular erosion	Subcutaneous perivascular inflammation	Synovial exudates
mo						
1	20	0*	0	0	0	0
3–4	20	9	7 (76%)‡	4 (44%)	2 (22%)	1 (11%)
5–6	66	50	42 (82%)	26 (54%)	19 (38%)	18 (34%)

* Numbers indicate mice affected.

‡ Parentheses indicate percent of arthritic mice with the indicated synovial or periarticular pathology.

subsynovial inflammatory infiltrates were either dispersed diffusely or in a perivascular distribution, mixed with larger mononuclear forms and rare neutrophils. Some of the hyperplastic synovia assumed papillary, villous configurations (Fig. 2). Erosion and destruction of articular cartilage by pannus were demonstrated in 54% of the affected diseased joints (Figs. 3, 4). Reactive osteoblastic activity or new bone formation were not seen. Perivascular infiltration by lymphohistiocytic cells, plasma cells, and poly-morphonuclear neutrophils with partial or complete vascular destruction were evident in the subsynovial or periarticular regions (82% incidence) involving muscles (Fig. 5), fasciae (Fig. 6), tendons, and nerves (Fig. 7). Similar inflammatory nodules were present in the subcutaneous regions in 38% of the arthritic mice (Fig. 8).

By electron microscopic examination, the subsynovial and perivascular cellular infiltrates consisted of mature and immature plasma cells, macrophages, and lympho-cytes (Fig. 9), some having nuclear and cytoplasmic characteristics of T cells. The macrophages were seen frequently attached to the cell membrane of both plasma cells and lymphocytes via their cytoplasmic processes (Fig. 10). In the affected blood vessels with light microscopic evidence of vasculitis, electron-dense granular deposits of varying sizes and shapes were seen in regions between the endothelium and internal elastic membrane (Fig. 11). The medial smooth muscle cells of the blood vessels showed varying degrees of degeneration with fraying of basement membrane-like materials.

Serologically, as illustrated in Table II, the 1-mo-old mice had minimal autoanti-body, IgMRF, or circulating immune complexes, as measured by the Raji cell assay. 30% of them had antibodies to gp70, present as Ig-bound gp70 complexes. By 3–4 mo of age, most mice had elevated anti-dsDNA, IgG, IgM, circulating immune complexes, and Ig-bound gp70. Increased levels of IgMRF were found in seven of the nine arthritic mice (averaging 23.7 μg/ml). None of the 11 nonarthritic mice had such elevated levels; they averaged only 9.5 μg/ml, similar to those of normal or nonarthritic SLE murine strains.

The 5–6-mo-old mice had marked increases in IgG, anti-dsDNA, circulating immune complexes, and Ig-bound gp70. Again, mice with joint disease tended to have elevated IgMRF levels, mean value 39.8 μg/ml—74% seropositive. Of the mice with elevated IgMRF, 95% had significant joint disease.

