

# Canine immune-mediated polyarthritides

B. Kohn<sup>(1)</sup>

## SUMMARY

Immune-mediated polyarthritides (PA) are defined by synovial inflammation, failure to identify a microbial aetiology and response to immunosuppressive therapy. These diseases have common immunopathogenic features and may be subdivided into erosive (e.g., rheumatoid arthritis [RA]) and non-erosive forms (e.g., “idiopathic” polyarthritides (IPA) type I; type II associated with infectious disease; type III with gastrointestinal disease; type IV with neoplasia; vaccination reactions, systemic lupus erythematosus, and others).

Typical clinical findings are a stiff gait, varying degrees of lameness, shifting leg lameness, fever, and bilaterally symmetrical swollen painful joints.

Diagnosis is based on radiographs, arthrocentesis and synovial fluid analysis of several joints. Blood and urine analyses, and diagnostic imaging of thorax and abdomen are helpful in identification or exclusion of underlying diseases. Further diagnostic testing is recommended in certain cases such as serology / PCR testing for infectious diseases, CSF analysis, cytology of lymph nodes, etc.

In IPA II - IV treatment is primarily directed against the underlying disease. If RA, IPA I or a vaccination reaction is suspected analgesics and often doxycycline are given initially. In most cases of IPA I and RA immunosuppressive therapy with prednisolone (and sometimes other immunosuppressive agents) is necessary.

IPA type I has a favourable prognosis and cure is possible, but the recurrence rate is high. Prognosis for vaccination reactions and IPA II - IV is good if the underlying disease can be treated.

This paper is based on the FECAVA Lecture delivered at the 13th FECAVA/CSAVS Congress in Cavtat, Dubrovnik.\*

## Erosive and non-erosive immune-mediated arthritides

Inflammatory joint diseases can be classified as infectious or immune-mediated. The immune-mediated polyarthritides are defined by (chronic) synovial inflammation, failure to identify a microbial aetiology on routine culture of the synovial fluid and clinical response to immunosuppressive therapy. These diseases have common immunopathogenic features and may be subdivided based on clinical, radiographic (erosive / non-erosive types), pathological and serological parameters (table 1). Classification of the arthritides is useful for deciding on treatment and prognosis [1, 2, 3].

## Rheumatoid arthritis (RA)

This is the most common type of erosive polyarthritides, however, erosive forms are very rare compared to the non-erosive forms [4, 5]. Small, middle-aged dogs are overrepresented. The diagnostic criteria for RA in the dog are adapted from those defined for humans [6]: 1. Stiffness, 2. pain on manipulation of at least one joint, 3. signs of arthritis for at least 3 months, 4. periarticular soft tissue swelling, 5. typical radiographic changes: subchondral bone destruction, irregularity of the articular surface or “punched out” erosions, demineralisation of the epiphysis, calcification of soft tissue around the joint, changes in joint space (increase or decrease), finally extensive bone destruction with gross joint deformity (Fig. 1), 7. inflammatory synovial fluid, 8. characteristic, symmetrical deformations of the distal joints, 9. detection of rheumatoid factors in serum, 10. characteristic histopathological changes in synovial membrane, 11. extra articular symptoms (tendosynovitis, lymphadenopathy). The presence of 5 of these criteria suggests RA, with 7 positive criteria the diagnosis is definitive.

(1) Clinic for Small Animals Free University of Berlin, Oertzenweg 19 b, D-14163 Berlin E-mail kohn@vetmed.fu-berlin.de  
\*Hosted by CSAVS (Croatia) held in Cavtat March - April 2007

Erosive	Rheumatoid arthritis
	Polyarthritis of Greyhounds
	Felty's syndrome (rheumatoid arthritis, splenomegaly, neutropenia)
Nonerosive	"Idiopathic" (IPA) (type I – no underlying disease, II - reactive, III - enteropathic, IV – neoplasia related)
	Systemic lupus erythematosus (SLE)
	Vaccination-associated
	Drug induced (e.g. trimethoprim-sulfonamide)
	Polyarthritis / polymyositis (e.g., Spaniel breeds)
	Polyarthritis / meningitis (e.g., Weimeraner, Boxer, Bernese mountain dog, German shorthaired pointer)
	Polyarteritis nodosa (mainly young Beagles)
	Sjögren syndrome (arthritis, keratoconjunctivitis sicca, xerostomia)
	Arthritis of adolescent Akita Inus
	Shar Pei fever syndrome (amyloidosis, often hock joints involved)
	Lymphocytic-plasmacytic gonitis

