Based on the classification of articular disease presented in Chapter 88, the immune-mediated articular diseases are categorized as inflammatory purulent, noninfectious. In the dog, two main types of immune articular diseases have been described: in the erosive type there is loss and destruction of articular cartilage and, in severe cases, subchondral bone; the nonerosive type bears many similarities to the erosive type, but articular cartilage destruction is not a prominent feature. (6) In addition, the erosive type is similar if not identical to rheumatoid arthritis (RA) of humans, while the nonerosive type occurs most frequently with systemic lupus erythematosus (SLE). The nonerosive type is by far the more common of the two in the dog.

**Erosive Joint Disease**

**ETIOLOGY**

Etiology of the immune-mediated articular diseases is not known. Both the erosive and nonerosive types are characterized by the production of antibody-antigen immune complexes. In the erosive type, the antigen is the host or affected animal’s own altered IgG immunoglobulin. In the nonerosive type, nuclear material becomes antigenic, stimulating the production of antinuclear antibodies. While it may be that dogs have been affected by immune-mediated articular diseases for a long time but that such diseases have gone unrecognized until recently, there is the possibility that they are truly recent afflictions much like parvovirus infections. RA in humans, in contrast to degenerative joint disease, is felt to be a disease of relatively recent times. Very little pathologic evidence exists in exhumed skeletal material of ancient civilizations that can substantiate RA in these populations. Hippocrates and other ancient medical writers did not clearly describe the disease, nor is it mentioned in other writings, such as the Bible or the works of Shakespeare, (9) that served as chronicles of the times in which they were written. Supposedly, the first written descriptions of clinical signs of a condition in humans that may have been RA appeared in 1676. (67) The first recognition of RA as a separate entity was published in 1800, and the term rheumatoid arthritis was introduced in 1859 by Sir Alfred Baring Garrod. (65) It could be, of course, that RA was present but classified as another disease, such as gout, or was rare because life expectancy was low and potential sufferers died before contracting or manifesting the signs of the disease. Be that as it may, there remains an interesting parallel between the rise and recognition of the disease in humans and in dogs.

Erosive immune-mediated articular disease of the dog is well recognized today. However, no published reports deal with investigations into its etiology. Because this condition bears similarities to RA in humans, a brief review of the history of the etiologic investigations of RA in humans is warranted. The etiology of immune-mediated erosive joint disease is unknown. Infectious agents have long been incriminated, yet extensive, repeated, elaborate investigations have failed to isolate an organism. Viruses, bacteria, mycoplasmal organisms, and their components (i.e., bacterial cell wall material) have all been suggested as the initiating cause of the erosive immunarticular diseases. Despite intensive investigations with negative results, the pursuit for the elusive pathogen continues. Certain observations make this line of investigation attractive.
Pathologic findings similar to RA are found in streptococcal infections of rabbits, mycoplasmal and Erysipelothrix infections in mammals and birds, and in rats treated with adjuvant and mycobacterium. Indeed, experimental Erysipelothrix infections in dogs have been used as a model for the study of RA. However, an organism responsible for the disease has yet to be isolated. Failure to recover an infectious agent from a naturally affected patient does not preclude its participation in the disease process. In support of this is the fact that in experimentally produced mycoplasmal or Erysipelothrix infections the organisms can be recovered from articular tissues early on, but later, when chronic inflammatory synovitis is well established, the organism can no longer be found. Also, it is known that nonbiodegradable bacterial cell wall products can sustain chronic joint inflammation.

Pursuit of a viral etiology of RA continues with zeal. To date, definitive electron microscopic visualization and direct viral identification have not occurred in affected tissues of humans or dogs. Certain viral infections of birds and some mammals produce a chronic synovitis that closely resembles that of RA.

Rather than identification of an intact replicating virus in the tissues of the host, it may be that viral genomes are incorporated into the nuclear material of host cells, thus producing and perpetuating the joint inflammations. Isolation studies have yielded an active infectious ribonucleic acid (RNA) component in the tissues of human RA patients that produces RA-like lesions in rodents.

The ability of affected persons to manifest immune tolerance is lost in RA. What causes this loss is not known, but there is no doubt that autoimmune reactions play a significant role in the initiation and especially the perpetuation of the inflammatory reactions. The autoimmune manifestations of RA may be stated as follows: host IgG molecules are altered, and this change in molecular configuration renders the IgG molecule antigenic because it is now perceived as foreign protein; this IgG antigen thus initiates or stimulates the production of IgM antibody; phagocytosis of the resulting antigen-antibody complex along with complement activation is the root of the inflammatory changes.

Why the IgG becomes altered is as yet unknown. If not caused directly by an infectious agent, it may be that the IgG-producing cells have become virally controlled and produce an abnormal or altered molecule, or it may be that the host is genetically predetermined to produce the altered IgG.

While environmental factors were originally thought to be more significant than genetic factors in RA, it is now believed that particular determinants on the D locus of the histocompatibility gene complex are more frequent in human RA patients than in those with other diseases. However, certain antigenic markers originally thought to be somewhat specific in certain rheumatoid patients may not be as specific as previously believed.

While studies of this kind have not as yet been reported in the dog, the likelihood of a genetic component in the disease of the dog must be real.

**PATHOGENESIS**

Whereas degenerative joint disease is often considered a condition in which articular cartilage is initially affected, in the immune arthritides it is the synovial tissues that are affected initially. Products of the ongoing inflammation result in articular cartilage and subchondral bone destruction. Three separate stages have been described in the pathogenesis of immune-mediated erosive joint disease: (1) initiation of synovitis, (2) the immunologic events that perpetuate the synovial inflammation, and (3) the continuing phenomena that cause joint damage.

As noted above, agents and activities responsible for initiating synovitis are not completely understood. However, the immune events that mediate the inflammation and the mechanisms of articular cartilage and subchondral bone destruction have been well defined. Both humoral and cell-mediated immune responses appear to participate in the immunopathogenesis of RA.

The humoral component of the immune response is related directly to the production of immunoglobulins, which participate in the formation of immune complexes. Lymphocytes and plasma cells, which appear in abnormally high numbers in rheumatoid synovial tissues, are the primary source for the production of these immunoglobulins. It has been shown that these antibody-producing cells are immunologically committed to a specific antigenic stimulus. In one study, explants of rheumatoid synovial tissues from patients previously stimulated by tetanus immunization produced negligible amounts of specific antitetanus antibody when compared with peripheral blood lymphocytes of the same patients. Rheumatoid factor, perhaps the most frequently studied antibody of the immune diseases, may be considered an anti-immunoglobulin antibody. It is, at least in humans, predominantly of the IgM class and is produced in response to altered host IgG. IgG and IgA rheumatoid factors have also been identified. These immunoglobulins can be found in the peripheral circulation, synovial fluid, and affected synovial tissues of nearly 75% of human patients with RA. It is important to note that not all RA patients...
have detectable levels of serum rheumatoid factor. Such patients are termed seronegative. However, rheumatoid factor may be detected in the synovial fluid of some seronegative patients. Also of importance is that rheumatoid factor is not specific for RA. It is found in approximately 5% of the normal population and may be detected in some cases of tuberculosis, sarcoidosis, bacterial endocarditis, and other diseases. Detectable rheumatoid factor is present in approximately 25% of the dogs affected with RA. It is also found in dogs with other immune-mediated diseases such as systemic lupus erythematosus. In addition, it has been reported in dogs with keratoconjunctivitis sicca and in normals.

The production and subsequent phagocytosis of immune complexes are believed to be the major factors resulting in articular tissue destruction of RA. Immune complexes are formed between the altered IgG, the IgM antibody produced in response to the altered Immune-Mediated Arthopathies IgG, and complement. The binding and activation of complement in the synovial fluid and synovial membrane lead to the formation of the chemotactic factor complex of the complement cascade, which in turn attracts polymorphonuclear cells to the synovial fluid. This appears to be the explanation for the relatively high concentration of such cells in the immune synovial fluid. Phagocytosis of immune complexes by polymorphonuclear cells of the synovial fluid and by phagocytic cells of the synovial tissues leads to the production and release of biologically active substances that are directly responsible for the damage and destruction to the affected joint.

Structural alteration of host immunoglobulin and association with rheumatoid factor is not the only method of immune-complex formation in articular disease. A number of other antigen-antibody complexes of potential pathogenic significance have been recognized. Nucleic acid, collagen, cartilage, and fibrinogen may all act as antigens under certain circumstances and elicit an antibody response. Soluble nuclease and deoxyribonuclease (DNA) derived from disintegrating granulocytes may complex with antinuclear antibodies. This, in fact, is one of the features of SLE. Antigen-antibody complex formation and phagocytosis are associated with release of material deleterious to the joint. Certain cartilage components and collagen in particular, are known stimulators of antibody production. Once cartilage destruction has begun, altered molecules of collagen and proteoglycan are released and recognized as foreign substances. Antibodies are produced and immune complexes formed. Phagocytosis occurs with release of material that causes further cartilage destruction and exposure of altered cartilage components. Thus, a self-perpetuating, self-destructive, autoimmune cycle begins. Indeed, this may be the mechanism by which the ongoing nature of articular tissue destruction of RA occurs.

Cell-mediated immunity is defined as those manifestations of the specific immune response that are conducted by B-lymphocytes. The initiating event of humoral immunity requires only the presence of circulating antibody, while the initiating event of cellular immunity requires the interaction of intact lymphocytes with antigen. Complement and vasoactive amines augment the humoral responses, while several soluble factors released by the lymphocytes initiate and enhance the biologic expression of the cell-mediated response.