In addition to serologic evidence of autoimmunity, the MRL/l mice showed significant lymphoid proliferation apparent at 3 mo. Quantitation of total splenic lymphocytes as well as subpopulations of T and B cells revealed both increased
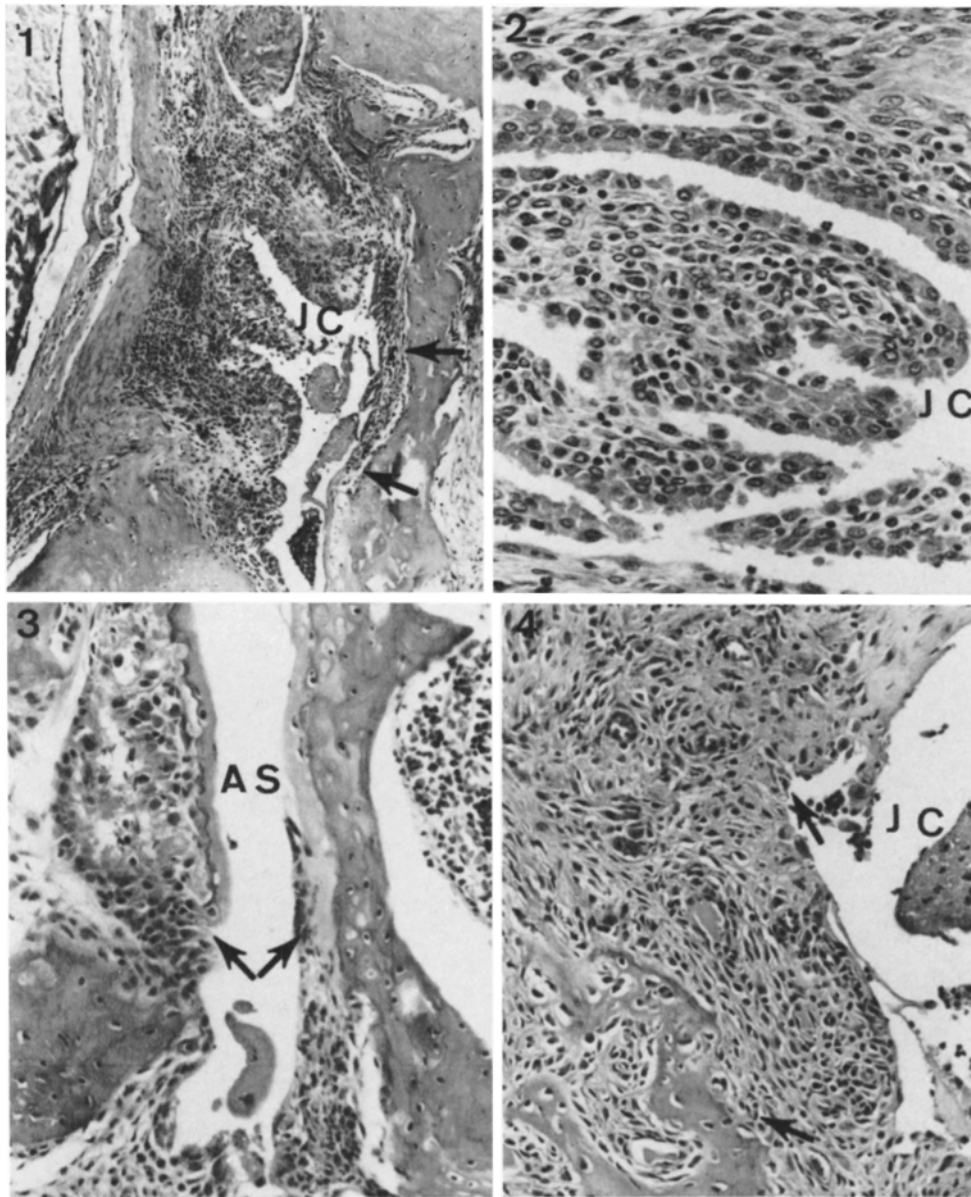
FIG. 1.   Acute arthritis with villous synovitis, fibrinous exudate, and destruction of bone and cartilage (arrows). J.C., joint cavity. HE × 63.

FIG. 2.   Villous synovitis consisting of synovial proliferation and subsynovial mononuclear inflammatory infiltrate. J.C., joint cavity. HE × 400.

FIG. 3.   Erosion and destruction of articular cartilage (arrowheads) by pannus (arrows). A.S., articular surface. HE × 400.