Table 1: Immune-mediated arthritides

### 'Idiopathic' polyarthritis (IPA)

This term includes all those cases of inflammatory arthropathies which can not be classified into the other groups, e.g., RA or SLE. Type I is by far the most common of all the immune-mediated arthropathies in the dog. The "idiopathic" type can be divided into 4 subcategories [2, 3, 7, 8]. Type I: uncomplicated IPA: This type accounts for approx. 50% of all the "idiopathic" cases. In

Fig. 1. Severe longstanding erosive rheumatoid arthritis in a 12 year old female Cairn Terrier: subchondral bone destruction, irregularity of the articular surface and "punched out" erosions, demineralisation of the epiphysis, changes in joint space, gross joint deformity.



IPA I, no underlying disease or trigger can be detected (diagnosis of exclusion).

Type II: IPA associated with infectious disease outside the joints (reactive form) (approx. 25% of all IPA cases): Infections of the respiratory tract (e.g. tonsillitis), urogenital tract, teeth, ears or skin, leishmaniasis, ehrlichiosis, anaplasmosis, borreliosis, and bacterial endocarditis have been reported in association with immune-mediated arthritis. The infectious process might provide an antigenic source for immune complex formation.

Type III: IPA associated with gastrointestinal disease (enteropathic / hepatopathic form): The diseased gut may show an increased permeability to potential antigens which might stimulate the production of immune complexes.

Type IV: IPA associated with neoplasia outside the joints (paraneoplastic form): e.g., squamous cell carcinoma, leiomyoma, mammary carcinoma, lymphoma. Neoplasia can stimulate an immune response by the host and thus the formation of circulating immune complexes.

### Vaccination reactions

An immune-based polyarthritis can follow vaccinations, either after the first injection or after booster vaccinations. The lameness is often only transient, lasting for several days. More severe forms have been described in Weimaraner and Akita Inu puppies. An accurate vaccination history is therefore important on all dogs presenting with PA [3, 9, 10].

### Aetiology and pathophysiology

The basic underlying immunopathological mechanisms are similar in all types of immune-mediated polyarthritis. Immune complexes, either generated locally within the joint and / or systemically within the circulation, are deposited into the joints (hypersensitivity reaction type III). The immune complexes may fix complement in the synovial membrane and in the synovial fluid. This results in local tissue damage and release of products chemotactic for polymorphonuclear leukocytes. The neutrophils release biologically active products which cause further tissue damage. These events are a normal immunological response aimed at eliminating a foreign antigen. If the antigen persists or immune dysregulation exists these events may result in chronic disease. Alteration of self antigens may lead to loss of immune tolerance of the individual and to formation of autoantibodies (e.g., rheumatoid factors [circulating autoantibodies against IgG immunoglobulins], antinuclear antibodies, and anti-heat shock proteins).

A type IV hypersensitivity component of immune-mediated polyarthritis is suggested by the perivascular infiltration of T- and B-lymphocytes, plasma cells, and macrophages into affected synovium [11]. Macrophages, synovial fibroblasts and T lymphocytes produce different cytokines. Release of matrix degrading enzymes (e.g. metalloproteinases) by such cells enhances inflammation and cartilage and bone degeneration and destruction which may result in erosive arthritis.

The underlying aetiological stimuli are unknown; although there is evidence to support the role of microbial infection (e.g. canine distemper virus in rheumatoid arthritis, infection elsewhere in the body stimulating immune complex formation, and joint



Fig. 2. Rhodesian Ridgeback, male, 1.3 years: stiff gait, reluctance to move, difficulty rising, several joints swollen and painful on manipulation 3 days after vaccination.



Fig. 3. Swelling of the hocks in a Labrador cross with idiopathic immune-mediated polyarthritis type I.

infections with persistence of microbial antigens) [12]. Potential antigens may also originate from non-microbial sources, such as tumour antigens, drug antigens/haptens, and dietary antigens. In addition, genetic factors (e.g. certain DLA-DRB1 alleles) might predispose to immune-mediated disease [1, 13].