Generally speaking, there are two types of lymphocytes: T-lymphocytes, which are thymus-derived and are the most important in cell-mediated reactions, and B-lymphocytes (bone marrow-derived), which are most active in the production of immunoglobulins. Both types of lymphocytes have been identified in the synovial tissue of humans with RA.

It has been shown in human RA patients that cell mediated immunity, as assessed by lymphocyte stimulation and intradermal antigen injection, is depressed. In contrast, lymphocyte migration assays show active cellular immunity when the peripheral lymphocytes of RA patients are incubated with autologous IgG. Although confusion and conflicting opinion exist, it is clear that both humoral and cell-mediated processes are important in the pathogenesis of immune articular disease because of the products produced and released during immune-complex phagocytosis and lymphocyte-antigen interaction.

Polymorphonuclear neutrophil leukocytes are the predominant cell found in the synovial fluid of immune-mediated articular disease. They are the typical cell of active inflammation. Chemotaxis, adherent cell antigen-antibody complement complexes, and phagocytosis are activities of the neutrophil prior to its release of inflammatory-mediating substances. Phagocytosis is designated to eliminate from the body any material that is recognized as foreign. During the phagocytic process, which occurs in intracytoplasmic vacuoles of the neutrophil, enzymes are secreted by a process that closely resembles the secretion of the thyroid, pancreas, or salivary glands. Most of the time these vacuoles remain closed and prevent extracellular escape of the enzyme produced. However, if there is too much to digest, the vacuoles may remain open, allowing escape of the enzymes, which then may attack host tissues. Collagenase, elastase, and certain cathepsins are the enzymes of primary importance. In addition, prostaglandins are released during the phagocytic process, and they, too, have a role in mediating and perpetuating the inflammatory reaction.

RA is characterized by severe inflammation of the synovial tissue. The proliferative lesion consists of an excess of connective tissue, blood vessels, macrophages, and mesenchymal cells with phagocytic and synthesizing functions. The proliferative nature of the synovial tissue becomes loosely organized into an invasive front of tissue with the capacity to destroy articular cartilage, subchondral bone, and tendons of the affected joint. Proteases, enzymes, and other substances are reproduced by the
invading tissue and are directly responsible for the destruction of the joint. (27)

Collagenases are enzymes capable of degrading native collagen. In its normal helical structure, collagen requires special enzymes for degradation. In a denatured or nonhelical form, this protein is susceptible to many proteinases. The primary sources of collagenase in the erosive joint are thought to be the polymorphonuclear leukocytes, which are found in great numbers in the synovial fluid, and fibroblasts in the synovial tissues. Collagenases with joint-destroying capabilities are also produced by activated macrophages and perhaps by the damaged articular cartilage. However, it is the synovial fibroblast and the polymorphonuclear leukocytes of the synovial fluid that are responsible for the majority of collagenase production. (28) In fact, activated synovial fibroblasts are reported to produce 10 to 1000 times more collagenase than stimulated macrophages. (49, 94)

Prostaglandins, also released by activated synovial fibroblasts, are responsible primarily for subchondral boneresorption. (49) Prostaglandins are a group of naturally occurring humoral agents characterized by a unique oxygenated low-molecular-weight fatty acid structure. They are formed by nearly all cells from membrane located phospholipids and are potent biologic mediators. (62) Unlike some other mediators of inflammation, prostaglandins are not stored but are synthesized and released immediately in response to specific stimuli. (23)

Prostaglandins are widely distributed in vertebrate tissue, and nearly all cells are endowed with the microsomal enzyme complex for their synthesis. (52) The activities for which they are responsible are many. Prostaglandins are known to cause erythema, sensitize pain receptors to mechanical or chemical stimulation, and act with other inflammatory mediators in producing edema. (23) Their activity in producing bone resorption is well documented. (17, 52) Collagenase release from rheumatoid synovial tissues can degrade bone collagen only after the mineral portion of the bone has been removed. It is now believed that prostaglandins promote bone destruction in the rheumatoid joint by aiding in the removal of the mineralized portion of the bone. (68)

**PATHOLOGY**

The principal lesions of erosive immune-mediated articular disease of the dog are found in diarthrodial joints. Systemic manifestations of RA in humans are well documented but have not been so in the dog. However, the joint changes are strikingly similar in both humans and dogs affected with RA. Very early lesions are not well documented grossly or histopathologically because of a lack of sample material. Present evidence indicates that the joint changes begin in the synovial tissues, and the articular cartilage, subchondral bone, ligaments, and tendons are all affected secondarily. Congestion of the synovial membrane and pitting and dullness of the articular cartilage are the early changes noted. (59) In later stages, the joint capsule thickens and loss of articular cartilage is evident. In advanced cases there is marked erosion of the articular cartilage. This articular cartilage loss begins at the joint surface periphery at the articular cartilage-synovial tissue interface. Cartilage loss in the central regions of affected joints may also be found (Fig. 89-1).

The synovial tissues manifest various degrees of inflammation depending upon the duration and severity of the condition. Characteristic gross findings include periarticular connective tissue proliferation and thickening of the synovial tissues with many large fingerlike villous projections extending over the articular cartilage surfaces. (53) This advancing front of fibrovascular proliferative granulation tissue is called pannus (Fig. 89-2). Articular cartilage destruction occurs beneath the pannus overgrowth, beginning at the joint space margins. In some cases, the granulation tissue will grow beneath the articular cartilage, resulting in subchondral bone destruction. This leads to joint surface collapse due to the loss of the underlying supportive structures. The synovial surfaces frequently show a brown discoloration, due primarily to hemosiderin deposition within the tissues. Clumps of fibrin are also found on some areas of the synovial tissue surfaces. (53, 59)

![FIG. 89-1 Scapulohumeral joint from a dog with erosive immune arthritis. Pannus overgrowth of the humeral head and extensive periarticular soft tissue proliferation are present.](image)

Histologically, the synoviocytic layer is several cells thick. The synoviocytes become hypertrophic, more ovoid than normal, and are occasionally separated from one another by interstitial edema (Fig. 89-3). In some areas of affected joints the synoviocytes lose their ovoid configuration, assuming a more cylindrical shape. Also, synovial cell orientation with regard to the joint space may change from parallel to more perpendicular. (53, 80, 81)
The subsynoviocytic regions also undergo dramatic changes. The inflammatory response is characterized by the presence of many plasma cells, lymphocytes, and small blood vessels. In addition, many fibroblasts are interspersed throughout the area. Hemosiderin and, in particular, hemosiderin-laden macrophages are also found. Polymorphonuclear leukocytes are occasionally seen but are not a prominent cell type. The plasma cells and lymphocytes often aggregate in the vicinity of small blood vessels. However, distinct lymphoid nodules or foci of necrosis are not frequently found. This feature of rheumatoid synovial tissue is seen with some frequency in humans.

Synovial tissue changes examined under transmission electron microscopy parallel the light microscopic changes. Plasma cells are the predominant inflammatory cell infiltrating the subsynoviocytic area. Evidence for humoral and cell-mediated immune reactions within the affected synovium is provided by the identification of T and B lymphocytes, as well as plasma cells, in affected tissues. Occasional extravasated erythrocytes and iron deposition within deep macrophages are also found. Synoviocytes are readily identifiable by type, with B and C cells being slightly more prominent than A cells.

Tubuloreticular structures (TRS), intracytoplasmic bodies frequently found in synoviocytes of human SLE patients, are found in the joint-lining cells of several dogs. These structures have also been found in tissues of dogs affected by certain neoplasms and viral infections. It seems that there is an association between the presence of TRS and rheumatic diseases, viral infections, and neoplasia. The nature and cause of TRS are not known. There are also crystalline arrays of tubules found in the endoplasmic reticulum or in membrane-bound dense bodies.

Changes compatible with secondary degenerative joint disease frequently develop in more chronically affected joints. These changes include periarticular osteophyte formation, fibrous periarticular soft tissue swelling, and articular cartilage fibrillation. These secondary changes are the result of joint instability and indicate the severity of the primary insult to the affected joint. In severely affected joints, intra-articular ligaments and periarticular ligaments are weakened or destroyed, thus adding further to the joint instability and inflammation. In some joints, particularly the carpus and tarsus, fibrous ankylosis may occur.

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CLINICAL PRESENTATION

Immune-mediated erosive articular disease affects primarily dogs of the smaller or toy breeds. No sex predilection is apparent. Affected animals range in age from 8 months to 9 years, with an average age at onset of 4 years.

Early clinical signs of the disease usually include a migratory shifting lameness with soft tissue swelling around involved joints. In very early cases, the only swelling detectable will be that of slight joint capsule distension due to synovial fluid effusion. Initially, only one joint may be painful, and therefore the lameness may not be shifting. However, careful palpation of other peripheral joints will frequently detect joint capsule distension. Frequently there is a cyclic nature to the clinical manifestations of the disease. Owners often report their pets' lameness to last for several days, only to subside spontaneously. During exacerbations the patients are often depressed, anorectic, and reluctant to move about; they may be febrile. Rectal temperature rarely exceeds 103.5°F. These signs, too, remit with the spontaneous disappearance of the lameness.

The disease is progressive, and over a period of weeks to months, the signs return. In addition, the time between clinical episodes decreases and the duration of clinical manifestations of the disease increases. Eventually, enough gross damage
occurs to the articular and periarticular structures to produce angular deformities of the limbs and rupture of ligaments. These angular deformities are more frequent in the carpal and tarsal joints and may progress to complete joint luxation. (53, 59)

Other findings on physical examination may include peripheral lymphadenopathy, occasional splenomegaly, and muscle atrophy of chronically affected limbs.