FIG. 4.   More advanced articular cartilage and bone destruction (arrows). Note absence of osteoblastic activity and PMN. J.C., joint cavity. HE × 400.
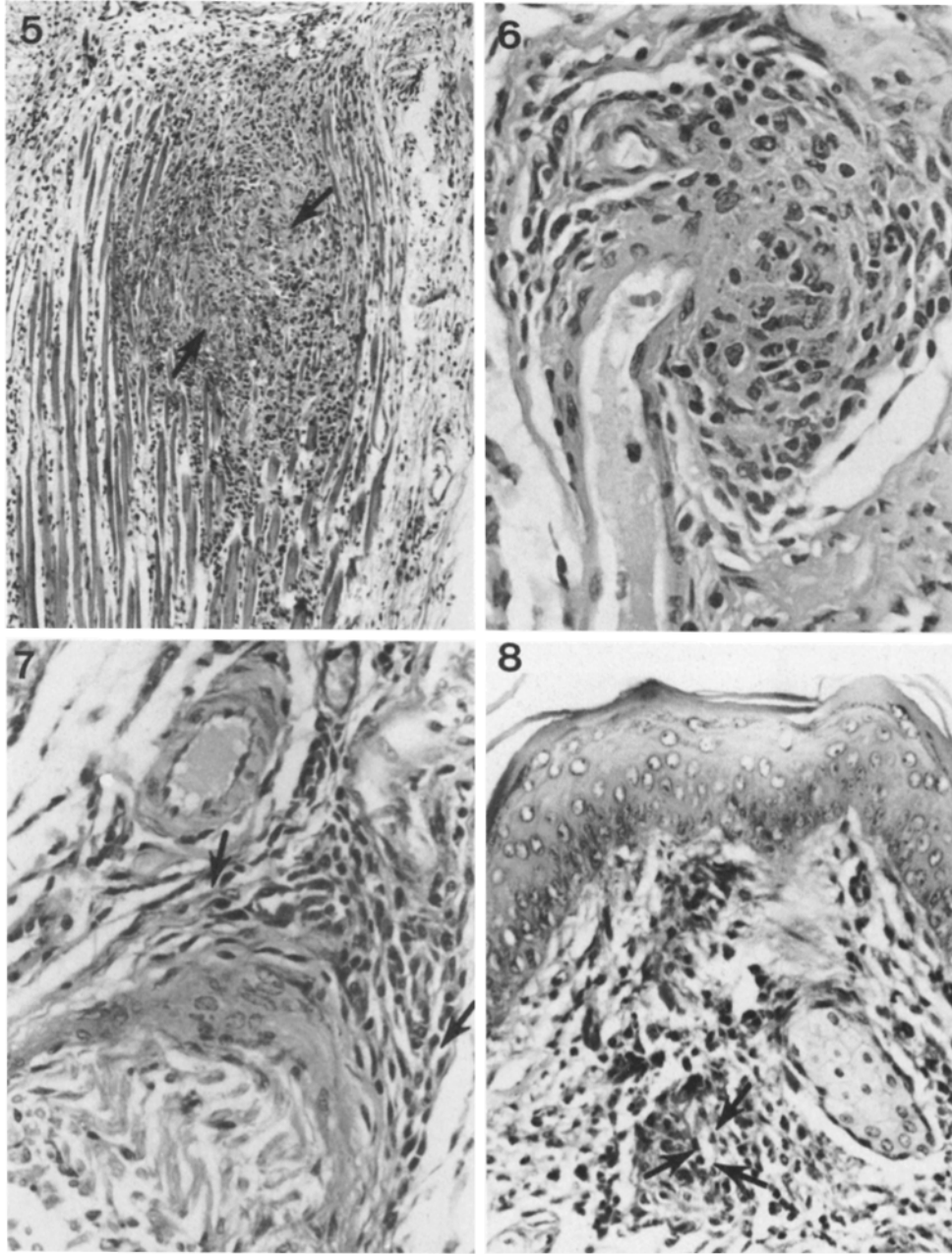
FIG. 5. Periarticular myositis consisting of inflammatory nodule with central necrosis (arrows). HE × 160.

FIG. 6. Periarticular vasculitis with predominantly chronic inflammatory cell infiltrate. HE × 400.

FIG. 7. Perineural mononuclear inflammatory infiltrate (arrows). HE × 400.