In the dog, only lymphadenopathy, splenomegaly, and anemia have been reported with frequency as extra-articular or visceral manifestations of RA. These changes also occur in humans affected with RA. In addition, pericarditis, scleritis and anterior uveitis, pleuropulmonary lesions, neuromuscular lesions, arteritis, and subcutaneous nodules have been reported in humans. (18) Subcutaneous nodules are the hallmark of seropositive RA in humans. They are asymptomatic themselves, causing no discomfort other than complaints of their cosmetic appearance. The nodules are rare in the epidermis but common in the subcutaneous tissues and, although they may appear almost anywhere on the body, are frequently found in the vicinity of affected joints. Histologically, they are composed of three distinct zones: a central area of subcutaneous fibrous granulation and necrosis; elongated, radially arranged connective tissue cells about the areas of necrosis; and enveloping granulation tissue in which chronic inflammatory cells are located. (80) While rheumatoid nodules have not been described in the dog with RA, they are of significance because of their inclusion in a list of diagnostic criteria for RA. Table 89-1 presents such a list, and Table 89-2, a list of "exclusions." A human patient manifesting 7 of the 11 features in Table 89-1 is classified as having classic RA, 5 of the 11 features constitutes a diagnosis of definitive RA, while 3 of the 11 defines probable RA. A diagnosis of possible RA requires two of the following: morning stiffness, tenderness, and pain on joint motion, history or observation of joint swelling, subcutaneous nodules, elevated erythrocyte sedimentation rate or C-reactive protein, and iritis. (65)

If a patient manifests any one of the features listed under "exclusions," a diagnosis of RA should not be made. Obviously, these lists are constructed for the purpose of disease classification and categorization. They help in the clinical reporting of a condition but do little to help insuggesting alternatives to diagnosis if a patient manifests many of the diagnostic features of Table 89-1as well as one or more of the features of Table 89-2. Until more detailed studies of immune-mediated articular diseases of the dog have been done, it may be best to use the classification of erosive and nonerosive.

TABLE 89-1 Criteria Diagnostic for Rheumatoid Arthritis

These lists might be borne in mind when attempting to classify the diseases of the dog and compare them with those of humans.

TABLE 89-2 Exclusions Precluding Diagnosis of Rheumatoid Arthritis

CLINICAL LABORATORY FINDINGS

Laboratory findings in erosive immune-mediated arthritis are those of inflammatory disease. While no single test is specific for this condition, the appropriate findings in a select number of tests strongly aid in its diagnosis.

Erythrocyte counts, hemoglobin, and packed cell volume are generally within normal limits but in some cases may be at the very lower limits of the normal range; mild anemia has been reported. (47, 53, 59) A normocytic, normochromic anemia is known to occur in many chronic inflammatory diseases of the dog. (22)

Mild leukocytosis manifested as a neutrophilia is a frequent finding. White blood cell counts range from normal to nearly 29,000/mm³. (47, 53, 59) While a few animals reported to have canine RA had concomitant bacterial dermatitis, which might account for leukocytosis, elevated white blood cell counts may be considered a normal response to tissue injury.
andinflammation without the presence of infection. The erythrocytesedimentation rate (ESR) may be used as a nonspecific assessmentof systemic inflammation. Although it is influenced by manyfactors including anemia, it has been described as the singlemost important laboratory test of inflammatory activity in theconnective tissue diseases. (3 )

Sedimentation rates are elevated in nearly 95% of human RApatients with active disease. Normal ESR values for the dogrange from 1 mm to 6 mm at 30 minutes to 1 mm to 25 mm at 60minutes. (6,13,70) Values were found to be increased at30 minutes in dogs with erosive immune arthritis and normal at 60 minutes. (47)

The Coomb's test determines the presence of antibodiesdirected against the patient's own erythrocytes. (70) A positive resultoften indicates an autoimmune process, such as autoimmune hemolytic anemia (AHA). Positive results on Coomb's tests are sometimes seen in dogs with SLE and have been reported in one case of RA of the dog. (53) While the early signs of AHA in the dog (malaise, anemia, pyrexia, peripheral lymphadenopathy, splenomegaly) may be seen with immune-mediated erosive joint disease, in a majority of cases, the results of the Coomb's test are negative.

Great variability has been found when measuring the quantities of serum proteins by electrophoresis in dogs with RA. Alterations have been found in all fractions and different fractions in the same dog at different times. (47) The gammaglobulin fraction contains the circulating antibodies, and elevation in this fraction would be expected. However, in dogs as well as in humans with RA, g-globulins vary and may be elevated or within normal limits. (3,53,58)

Increases in alpha2-globulin and fibrinogen occur nonspecifically in the presence of inflammation. (3) Both of these proteins are frequently elevated in dogs with RA. (53,60) Hypoaalbuminemia is also seen with frequency. While the specific cause of decreased serum albumin is not known, it has been related to a state of hypermetabolic activity in human RA patients, probably influenced by the inflammatory process of the disease. (3)

Serum complement levels as assayed by total hemolytic complement (THC) levels are often increased in dogs with RA and decreased in those with SLE. Those findings are analogous to those of humans with the same conditions. (92) It should be noted that changes in serum THC occur in other inflammatory conditions as well. THC is decreased in dogs with glomerular nephritis and hemorrhagic gastroenteritis and increased in a number of conditions including hyperthyroidism and neoplasia. (42) Comparison of paired samples of synovial fluid and serum complement levels has been used in humans for prognostic purposes in RA. (10) In severe cases of human RA, serum complement levels may be normal or slightly elevated while synovial fluid levels are decreased. Similar studies in the dog have not been reported.

Serum rheumatoid factor may be detected by several methods. The more common systems involve the sensitization of particles with antigen and agglutination of the particles with varying dilutions of serum suspected to contain rheumatoid factor. Latex beads or specially treated sheep red blood cells are commonly used.

Interpretation of rheumatoid factor findings requires knowledge of the type of test system used for its detection. Test systems in which human IgG is used to coat the particles have been reported to be less specific and less sensitive for rheumatoid factor in dogs than systems using canine IgG-coated particles. (47,93) Also, test systems using sheep erythrocytes, which are coated with subagglutinating doses of rabbit or dog antisheep serum, may detect a different rheumatoid factor than the canine IgG coated latex particle system. (93)

In humans, approximately 5% of the normal population has detectable rheumatoid factor in concentrations found in those affected with RA. In addition, rheumatoid factor is found in insignificant dilutions in persons with a variety of diseases not related to RA. (12) As noted, rheumatoid factor is found in approximately 25% of dogs affected with RA. (61A) and may also be present in normal dogs as well as some affected with other conditions. (34A) If rheumatoid factor is found in significant dilutions in dogs in conjunction with others of RA, it should add great weight to a diagnosis of RA. If it is not found when an appropriate test system has been used but all other findings indicate RA, the diagnosis should be made.

Gamma-globulins capable of reacting with nuclear material are referred to as antinuclear factors. (3) The antinuclear reaction is found in humans with a variety of connective tissue diseases but is most frequently seen in those with SLE. These autoantibodies are present in most cases of SLE in the dog. Occasionally they are found in dogs with erosive immune-mediated articular disease. Their presence in dogs with RA is of no clinical significance. (47) However, when found in conjunction with lupus erythematosus (LE) cells, the condition cannot be classified as RA, since LE cells appear on the list of diagnostic exclusions. (65)

LE cells are neutrophilic leukocytes of blood and bone marrow containing cytoplasmic inclusions. These inclusions arise from the LE phenomenon, which is initiated when an LE factor or antibody reacts with cellular nuclear material. Cell injury allows the LE factor to associate with the nuclear protein, which in the presence of complement forms an immune complex. This complex is then taken up by phagocytic cells forming the cytoplasmic inclusions.
LE cells are typically found in dogs with SLE but on rare occasion have been found in some with RA. Their presence in large numbers prevents a clinical condition from being classified as RA. Although the immune-mediated arthropathies are inflammatory and may affect body parts other than joints, the liver is most often spared. As a result, serum levels of liver enzymes are usually within normal limits. Significant elevations of serum levels of glutamic-pyruvic transaminase (GPT), glutamic-oxaloacetic transaminase (GOT), and serum alkaline phosphatase (SAP) have not been found in dogs with RA. Levels of serum lactatedehydrogenase (SLDH) and creatine phosphokinase (SCP) may be elevated in various diseases affecting the liver, muscle, or bone. Elevations in levels of these enzymes have been reported in RA of the dog.

**RADIOGRAPHIC FINDINGS**

A variety of radiographic changes involving the joint surfaces and periarticular tissues are found in erosive immune-mediated articular disease. These changes may include periarticular soft tissue swelling, joint capsule effusion, joint space widening and later joint space narrowing, loss of subchondral and juxta-articular bone, subluxation, luxation, ankylosis of the affected joint, soft tissue atrophy, periarticular soft tissue mineralization, and changes characteristic of degenerative joint disease (Fig. 89-4).

Periarticular soft tissue swelling and joint capsule distension are early radiographic findings. The swelling is usually confined to the limits of the joint capsule and may displace but not obliterate, fascial planes. These changes are nonspecific. The joint effusion and distended joint capsule may cause the joint space to appear wider than normal. However, evaluation of joint space width is difficult with routine recumbent projections. Obliquity of the x-ray beam, patient malpositioning, and traction on the limb during restraint for positioning may cause changes that could be erroneously interpreted as increase in joint space width. Judgments regarding increases in joint space width should be tempered unless the patient was fully weight-bearing on the joint in question at the time the radiographs were made.

Osteoporosis of juxta-articular bone may be the earliest radiographic bony change. It occurs several weeks to months following the onset of the disease. With disease progression, the characteristic findings of erosive joint disease become obvious. These begin as lucent cystlike areas in the subchondral bone varying in size from large to small and having either sharply demarcated or poorly defined borders.

Articular cartilage loss begins at the joint margins. Radiolucent areas are frequently seen at the juxta-articular attachment of ligaments as well. As the condition progresses, loss of articular cartilage and subchondral bone continues, frequently resulting in a collapse or narrowing of the joint space.

Many rheumatoid joints will show changes of secondary degenerative joint disease. These changes are represented...
by osteophytes, sclerosis of subchondral bone, and mineralization of periarticular soft tissue and joint capsule. In some cases, luxation or subluxation is present owing to changes of joint surface architecture and loss of ligamentous support. Angular deformities of the carpal, tarsal, and interphalangeal joints may result, particularly in advanced cases (Figs. 89-5 through 89-7) (8,55)


THERAPY

RA is a chronic lifelong disease for which there is no known cure. There are a variety of measures that when used alone or in combination will lead to a significant improvement of the patient's condition. Relief of patient discomfort, prevention of further joint damage, and preservation of joint function are the goals of therapy.

Because the etiology of RA is unknown, treatment regimes may be considered nonspecific. Their aim is to reduce the active, destructive inflammatory activities occurring within the affected joints. Rest and physiotherapy are important aspects of treatment. Drugs used include salicylates, gold, corticosteroids, nonsteroidal anti-inflammatory drugs, and immunosuppressive drugs. Penicillamine and antimalarial drugs have also been used in humans with RA.

General Considerations

Because the disease is chronic and unremitting, client education is important. The owner must be told that a cure will probably not occur; that even with therapy, exacerbations of signs may occur; that there are several systemic complications that likewise may occur, causing further problems for them and discomfort for their pet; and finally, that relief of signs may take some time even though drugs are being given.

Exercise is important, particularly to prevent disuse atrophy of muscles and contracture. Some patients, even with severe damage to articular tissues, will respond dramatically to therapy, particularly to corticosteroids. Excessive exercise in these patients can lead to secondary damage of the affected joints. Controlled exercise is mandatory. Each patient must be observed carefully and an exercise program tailored to his abilities. As the patient responds to therapy, length of exercise periods and stressfulness of each period may be increased. Leash walking for increasing distances, depending upon patient response, is an excellent way to maintain muscle tone and joint function. Running or jumping should be discouraged, particularly in the early stages of therapy.

Owners must be taught to recognize the signs of excessive exercise and to gauge the physical activities of their pets based on these signs. Stiffness and soreness several hours following activity, changes in gait pattern, or general reluctance should be noted. In addition, even those patients who are responding well to therapy may appear stiff and reluctant to move after long periods (several hours) of inactivity. This is classic morning stiffness. Morning stiffness should not be confused with the signs related to overactivity.

Animals who are overweight must be put on a diet. Caloric requirements of the animal must be calculated based on its ideal weight and expected activity. A dietary plan must then be established and incorporated into the overall treatment plan.

Patient activity, even when signs of disease are in remission, must be carefully controlled. Little true healing or repair of damaged tissue occurs during remission, and excessive activity may hasten the onset of secondary degenerative changes. Forced inactivity or patient rest, particularly during active, acute stages of the condition, is most important. (79)

Drugs

A great variety of drugs are now available for the treatment of immune-mediated articular diseases. Aspirin and other nonsteroidal anti-inflammatory drugs exert their effects primarily by interfering with the production or release of prostaglandins. Some of these compounds may also be mildly analgesic. Gold salts are frequently used in humans with RA but have been used sparingly in dogs. Cytotoxic agents are also used in humans and have been used with success in the dog as well. Corticosteroids remain the drug most commonly used by the veterinary practitioner for the treatment of immune joint disease.
It must be borne in mind that regardless of the treatment regime used, RA will not be cured. Drugs are given to reduce inflammation and discomfort and to increase joint function. One of the goals of therapy should be to reach the point at which the patient remains in remission while receiving the smallest amount of drug possible. There may even be times when no drugs need be given to maintain remission. Treatment regimens, therefore, must be tailored to ever decreasing dosages of drug while maintaining careful observation of the patient for adverse reactions to the lower dosages. A decreasing dosage regimen should be implemented after the patient has passed through the initial acute inflammatory stages of the disease.

Various drugs or drug combinations may need to be given before patient relief is obtained. Patient stabilization then follows, with drug levels maintained at the dosages used to overcome the initial phases of disease. Once stabilization has been achieved as judged by return of more normal patient attitude, appetite, and desire to participate in daily activities, dosages may be gradually decreased.

The usual course is to decrease the amount of drug given by one half. Medications that are given three or four times a day are still given at the same frequency, but the dosages are decreased. Each new dosage level is maintained for approximately 2 weeks before another reduction is attempted. Decreasing dosage schemes must be tailored not only to patient response, but to the pharmacokinetics of the drugs given. As an example, abrupt decreases in long-standing high-dose corticosteroid therapy may produce severe adverse effects that are related to drug withdrawal, not to exacerbation of the condition being treated.

**ASPIRIN.**

In humans, aspirin is the cornerstone of drug treatment for RA. A general principle of aspirin therapy in humans is to gradually increase the dosage to produce mild toxic effects and then reduce the dosage to tolerable levels. Tinnitus and gastrointestinal distress are the most common side-effects of excessive aspirin dosages. (46)

In the dog, plasma salicylate concentrations of 50 mg/liter are satisfactory to produce analgesic and antipyretic effects, and concentrations of 200 mg/liter are necessary to produce anti-inflammatory effects. Concentrations greater than 300 mg/liter are commonly toxic. (16) Orally administered aspirin given at 25 mg/kg of body weight three times per day will maintain anti-inflammatory plasma concentrations. Although it may take up to 2 weeks to observe benefits from the aspirin, the dosage may be increased within 4 to 5 days if the desired effects have not been achieved. Dosages of 50 mg/kg frequently produce emesis. (95) Aspirin compounds, even the buttered type, should always be given with food. Those patients in whom severe gastric upset is produced by aspirin may benefit from salicylate products that contain magnesium-aluminum hydroxide.

Once relief of clinical signs has been achieved and the patient has been maintained for a minimum of 2 weeks, the aspirin dosage may be reduced. The amount given is usually reduced by one half while continuing the three times per day dosage schedule. If the patient can be maintained thus for another 2 weeks, the amount given is again reduced by one half:

While aspirin has been used with some success in dogs with RA, (53) other investigators have found it to be less effective. (59) While aspirin may not produce the desired effects in all cases, it should be given in proper dosages for an appropriate period of time before being abandoned. Aspirin, when taken at usual therapeutic levels, is relatively free of side-effects, and of the drugs available for the treatment of RA, it is the least expensive.

A difficulty that may be encountered during therapy is convincing the pet owner that such large amounts of aspirin are needed and that the drug must be given regularly and for the prescribed length of time. Owners must be convinced that to a great extent the success of therapy resides with their conscientious administration of the prescribed medication.

**NONSTEROIDAL ANTI-INFLAMMATORY DRUGS**

exert their efficacy by inhibiting either synthesis or release of inflammation-producing prostaglandins. To date, there is no data comparing the efficacy in the dog of these drugs with that of aspirin. Their use in humans with RA is well documented. Most reports agree that the primary advantage of nonsteroidal anti-inflammatory drugs over aspirin is the fewer side-effects, particularly involving the gastrointestinal tract. On a comparable dosage basis, the anti-inflammatory, antipyretic, and analgesic properties of aspirin and most other nonsteroidal anti-inflammatory agents are nearly equal.

Ibuprofen and indomethacin are frequently used in humans with RA. While there are no reports of their use in dogs with RA, they may find a place in the therapy of those animals not responding well to aspirin. The dosages of each drug recommended for the treatment of degenerative joint disease (see chapter 87) can be used initially for the treatment of RA. Increased dosages should be given if the initial response is not satisfactory.

Phenylbutazone has not been used as extensively for RA as it has been for degenerative joint disease. In the patient not responsive to salicylates, it may be of some benefit, although no data exist to support this. Dosages would be comparable to those used for the treatment of degenerative joint disease. Of prime importance is the need to individualize dosage, particularly with aspirin, the nonsteroidal anti-inflammatory agents, and corticosteroids. Because of the great variability in response to therapy and the development of side-effects, patients must be monitored closely and adjustment in
dosages made as needed. Thus, under certain circumstances the use of drugs in combination may be advantageous. However, the concomitant use of aspirin and other nonsteroidal anti-inflammatory agents has been shown to be no more effective than when either is used alone. (57)

GLUCOCORTICOIDS.
The anti-inflammatory properties of glucocorticoids are well known. In spite of the inevitable, sometimes detrimental side-effects, systemic glucocorticoids add a spectacular dimension to the overall management of rheumatic diseases. However, other forms of therapy should be considered first in the treatment of RA. The exception may be those cases in which the patient is so debilitated by disease that immediate relief is mandatory. The long-term side-effects of chronic corticosteroid administration are well known and should be avoided whenever possible. The glucocorticoids recommended are the intermediate-acting synthetic agents, prednisone and prednisolone. The advantage of these agents over longer acting compounds such as dexamethasone is that if used in single daily or alternate day dosages, adrenal suppression is less. (37) It must be kept in mind that glucocorticoids do not retard the progress of RA. Although they are potent suppressors of inflammation, the disease processes are continuing. The deleterious effects of glucocorticoids on articular cartilage have been cited in Chapter 88.