FIG. 8. Subcutaneous inflammatory nodule surrounding blood vessel (arrows). The epidermis is intact. HE × 400.
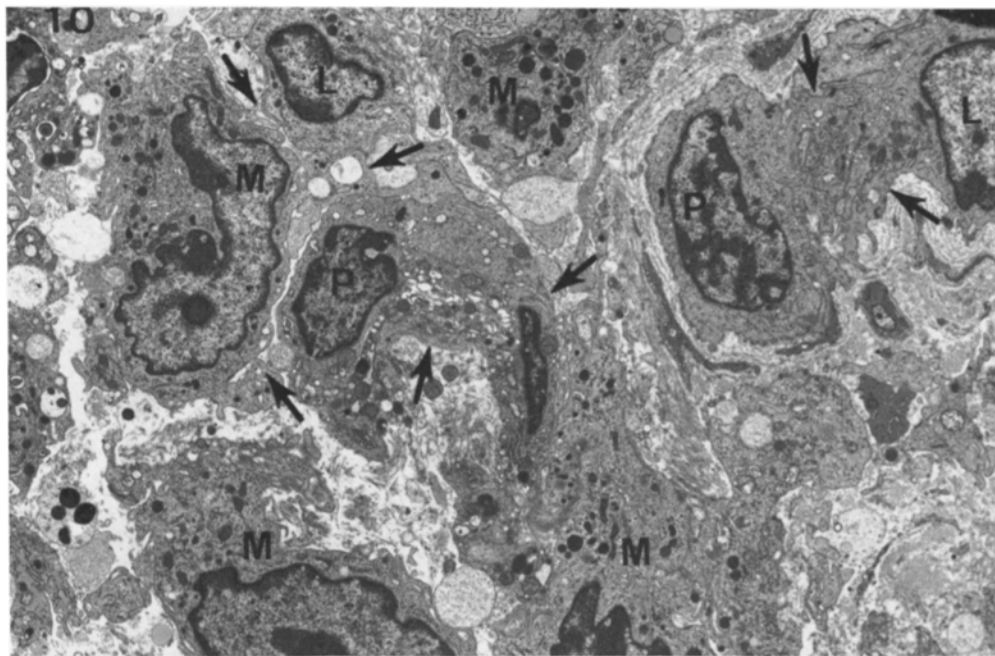
FIG. 9. Ultrastructural appearance of synovitis consisting of perivascular accumulation of inflammatory cells; M, macrophages; P, plasma cells, and L, lymphocytes; lu, vessel lumen; syn, synovial surface. Uranyl acetate and lead citrate × 2250.