In cases of canine RA unresponsive to aspirin, glucocorticoids have been used with some success. (53) It has also been found that some cases are responsive for only a short time, with recurrence occurring even when the drug is given in increasing amounts. (59) In such situations, other forms of therapy such as immunosuppression with cytotoxic agents, with or without concomitant glucocorticoid therapy, are frequently effective. (59)

In those animals that may benefit from glucocorticoid administration, the following dosage schedule may be used: initially, prednisolone is given parenterally at a dose of 1 mg to 2 mg/kg of body weight twice daily; this is followed by oral maintenance dosage of 0.5 mg to 1.0 mg/kg twice daily. Favorable response is usually evident within 24 to 48 hours after the drug has been given. If so, the dosage is maintained for several days and then smaller amounts are given. Because of individual variability in response to medication and severity of disease, dosage schedules and regimes are established for each patient on a trial-and-error basis. Once maintenance is established for several days, attempts are made to decrease the amount of corticosteroids given. Usually, the amount being given is reduced by one half while the frequency of administration is maintained. For example, if 2 mg/kg twice daily was being given, the new dose would be 1 mg/kg twice daily. Once low dosages are reached, once a day administration or even alternate day administration may be possible. However, exacerbations are not uncommon.

Aspirin administration may be beneficial after the initial inflammatory episode has been controlled with corticosteroids. In some cases in which the corticosteroids cannot be reduced beyond a certain dosage without return of signs, aspirin may be effective in controlling the situation, allowing continued lowering of the glucocorticoid dose. While this regime may be beneficial, the patient must be monitored carefully for gastrointestinal disturbances such as melena.

INTRA-ARTICULAR CORTICOSTEROID THERAPY.
The intra-articular injection of corticosteroids as a treatment for RA remains a somewhat controversial topic. In humans there is no doubt that when used improperly, that is, under inappropriate circumstances or at inappropriate dosages, more harm than good may result. Conversely, in selected human patients under rigid asepsis and at proper dosages, symptomatic relief of weeks to months may be obtained in the injected joint. (31)

While the practice has been performed in dogs for a variety of conditions including RA, results have not been reported. Until such information is available, the recommendations and precautions of intra-articular injections described for human RA patients may be followed.

Indications for intra-articular corticosteroid injection in the treatment of RA in humans include the following: involvement of one or only a few peripheral joints and exclusion of infection as a cause; as an adjunct to systemic therapy; and when systemic therapy may be contraindicated. (31) Contraindications include presence of infection in or near the joint, or bacteremia; severe inflammation in many joints; severe joint destruction or deformity; and lack of positive response to trial injections. (31)

Before injecting corticosteroids into a joint, one must bear in mind that corticosteroids must not be injected into a joint until a diagnosis has been established, and that injection of corticosteroids into a joint is neither specific treatment nor cure for joint inflammation. In humans, a maximum of 20 mg of corticosteroids is recommended per injection and frequency of injection per joint should not exceed once every 6 weeks. (31)

Injections should be performed under aseptic conditions. (See chapter 86.) A volume of synovial fluid at least equal to the volume of material to be injected should be aspirated from the joint prior to injection to avoid joint capsule overdistension.
IMMUNOSUPPRESSIVE THERAPY.
Azathioprine and cyclophosphamide are frequently recommended for the treatment of RA that has not responded well to aspirin or other nonsteroidal anti-inflammatory agents. These drugs are better known as cancer chemotherapeutic agents. However, with the recognition that immunopathogenic mechanisms are important in the pathogenesis of rheumatic diseases came use of immunosuppressive agents.

The precise mechanisms by which azathioprine acts to suppress immune activities are not known. As a cancer treatment, the drug alters the production of cellular purine, thus inhibiting cell multiplication. The connection between purine antagonism and immunosuppression is not well understood. The immunosuppressive effects of experimentally administered azathioprine have been substantiated by the following: decreased antibody response in antigen-challenged rabbits; prolonged skin graft survival in noncompatible mice; decrease in delayed type hypersensitivity reactions in rabbits; and suppression of adjuvant arthritis in mice. In humans, the drug has caused an increase in renal transplant survival, a 33% decrease in IgG synthesis, a 40% decrease in IgM synthesis, and a decreased primary antibody response after bacterial antigenic challenge.

Cyclophosphamide, the most potent alkylating agent known, is closely related structurally to nitrogen mustard. In contrast to purine antagonists, which attack cells primarily when they are rapidly dividing, alkylating agents react extensively with nondividing cells. They are most toxic, however, to cells that are in the S phase of the cell cycle, that is, during DNA synthesis. Cyclophosphamide acts by altering amino acid sequence and the intrastrand and interstrand cross linkages of DNA.

Cyclophosphamide blocks some of the basic processes of the immune response such as antigen uptake, antigen recognition, and antibody production. It is rather specific in its activities in suppression of Lymphocyte function. Because of the thin margin between effectiveness and toxicity, these drugs must be given with caution. The administration of these immunosuppressives to an inappropriate patient or on casual whim is to be emphatically discouraged. This form of therapy is not curative, nor does it produce its palliative effects with few complications as does aspirin.

Immunosuppressive therapy with a combination of cyclophosphamide, azathioprine, and prednisolone has been used in dogs with RA. Since these drugs are cancer chemotherapeutics, dosages of cyclophosphamide and azathioprine are calculated according to square meters of body surface area. The dosages for immune joint disease expressed in milligrams per kilogram of body weight are slightly less than those for cancer therapy. The treatment regimes are similar, however, that is, the drugs are given for 4 days with a 3-day break in between. This is mainly to avoid adverse reactions and toxicities.

A treatment regime for immune-mediated arthritis based on immunosuppressive therapy is as follows: cyclophosphamide is given orally at a dose of 1.5 mg to 2.5 mg/kg for 4 consecutive days of each week. Dogs weighing 10 kg and less receive 2.5 mg/kg, those 10 kg to 25 kg receive 2 mg/kg, and dogs weighing more than 25 kg receive 1.5 mg/kg. Azathioprine is given orally at a dose of 2 mg/kg daily. Prednisolone is given at a dose of 1 mg to 2 mg/kg orally, with larger dogs receiving the lower dose. White blood cell counts are monitored weekly for the first several months of therapy. The dosage of the cytotoxic drugs is reduced by one half if the count falls below 7000/mm3. As remission occurs, the azathioprine is discontinued first, and the prednisolone is given every 48 hours. When complete remission has been present for 3 consecutive months, the cyclophosphamide may be discontinued. Many dogs will require continuous prednisolone or continuous prednisolone-cyclophosphamide therapy for disease control. Chronic maintenance dosages should be as low as possible.

Adverse reactions to cyclophosphamide in the dog include vomiting, bloody diarrhea, salivation, changes in body temperature, anorexia, weight loss, and hematuria. Urinary cystitis is also a frequent complication of therapy. Side-effects of azathioprine are similar to those of cyclophosphamide. In addition, azathioprine may be mildly hepatotoxic. Because of its immunosuppressive actions, a potentially serious complication of azathioprine treatment is the development of neoplasia.

Signs of toxicosis should herald the cessation of cyclophosphamide and azathioprine administration. Therapy may be begun again at lower dosages after symptomatic treatment for the adverse reactions has been completed.

Because of the myriad difficulties with toxicity, guidelines were established for the use of immunosuppressive agents in the treatment of rheumatic diseases in humans. Patients must meet all of the following criteria: disease of a seriously crippling nature but with potentially reversible lesions; failure to respond to conventional therapy; absence of active infection; and absence of hematologic complications. Also included were recommendations of informed consent by the patient and therequirements of meticulous patient monitoring in response to therapy and long-term patient follow-up.

GOLD COMPOUNDS.
Chrysotherapy, the use of gold compounds, has been used in human RA patients since 1928. It is frequently used in patients with fairly acute cases who have not responded well to other treatment. The exact mechanism of action of the gold compounds is not well understood. The gold compounds appear to act primarily at the level of the lymphocyte and macrophage, preventing the release of substances that stimulate the production of antibodies.

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compounds is not known. They may in some way be involved with the inhibition of synthesis or release of the inflammation producing prostaglandins, they may stabilize lysosomal membranes, or they may prevent the elaboration of lysosomal enzymes. (20)

A number of gold compounds are available, but only two, goldsodium thiomalate and aurothioglucose, have been used extensively in the United States. (99) To date, the use of gold to treat RA in dogs has been reported on only a limited number of cases. (54) Goldsodium thiomalate was administered intramuscularly at a dose of 1 mg/kg of body weight per week.

As in human patients treated with gold, improvement was not seen for several weeks. Of the three rheumatoid dogs so treated, improvement was seen at 8 and 10 weeks in two dogs and the other dog remained unchanged, but the disease progression was halted. In the third dog, the gold treatments were discontinued after 24 weeks. Six weeks later, the disease exacerbated and alternate-week gold therapy was then begun. Treatment was stopped in the other two animals after 12 and 16 weeks, respectively. Both animals remained in remission for the length of the follow-up period, which was 9 and 6 months.

Side-effects of gold therapy occur in approximately 35% of human rheumatoid patients. (99) A nondescript pruritic dermatitis is seen most frequently. Anaphylactic reactions are also recorded, although they are rare. Toxic manifestations may occur at anytime during the course of therapy. Hospitalization and close observation for 24 hours following initial therapy in dogs has been recommended. (54) In addition, frequent assessment of renal function and hematologic evaluation is suggested. (8)

New gold compounds, some of which may be administered orally, are being investigated. Controlled studies in the dog are needed to further assess the efficacy of both oral and parenterally administered gold compounds. The initial results with intramuscular administration of gold to dogs with RA is encouraging.

**DRUGS.**

Levamisole hydrochloride is a broad-spectrum anthelmintic that has been recommended for the treatment of canine heartworm disease. (36) It is capable of augmenting the effector phase of immune and inflammatory processes by increasing chemotaxis and phagocytosis by polymorphonuclear cells and macrophages. Its effect is most pronounced when the patient is immunodeficient but minimal when immune functions are normal. (31) Levamisole has been found to be of some value in the treatment of humans with RA, but its use in the dog for this condition has not been reported.

The antimalarial drugs hydroxychloroquine sulfate and chloroquine are sometimes used to treat RA in humans. At appropriate dosages, these drugs have produced beneficial effects when compared with control patients receiving other medications. (11) Retinopathy is a serious side-effect of the drug. Results of treatment are usually not seen until the drug has been given for several months. For this reason, it is not amenable for the treatment of acute disease. The use of these drugs has not been reported in the treatment of RA in the dog.

Penicillamine is another drug that seems to bring relief to some human RA patients. (11) Its use in the dog with RA has not been reported, although it is used for the treatment of lead poisoning (40) and cystine urinary calculi. (42) The D-isomer of this drug is now used, since the L form was found to be too toxic. The use of penicillamine, which is related structurally to penicillin, for the treatment of RA came after it was discovered that the drug caused a dissociation of macroglobulins. It will also dissociate rheumatoid factor. In addition, it inhibits cross linkage of collagen and has an in vitro inhibitory effect on Lymphocyte transformation and may, under certain circumstances, enhance lymphocytic reactivity and cause a decrease in circulating immune complexes. (11) Side-effects include leukopenia, which may develop suddenly, thrombocytopenia, dysgeusia (loss of taste) and nephrotoxicity. (82)

**Irradiation**

Recent reports of total Lymphoid irradiation for the treatment of intractable or refractory RA in humans have been encouraging. (39, 86) Patients with long-standing disease (3-28 years) not controllable with other regimes received fractionated dosages of irradiation to a maximum of 2000 rads to 3000 rads. Maximum improvement in most patients occurred approximately 6 months after irradiation and continued for as long as 18 months. This approach to RA therapy is thus far recommended only for the chronic, severely affected patient.

**Surgery**

Surgery has not played as prominent a role in the treatment of immune arthritis of the dog as has systemic medical therapy. Synovectomy is a routine procedure in the treatment of humans with RA. Indications for synovectomy include persistent synovitis, minimal but progressive roentgenographic changes, and unremitting pain. (35) Some joints, such as the hip, are not routinely subjected to synovectomy because of the difficulty in reaching the joint tissues. (77)

The advantages of synovectomy are that it removes the affected synovial tissue, increases joint range of motion, slows the progressive destructiveness of the disease, and often produces a pain-free joint. Results of synovectomy in humans show that
nearly 80% of those operated on still had satisfactory results 2 years later. This drops to between 50% and 70% at 5 years following surgery. (77)

If the following modified criteria, originally established for synovectomy of the knee in humans, were applied to the dog, some benefit might result: several months of sound but unsuccessful medical therapy, persistent pain, intermittent or constant effusion, mild joint deformity, and mild radiographic evidence of joint involvement.

Arthrodesis has been recommended for humans (35) and for dogs (59) in whom joint destruction is severe and pain cannot be controlled medically. Depending upon the joint operated on, the procedure will restore some function to the limb but will obviously limit the patient's capabilities.

Excision arthroplasty is recommended for those patients in whom all other forms of therapy have proven unsatisfactory. Excision of the radial head, distal ulna, and femoral head and neck is performed in humans with RA, but only in those meeting specific criteria. (35, 77) The procedure is performed almost exclusively on the femoral head and neck in the dog but has not been reported as a treatment for RA.

**Nonerosive Immune-Mediated Articular Disease**

Nonerosive immune-mediated articular disease of the dog is most commonly associated with SLE. The etiology of this disease is unknown, but it may affect many organ systems. Polyarthritis, myositis, glomerulonephritis, dermatitis, and anemia are frequent manifestations of the condition. An infectious cause has not been found. However, in humans SLE may be precipitated by the administration of certain drugs, most notably procainamide. (95) Although procainamide is used frequently in dogs to control cardiac dysrhythmia, as of this writing its administration has not been noted to cause SLE.

SLE is associated with the formation of detectable immune complexes that are found in various tissues. Autoantibodies participate in immune complex-mediated tissue injury, and this pathogenic mechanism is the major cause of disease activity. (84) The nature or manifestation of the disease is dependent upon the type of antibodies formed and their distribution or localization in tissue. (24) Circulating autoantibodies are not harmful until they combine with antigen.

In humans, a variety of antigens have been detected in patients with SLE. These include the nuclear material antigens DNA, histones, and nuclear protein; the cytoplasmic antigens RNA, ribosomes, and lipids; antigens of erythrocytes, T and B cell lymphocytes, and platelets; and tissue-specific antigens of thyroid, liver, muscle, stomach, and adrenal glands. (34)

Antibodies to nuclear material (ANA) are the most prominent of the autoantibodies associated with SLE. In humans they are divided into four main groups: those directed toward DNA; those directed toward a molecular complex of DNA and histones; those directed toward histones (a family of proteins within the nucleus); and those directed toward acidic or nonhistone nuclear proteins. Within each of these broad categories, more specificity is found. For instance, there are antibodies that react only with single-stranded DNA and those that react only with double-stranded DNA. In addition, there are at least four different antibodies that react with various types of acidic or nonhistone nuclear protein. (84)

In dogs with SLE, antibodies to native double stranded DNA, heat-denatured single-stranded DNA, and antibodies to nonhistone nuclear protein have been detected. (43, 51) Not all types of ANA are present in all SLE patients. The significance is that different clinical expressions of the disease are manifested depending upon the type of ANA present.

ANA are detected by indirect immunofluorescence. Patient serum is reacted with specially prepared tissue or blood smears. Mouse liver and blood are frequently used. (85) Fluorescent reactivity of the serum ANA with the nuclear material of the tissue samples is noted by fluorescent microscopy. Various patterns of fluorescence are characteristic of the different ANA. For example, nuclear rim staining is produced by antibodies to native DNA and histones; a homogenous pattern is produced by antibodies to histones; and a speckled pattern of nuclear staining is shown by the antibodies to nonhistone nuclear antigens. (51)

In a recent survey of 20 dogs with SLE, clinical signs were correlated with the type of ANA present as suggested by immunofluorescent staining patterns. Although all dogs had polyarthritis, proteinuria was absent or transient in 15 of the dogs. ANA staining from each of these dogs resulted in an aspeckled pattern. The other dogs, who had prominent persistent proteinuria, demonstrated a homogenous fluorescent staining pattern. (51)
ETIOLOGY

Although much is known regarding the autoimmunologic events of SLE that result in tissue damage and disease, the initiating cause or causes are not known. Certain findings in humans, such as the familial tendency to SLE and inherited complement-component deficiencies in some SLE patients, lead to the belief that genetic factors may play a role in the distribution and appearance of the disease. However, this has not been confirmed. (69)

Extensive genetic and breeding studies on a colony of SLE dogs have not been able to confirm any conventional genetic mechanisms by which the disease may be transmitted. (44)

Viral studies on both canine and human SLE patients have been unrewarding. On occasion, certain findings in particular patients may suggest that a virus is responsible for the disease, but these findings have not been consistent. (69)

A hypothesis had been offered that a relationship existed between human and canine SLE patients. (4) This was suggested when the dogs of two separate families in which several members were affected by SLE were found to have some serologic abnormalities and in one case some clinical abnormalities often associated with SLE in the dog. Two studies have since shown the hypothesis to be untrue. One study compared the serologic findings of dogs owned by SLE patients to age-, breed-, and sex-matched dogs owned by persons not affected by SLE. (34) The other studied normal persons who own dogs that had serologic evidence of SLE. (66) The conclusion of both studies was the same: SLE is not transmitted from dogs to humans or vice versa.

As noted, certain drugs administered to humans may induce a condition indistinguishable from "spontaneous" SLE. The mechanism by which these drugs produce SLE is not known. It has been proposed that the drug may act as a hapten and stimulate production of antibody against the carrier protein of the drug, or the drug in some way may render nuclear material antigenic. (96) Signs and symptoms usually subside when administration of the drug is ceased, and ANA, positive tests for LE cells, and other manifestations of the disease stop as well. Procainamide has been the drug associated most frequently with inducing SLE. Other drugs implicated include penicillin, phenylbutazone, diphenylhydantoin, tetracycline, and streptomycin. (96) Drug-induced SLE has not been reported in dogs.