FIG. 10. Higher magnification of perivascular inflammatory infiltrates (Fig. 9) demonstrating close contact among macrophages (M), plasma cells (P), and lymphocytes (L), via interdigitations of cytoplasmic processes (arrows). Uranyl acetate and lead citrate × 5500.
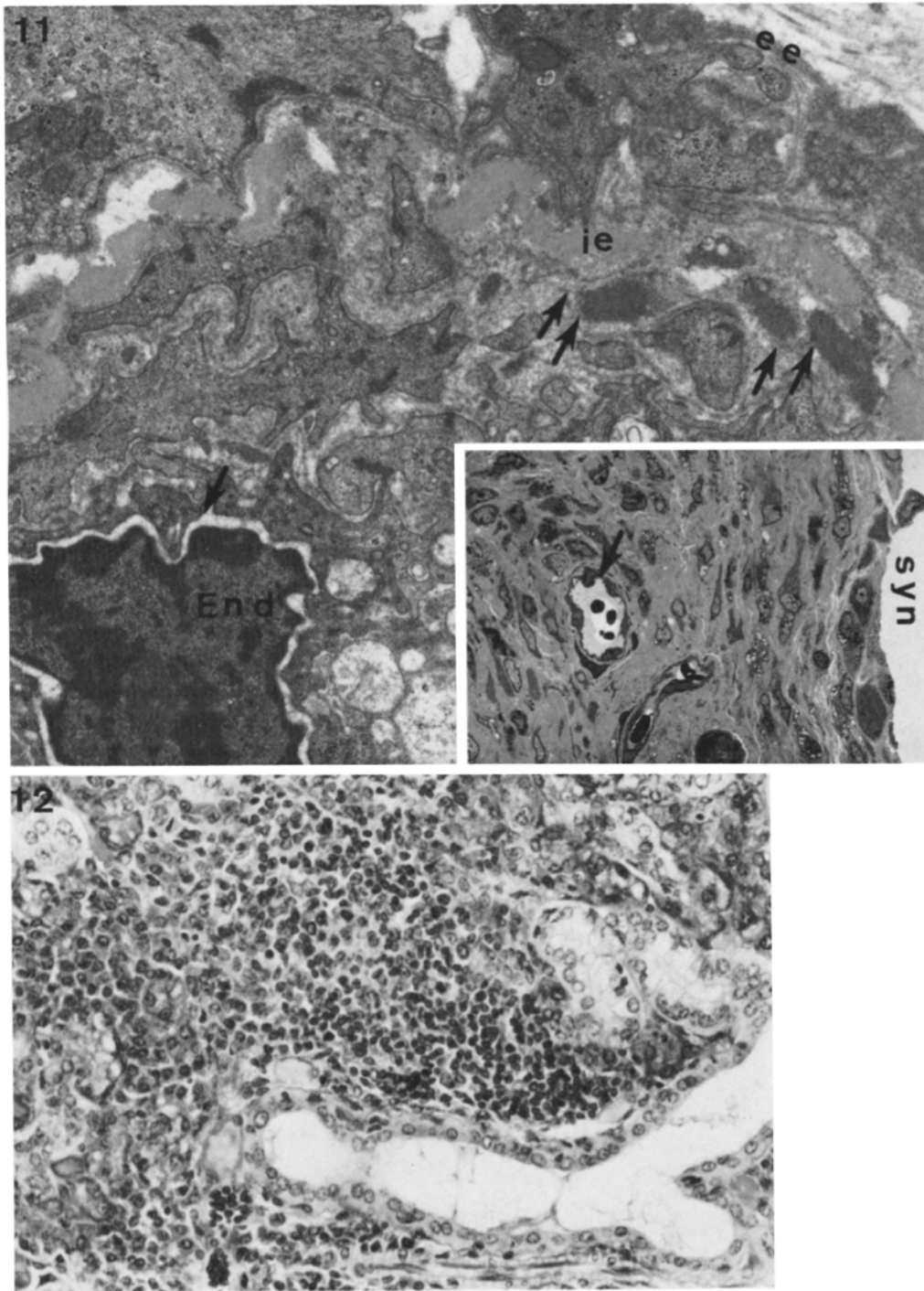
Fig. 11. Subsynovial blood vessel with electron-dense deposits adjacent to internal elastic lamina (double arrows) and disruption of lamina. Insert shows thick section of involved vessel with arrow indicating field of electron micrograph. End, endothelial cell, ie, internal elastic lamina; ee, external elastic lamina; syn, synovial space. Uranyl acetate and lead citrate × 12,000.

Fig. 12. Salivary gland with periductal mononuclear inflammatory infiltrate of plasma cells and lymphocytes. There is destruction of acini but sparing of ductal epithelium. HE × 400.

TABLE II

Correlation of Arthritis with Cellular and Serological Parameters of MRL/l Mice

Age	RA	Number of mice	Spleen cells		IgG	IgM	IgM/RF		Immune Complex		Increased Ig bound gp70 (Number positive)‖	Anti-dsDNA average percent binding
			T	B			Mean	Number positive*	Mean AMG‡	Number positive§		
mo			× 10⁶		mg/ml		µg/ml		µg/ml			
1	+	0	—	—	—	—	—	—	—	—	—	—
	−	20	12.6	12.1	12.9	0.7	8.7	0	8.7	0	6 (30%)	4.1
3-4	+	9	55.9	36.3	26.1	1.4	23.7	7	54	6	5 (55%)	16.7
	−	11	59.1	32.2	24.1	1.2	9.5	2	79	10	6 (54%)	12.4
5-6	+	50	80.9	29.8	36.3	1.56	39.8	37	2478	47	38 (76%)	33.5
	−	16	—	—	34.7	1.04	12.9	2	1325	14	13 (80%)	34.1