PATHOLOGY

SLE is a chronic inflammatory disease affecting the joints, skin, kidneys, muscles, myocardium, pleura, and the hematopoietic tissues. Most of the pathologic lesions appear to be the result of immune-complex deposition and complement activation. Thrombocytopenia, AHA, leukopenia, and consumption coagulopathy may result from the presence of specific antibodies directed against erythrocytes, thrombocytes, and anticoagulation factors. These antibodies, in the presence of complement, cause cell destruction leading to specific pathologic changes and clinical manifestations. (19, 24)

Articular tissues are affected in nearly 80% of dogs with SLE. Histologically, the synovial tissue is characterized by synoviocytic proliferation and fibrinous villous synovitis. The subsynoviocytic tissues become infiltrated with plasma cells, monocytes, and neutrophils. In the deeper regions of the subsynoviocytic tissues, perivascular cuffing by inflammatory cells may be seen. While villous hypertrophy and increased vascularity of the subsynoviocytic tissues are frequent findings, pannus formation and articular cartilage destruction are not prominent features (Figs. 89-8 through 89-10). (24, 61)

In some cases, changes associated with secondary degenerative joint disease may also be found. They result from joint instability due to ligament rupture. However, the progressive destructive lesions of articular cartilage seen in RA are not a feature of SLE.

FIG. 89-8 Synovial membrane from a dog with nonerosive immune arthritis. The subsynoviocytic region is thickened and infiltrated by lymphocytes and plasma cells. (H & E x 10)
Skin lesions are the result of immune-complex deposition at the dermoepidermal junction and are present in nearly 50% of patients. Histologically, there may be a thinning or thickening of the epidermis frequently associated with hydropic degeneration of the basal cell layer. Fibrinoid degeneration of dermal connective tissue may occur, as well as mononuclear cell infiltration of periadnexal areas. Glomerulonephritis due to immune-complex deposition is another relatively frequent lesion seen in approximately 50% of patients. The classic lesion is a thickening of the glomerular basement membrane. In acute cases, increased cellularity of the mesangium, swelling of the endothelium, and neutrophilic infiltration of the glomerular tufts will be seen. Immunofluorescent staining will frequently show immunoglobulin and complement deposition along the basement membrane of the glomeruli. Eventually, sclerosis and hyalination of the glomeruli occur.

Less frequent lesions of SLE include myositis, arteritis, and pleuritis. Myositis is characterized histologically by skeletal muscle myofiber necrosis, degeneration and vascularization, and perivascular and interstitial infiltration of macrophages, lymphocytes, and plasma cells. Vascular lesions may affect any organ. The small muscular arterioles are affected with lesions ranging from acute necrotizing vasculitis to chronic segmental fibrinoid change. These lesions are frequently seen in the kidney. In addition, ischemic necrosis and myofibril degeneration secondary to vasculitis have been found in the myocardium of some dogs with SLE.

The serous membranes of the pleura and pericardium may be affected. Changes include a thickening of the tissue with edema as well as a covering of fibrinous exudate.

### CLINICAL SIGNS

There is no specific pattern to the presenting signs of SLE. Clinical manifestations of the disease will vary with organ involvement. The disease is characterized by the sequential or simultaneous development of polyarthritis, dermatitis, proteinuria, myositis, hemolytic anemia, and thrombocytopenia. Not all of these problems occur in every SLE patient, and there may be a long interval between the involvement of one organ system and another.

SLE is primarily a disease of medium and large breed dogs, although it may occur in smaller breeds as well. This is in contrast to RA, which more commonly affects small and toy breeds. Some reports show females to be affected more frequently than males; other reports describe the opposite. If the cases from these reports are pooled, there are 72 dogs affected with SLE, 40 female and 32 male. In another report in which dogs affected with SLE were selected for study based on the presence of joint involvement, there were 19 males and 10 females. Animals as young as 8 months of age and as old as 13 years of age have been diagnosed as having SLE. Mean age at the time of diagnosis is approximately 5.8 years.

The signs of SLE are frequently manifested in an episodic manner. Owners may first notice the animal to be somewhat depressed, anorectic, and reluctant to move about. Fever (103°-106°F) may also be present during these episodes, each of which lasts for several days. Spontaneous remission of days to months will occur only to have the signs return. Musculoskeletal disorders, particularly polyarthritis, are the most frequent problems. In most animals more than one joint is involved and frequently the carpus and tarsus are the joints affected initially. In about half the cases there is widespread (more than five) joint involvement. These animals are reluctant to move about, and when they do, they move somewhat rigidly, taking short purposeful steps. Palpable enlargements of the affected joints are usually detectable and may be in the form of periarticular soft tissues swelling or joint capsule distension. In addition, the affected joint may be warm to the touch when...
compared with nonaffected joints. In more chronic cases joint enlargement is more often due to periarticular soft tissue fibrosis than to joint effusion. Synovial fluid analysis will confirm the noninfectious, pungenent inflammatory process in the joints. Analysis of synovial fluid from other joints that do not appear to be affected will usually confirm the systemic inflammatory nature of the disease.

Palpation of affected joints usually does not elicit pain; however, a decreased range of motion may be present owing to the swelling of surrounding soft tissues and joint effusion. In longer standing cases periarticular or intra-articular ligamentous damage may be present. This will lead to joint instability and the changes associated with secondary degenerative joint disease.

Anemia occurs in over 50% of dogs affected with SLE. While AHA was thought to be the most common type, anemia of chronic disease may be more prevalent. (24) The anemia, if severe, may be manifested by anorexia and lethargy, although these signs frequently occur in SLE dogs who are not anemic. With AHA, jaundice, hepatomegaly, and splenomegaly may be present.

Petechia may be found in those animals with thrombocytopenia and impaired coagulation mechanisms. The petechia may arise on any mucous membrane surface. When present, they are frequently observed on the gingiva and mucous membranes of the prepuce or vagina. Petechia may appear on the skin also. The thrombocytopenia is usually caused by increased peripheral destruction, although a compensatory increase in platelet production may maintain an abnormal level of circulating platelets. (24) Skin lesions vary widely; however, nearly one third of all dogs affected with SLE will manifest some type of cutaneous abnormality. These abnormalities include maculopapular, discoid, purpuric, urticarial, vesicobulbous, or seborrheic eruptions and diffusive patchy alopecia. (26)

CLINICAL LABORATORY FINDINGS

The two most important laboratory tests in establishing a diagnosis of SLE are the LE cell test and antinuclear antibody test. LE cells are polymorphonuclear phagocytes, predominately neutrophils, that have engulfed antibody-coated nuclear material of another cell. The process by which one cell phagocytizes the nuclear material of another is termed the LE phenomenon. (84) The process begins with the formation of an antibody referred to as an LE factor. Stimulation for the production of this antibody is the nuclear material of damaged or ruptured leukocytes. The LE factor or antibody then coats (combines with) the antigen or nuclear material, forming an LE body. Phagocytosis of this immune complex follows. Phagocytic cells that have engulfed the LE body are termed LE cells. It must be remembered that the LE phenomenon is primarily a laboratory reaction and only rarely does it occur in vivo. LE factor cannot penetrate living cells.

ANA as detected by immunofluorescence are present in nearly 90% of affected dogs. (19,24) As noted above, the pattern of immunofluorescence corresponds to different types of antinuclear antibodies and clinical signs may vary depending upon the type of ANA present. The ANA test is more sensitive than the LE cell test. It is more frequently positive at the onset of the disease and often remains positive even during treatment and remission. In comparison, the LE cell test may not remain positive or may not become positive until after clinical signs have been present for some time.

Anemia of the normocytic, normochromic type is present in about 50% of dogs with SLE. Positive results on the Coomb's test indicative of antieyrocyte antibodies may be present in about one third of the cases. However, acute hemolytic episodes are not very common. (23)

Leukocytosis with an absolute neutrophilia is a common finding. (19,24,51) Leukopenia associated with antileukocyte antibodies is frequently found in human SLE patients. (69) While leukopenia has been reported in several canine SLE patients, it is unusual. (19) Direct causes of both the nonhemolytic anemia and the leukocytosis have not been found, but both findings are indicative of inflammatory disease. Thrombocytopenia is found less frequently than anemia or leukocytosis. In one report in which the SLE patients were selected on the basis of articular involvement, fewer than 3% were thrombocytopenic. (61) Another report listed 17% of the SLE dogs as thrombocytopenic. (24) Circulating antiplatelet antibodies are probably responsible for the decreased number of platelets.

As in dogs with RA, serum g-globulin levels may be increased in those with SLE. In addition, plasma fibrinogen concentrations may also be elevated, indicative of nonspecific inflammation. (61) In contrast to the findings in RA dogs, serum complement levels are more frequently decreased in dogs with SLE. (92) A reason for this difference is not known.

Serum levels of liver enzymes are almost always within normal limits in dogs with SLE. (19,24) This is also true for the serum levels of muscle enzymes. Myositis may be an accompanying feature of canine SLE, but its laboratory documentation has been limited. Serum levels of muscle enzymes in dogs with non-SLE polymyositis are elevated in only a few cases; the
Proteinuria is found in over 50% of the dogs with SLE; the range of urine protein varies between 30 mg and 1000 mg/dl. The protein loss is most likely related to immune-complex deposition in the glomerulus. Because tubular function is rarely impaired initially by glomerular lesions, renal concentrating ability is maintained. Azotemia may be present but is not a constant finding.

Synovial fluid cytology will confirm the systemic inflammatory nature of the disease. White blood cell counts may vary from several hundred to over 100,000/mm³ but are usually in the 10,000 to 20,000 range. Polymorphonuclear cells comprise 50% to 80% of the cells, the remainder being a mixture of lymphocytes, monocytes, macrophages, and plasma cells. On rare occasions an LE cell will be seen. Synovial fluid samples should be taken from more than one joint. In those patients in whom only one or two joints appear to be involved, samples should be taken from a "noninvolved" joint as well as from the affected ones. In the majority of cases cytology of the clinically unaffected joint will also contain cells of an inflammatory purulent nature, thus confirming the systemic involvement of the condition.