* >15 µg/ml considered positive.
‡ AMG, aggregated mouse gammaglobulin.
§ >100 µg/ml considered positive.
‖ >20% absorption of gp70 by *Staphylococcus* protein A considered as evidence for increased gp70 bound to IgG.

lymphoid mass and T lymphocytes. The 3-mo-old mice showed a three- to fourfold increase of T and B cells. By 5-6 mo of age, the average splenic T and B cell numbers showed a sevenfold and threefold increase, respectively, whereas negligible increases were seen in the congenic MRL/n mice that lack the *lpr* gene and develop late-life SLE. By light microscopy, accumulations of small lymphocytes and plasma cells were seen in the perivascular regions of lung parenchyma, renal pelvis, and salivary glands. In the salivary glands, these mononuclear infiltrates were also periductal in distribution; some glands showed expansion of the inflammatory infiltrates beyond the periductal region with destruction of acini but preservation of ductal epithelium (Fig. 12). Approximately 60% of both the arthritic and nonarthritic mice had salivary glands with these changes. Neither elevated IgMRF nor significant joint abnormalities were present in the various normal and autoimmune murine strains examined (NZB × W F₁ females, MRL/n females, BXSB males, and C57Bl/6 females) of comparable age or older.

Discussion

Since 1895, when "rheumatoid arthritis" (RA) was described as a distinct disease entity characterized by inflammatory polyarthropathy (12), the pathogenesis of RA has remained an enigma. Many agents, i.e., viral, bacterial, and chemical, have been suspected. The more recent advances in immunological assays have led to identification of antibodies to IgG and other autoantigens (collagen, nucleoproteins, etc.) in sera and synovial fluids of patients with RA (13), indicating an autoimmune component in the disease.

Our present study of MRL/l mice reveals a joint disease quite similar to human RA. In contrast to the many other experimentally induced arthritis models, the MRL/l arthritis lacks (a) the osteoblastic proliferation seen in the arthritis induced by

type II collagen and Freund's adjuvant, and (*b*) the arthus-type inflammation seen in those induced with intra-articular antigen-antibody reactions. The spontaneous polyarthropathy in this murine strain possesses not only the typical pannus formation with erosion and destruction of articular cartilage, but also the serologic complements of rheumatoid factor, hypergammaglobulinemia, and elevated circulating immune complexes. Furthermore, the inflamed MRL/l synovium has, by light and electron microscopy, a very similar cellular composition to that seen in human RA synovium, as described by Janossy et al. (14) and Ishikawa and Ziff (15). These authors suggest that the intimate contacts among macrophages, lymphocytes, and plasma cells are evidence of interactions by all three cell types—T, B, and macrophage/accessory cells—in generation of the synovial immune response. Preliminary study of human rheumatoid synovium revealed predominance of OKT4+ (inducer type) lymphocytes to be in close contact with macrophages and plasma cells (14). It is of interest to note that MRL/l mice are resistant to induction of arthritis by type II collagen, and that they do not develop anticollagen antibodies in the course of their spontaneous arthritis (unpublished data).

Our analysis of the various histological and serological parameters in the individual mice with polyarthropathy point out the following associations: (*a*) coexistence of synovial proliferation with subsynovial/periarticular vasculitis, (*b*) correlation between presence of circulating IgMRF and demonstrable synovial and/or joint pathology, because 95% of the mice with detectable IgMRF showed evidence of arthritis, and (*c*) similarities in anatomical locations (subsynovial/periarticular/subcutaneous) of the MRL/l inflammatory nodules and the human rheumatoid nodules. Serial sections of these nodules often revealed residual vessel lumens within the necrotic fibrinoid centers. These observations lend support to the postulation of Sokoloff et al. (16, 17) that the pathogenesis of rheumatoid inflammation (rheumatoid nodules and myositis) may be a vasculitic process. The demonstration of electron-dense deposits along the subendothelial zones of these affected blood vessels suggests an immune complex-mediated vascular injury. Our present study points to a close relationship between joint disease and IgMRF, because the arthritic mice can be best characterized by the presence of RF and not total levels of circulating immune complexes as measured by the Raji cell assay or Ig-bound gp70 complexes.

This close interrelationship between RF, subsynovial/periarticular inflammation (vasculitis), and arthropathy observed in the MRL/l mice makes it tempting to consider that the initiating factor of their arthritis may very well be the deposition and/or *in situ* formation of immune complexes (IgG-IgMRF, or IgG-IgGRF) along synovial surfaces and periarticular blood vessels. That such immune complexes might activate the complement cascade, generating factors that promote inflammation and enzymatic destruction of the affected joints, has long been proposed by others (reviewed in 13) and is a very attractive mechanism to entertain as the pathogenesis of both murine and human arthritis. Identification of immune complex deposits along blood vessels of seropositive RA patients has been documented (18). The diseased synovia have been shown to synthesize immunoglobulins in vivo (19) and in vitro (20). They also have surface receptors for IgG F_c and C3 (21) and self-associating RF present as complexes have been identified within cells of the RA synovia (22). It is of interest to note that in addition to IgMRF, intermediate-sized anti-IgG complexes (IgG-IgGRF) detected almost exclusively in sera of the MRL/l mice (and not in other

SLE-prone murine strains) (23) are very similar to those in sera and synovial fluids of RA patients with demonstrable vasculitis (24, 25). Whether these intermediate-sized complexes contribute to the development of vasculitis and arthritis remains to be determined; however, their absence in the other SLE murine strains (NZB, NZB × W, BXSB males) that have neither vasculitis nor arthritis seems to point to possible associations. On the other hand, although anti-IgG antibodies have been detected in normal murine strains housed in isolated mouse colonies (26) and in human patients after bacterial infections (27), these incidences were transient and were not associated with vascular or joint pathology.

One of the extra-articular abnormalities of RA patients is the occurrence of lymphoid infiltrates in their salivary glands (Sjogren's syndrome) as reported by Talal et al. (28, 29), and similar periductal infiltrates were detected in the MRL/1 mice. However, this abnormality of the salivary glands has no specific relationship with arthritis in the mouse, because it occurred with equal frequency in both the arthritic and nonarthritic mice. Furthermore, similar lymphoid infiltrates are seen in the lung parenchyma and renal pelvis of the MRL/1 mice. NZB × W mice, which do not have IgMRF, vasculitis, or polyarthropathy, have identical salivary gland and pulmonary infiltrates.

Our model, the MRL/1 arthritis, represents the first spontaneous animal disease model having the full components of the human disease counterparts. Although these two joint diseases share many serological and morphological characteristics, whether they have analogous immunopathoetiologies and cellular immunoregulatory defect(s) remains to be investigated. It is clear that the predominant immunogenic abnormality in the MRL/1 mice is genetically determined by a single autosomal recessive lpr gene, expressed as a massive T cell proliferation in their spleen and lymph nodes with resultant enhanced T helper activity (30, 31). In humans, a genetic predisposition to RA has been suggested by the frequent associations with HLA Drw 4, 7, and 10 (32, 33), and hyperactivity of T lymphocytes and macrophages has been proposed by Tannenbaum et al. (33), Van Boxel and Paget (34), and Janossy et al. (14) as the underlying mechanism for the articular tissue inflammation and destruction, based on cellular analysis of RA synovia.

Summary

MRL/1 mice spontaneously develop an arthritis very similar in many respects to human rheumatoid arthritis. A detailed morphologic and serologic analysis of this disease revealed the following: (a) a 75% incidence of synovial and periarticular inflammation, very similar to human rheumatoid arthritis, in 5–6 mo-old females, (b) close associations between presence of joint inflammation and subsynovial and/or periarticular vasculitis, and (c) a close correlation between presence of circulating IgM rheumatoid factor (RF) and demonstrable synovial and/or joint pathology, i.e., 95% of mice with significant levels of IgMRF had synovitis and/or arthritis.

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