RADIOGRAPHIC FINDINGS

Although lameness is one of the most common presenting signs of SLE, the radiographic features of the disease are not very striking, particularly when compared with those of RA. The inflammatory joint changes of SLE are described as nonerosive because only a small percentage of cases have radiographic evidence of articular cartilage destruction. In acute stages of the disease, common radiographic findings include joint capsule distension and periarticular soft tissue swelling. In chronic cases, increased density about the affected joints is usually due to soft tissue fibrosis. Periosteal reactivity may be seen at the bony attachments of ligaments and joint capsule. In addition, these secondary changes of degenerative joint disease may be seen in chronic cases, particularly those in which ligamentous damage has occurred (Fig. 89-11).

THERAPY

SLE is a disease for which there is no known cure. The best that can be accomplished is to keep the disease controlled and in remission. In most cases medication will control the disease for long periods of time; some cases may undergo spontaneous remission lasting for several weeks to months, during which time medication is unnecessary. However, the condition eventually returns and patients ultimately die of one complication or another.

Prednisolone is the drug most frequently administered and brings about rapid relief of signs in the majority of patients. Cyclophosphamide and azathioprine may be given in addition to prednisolone if the need should arise. Dosages and schedules for drug administration are identical to those described above for RA.

Patients exhibiting only articular signs of disease may benefit initially from aspirin alone or aspirin in combination with low doses of prednisolone. Those patients with systemic involvement will benefit little from aspirin and will require corticosteroids and perhaps the cytotoxic agents.

Periodic patient monitoring even during periods of disease quiescence is important in the overall management of the condition. Owners must be made aware of the myriad ways the condition may manifest itself and how their animals may react under the circumstances of new organ involvement. For instance, the signs of renal involvement should be explained so that they may be recognized and treated promptly. In addition, the patient's response to treatment as evidenced by laboratory findings must be noted so that future exacerbations can be properly interpreted. In some cases, ESR will return toward normal following therapy, or titers of ANA will decrease. In other cases, parameters may not be affected by therapy even though the patient is clinically improved.
Other drugs used in the treatment of RA, such as gold or themany nonsteroidal anti-inflammatory agents, are not often usedin the therapy of SLE. Whether this is because they areineffective or because they have never been tried is unknown.Exercise, diet, and weight control should be an important partof overall patient management.

**IMMUNE ARTHRITIS AND OTHER CONDITIONS**

Nonerosive arthritis in the dog has been reported as anaccompanying feature of chronic infectious disease includingbacterial endocarditis,(7) dirofilariasis, pyometra, chronic otitis media and externa, and some fungalinfections.(61) One or more joints may beaffected; the carpus and tarsus are frequently involved. Thearthritis is usually a minor part of the total disease syndrome,although in some dogs lameness may be the primary observation bythe owner and the initial reason for seeking medical attention.

The infection is confirmed by culture or histologicexamination of the primary infectious lesion; however, organismsare usually not identifiable in the synovial fluid or synovialmembrane of affected joints. Leukocyte counts of synovial fluidare usually increased and may be in excess of 150,000 cells/mm3,with neutrophils predominating. Radiographic changes of affectedjoints are usually absent. Synovial membrane histopathology isvery similar to that of SLE.

The joint disease in such cases usually subsides with time as the primary infectious problem iseliminated. Treatment is directed at the primary problem, although low doses of prednisolone may be beneficial in bringingthe joint disturbances under control.

Nonerosive, noninfectious arthritis may also occur in dogs in whom serologicabnormalities of SLE cannot be confirmed.(61) in these dogs infectious disease processes will not bepresent. Clinical presentation, history, synovial fluidanalyses, and synovial tissue changes are identical to thoseseen with SLE. Etiology of this condition is not known. Treatment is the same as that for SLE.

An erosive polyarthritis of young racing greyhounds has been reported.(32) Histopathologic changes of articular cartilage and synovial membrane were similar to those of RA. Extensive study by electron microscopy, microbiologic culture, and serologic testing could not identify an infectious cause.

**Immune-Mediated Articular Disease of Cats**

Chronic progressive polyarthritis (CPP) is an immunemediated articular disease of cats that is linked etiologically to feline leukemia virus (FeLV) and feline syncytial formingvirus (FeSFV) infection.(60) To date, the condition has been reported only in male cats. Age of onset isusuually between 1-1/2 and 5 years. Two forms of the disease arerecognized: the most common is associated with periostealproliferation and new bone formation around the affected joints; the second form is characterized by marginal subchondral bonydestruction, joint instability, and joint deformity. Clinically theperiosteal proliferative form begins as a tenosynovitis. Affected animals frequently have a fever and manifest a generalized stiffness. Pronounced edema and erythema of the skin subcutis overlying the carpus and tarsus are often present. Animals walk with great difficulty, and manipulation of affected swollen joints elicit apparent severe pain. Regional lymph nodes are frequently enlarged.

As the condition progresses the animals become cachectic, even though they may continue to eat. Characteristic radiographic changes of periosteal exostosis become apparent several weeks after the initial onset of disease.

The deforming type of the disease develops moreslowly than the proliferative type. An acute initial febrileepisode does not occur. Lameness and stiffness graduallyincrease in severity, and gross deformities of the distal limbsdevelop owing to erosion of joint surfaces and joint laxity.

Both forms of the disease produce similar clinical laboratoryfindings. Leukocytosis manifested as an absolute neutrophilia iscommon. Plasma fibrinogen and serum alpha2-globulin levels arefrequently elevated while gamma-globulin concentrations areeither normal or slightly increased. Chronically ill cats frequently have a low-grade normocytic normochromic anemia. Cats with concurrent FeLV infection often have severe anemia and leukopenia.

Synovial fluid white blood cell counts may rangefrom 4,000 to 70,000 cells/mm3, the majority of which are polymorphonuclear neutrophils. Lower cell counts are more prevalent in the deforming type of the disease.
Results of rheumatoid factor and fluorescent ANA tests are negative. Radiographic changes of the proliferative form of the disease vary directly with duration of clinical signs. Early findings include periarticular soft tissue swelling about the carpus and tarsus, which are usually the joints affected first. Pronounced joint capsule distension is usually not seen. With time, fluffy periosteal new bone formation is seen around affected joints. Extensive periosteal reaction is particularly evident at the attachments of the fibrous joint capsule and external ligaments and tendons.

The deforming type of CPP is characterized radiographically by subluxation and joint instability of the interphalangeal joints, radiocarpal joint, or the metacarpophalangeal or metatarsophalangeal joints. Accompanying radiographic signs may include both erosions at the joint capsule attachments, subchondral bone cysts, and periarticular osteophytes. Bony destruction may also occur at the attachments of the gastrocnemius tendon to the os calcis or the triceps tendon to the olecranon. All of the changes are of a chronic nature. The early radiographic appearance of the deforming type of the disease is not well documented. However, progression of the proliferative type to the deforming type does not seem to occur (Figs. 89-12 and 89-13).

Pathologic changes in articular tissue are similar to those in dogs with immune-mediated joint disease. In the acute stages of the proliferative form, the synovial tissue contain migrating neutrophils and mononuclear cells. The synoviocytic layer is hyperplastic, and the vasculature in the underlying subsynoviocytic area is congested. Exudate within the joint space is composed of fibrin, amorphous protein, and neutrophils.

In the more chronic stages of the disease, the synovial reaction is still evident, but plasmacells and lymphocytes are more common than neutrophils. In addition, fibrosis of the outer layers of the joint capsule becomes more pronounced.

In those animals with joint surfacedestruction, a granulation tissue originating from the synovial membrane overgrows the cartilage and erosion is seen at the cartilage-pannus interface.

Microscopic evidence of glomerulonephritis may be present in some cats. In some animals with peripheral lymphadenopathy, the lymph node changes may be dramatic that a diagnosis of lymphosarcoma may be made by mistake.

Early pathologic changes of the deforming type of disease have not been described. Synovial tissue from animals with chronic disease appears hyperplastic and contains aggregates of lymphocytes and plasma cells; freemigrating inflammatory cells are not common. Bone and other joint changes are typical of chronic bony destruction and instability.

FeSFV and FeLV may frequently be cultured from the blood, synovial fluid, and synovial tissues of cats with chronic progressive polyarthritis. In addition, examinations for FeLV by the indirect fluorescent antibody procedure on peripheral blood smears and serologic studies for FeSFV may be positive even if the viruses cannot be isolated by tissue culture. While only indirect evidence is available, the involvement of these viruses in the pathogenesis of CPP cannot be dismissed. It has been postulated that FeSLV is responsible for the local antigenic stimulation and ultimately for the immunopathologic disorders occurring in the joint tissue in addition, because CPP has so far been reported only in malecats, there may be sex and genetic factors that play a role in the virally infected animals to express the disease. Further, FeLV may potentiate the pathogenic effects of FeSFV in the appropriate animal.

Treatment with prednisolone frequently reduces the joint pain and swelling. However, the condition is progressive. Cyclophosphamide and azathioprine, in addition to prednisolone, may also slow the progressive nature of the disease. In some cases combination therapy may produce clinical remission; however, relapses or complications of immunosuppressant therapy may develop.
SLE occurs in cats also, although the reported incidence is much lower than that in the dog. The primary presenting signs of feline SLE are usually alopecia or dermatitis (74); anemia, oral ulcers, and azotemia probably due to immune-mediated glomerulonephritis have also been reported. (24, 76) Joint involvement has not been described as a prominent feature of the disease in the cat.

References

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