## Pathology

Typical findings are a synovitis, generally affecting several joints simultaneously, with a thickened and discoloured synovial membrane. The chief inflammatory cells in the synovial membrane are lymphocytes and plasma cells, whereas in the synovial fluid polymorphonuclear leukocytes predominate. Inflammatory fibrovascular proliferations of the synovial membrane develop; this granulation tissue might cover the articular surface, a condition referred to as pannus. Depending on the stage of the disease irreversible cartilage and subchondral bone destruction with deformity and irregularity of the joint surfaces may develop.

## Clinical findings

Dogs of all ages and breeds may develop immune-mediated polyarthritis, certain types are described only in certain breeds (table 1). Typical clinical findings are a stiff gait ("walking on eggs"), reluctance to move, lethargy, fever (polyarthritis is an important differential diagnosis for "fever of unknown origin"), and often inappetence (Fig. 2). However, some dogs may present as chronic lameness without signs of systemic disease. The severity of lameness can vary markedly, and a shifting leg lameness often occurs. In the least severe cases, no more than a vague stiffness may be noted, whereas severely affected dogs may be unable to stand or walk. Typical, but not always present, are bilaterally symmetrical thickened or swollen joints with pain on motion (Fig. 3). Muscle atrophy may be apparent. Immune-based arthritis is principally a polyarticular disease (6 or more joints involved), although some cases involve fewer joints (oligoarthritis, 2-5 joints) and, occasionally, only a single joint is diseased (monoarthritis). Opening of the mouth or neck movement can be painful if the mandibular articulation or vertebral articular facets are involved or if meningitis is present [14].

Depending on the form of immune-mediated arthritis other symptoms such as dermatitis, glomerulonephritis, meningitis, myositis, uveitis, lymphadenopathy, cardiac murmur, thrombocytopenia and anaemia will be apparent.

## Differential diagnoses

Infectious (e.g., due to borrelia, rickettsia, leishmania, mycoplasma or fungal infection) and immune-mediated arthritides may be difficult to differentiate by clinical examination, radiology or synovial fluid analysis. Moreover, infectious diseases may give rise to immune-mediated disease (IPA type II). Septic arthritis manifests usually in only one joint.

Other differentials include degenerative, traumatic, haemophilic and neoplastic arthropathies, which are usually monoarticular. Together with primary bone marrow disease (e.g., leukaemia, multiple myeloma) immune-based arthritides are a major cause of "fever of unknown origin". Other causes are infectious diseases (e.g., discospondylitis, bacterial endocarditis, urinary tract infection, pyothorax, leishmaniasis, toxoplasmosis, viral disease), neoplasia (e.g. lymphoma), splenic torsion, and others [15, 16].

## Diagnosis

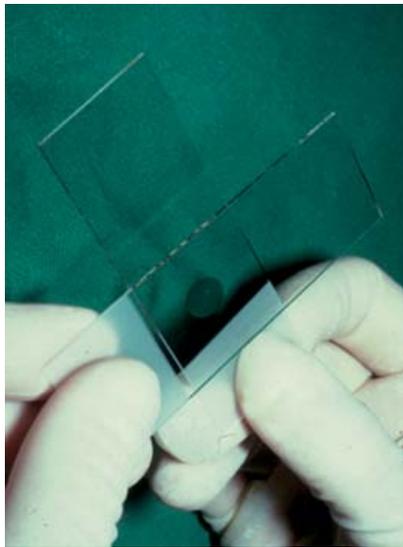
Haematology, clinical chemistry, urinalysis and urine culture, and radiography and ultrasonography of thorax and abdomen are helpful in exclusion of other diseases and may point to specific forms of immune-mediated arthritis (e.g., anaemia, thrombocytopenia and proteinuria in SLE). Radiographs of several joints should be performed in order to differentiate erosive and non-erosive types. In non-erosive forms, joint-radiographs may either not show obvious abnormalities or show soft tissue swelling and synovial effusion.

Diagnosis of inflammatory polyarthritis is based on arthrocentesis and synovial fluid analysis of several joints. Arthrocentesis is performed in anaesthetised animals, the joint tap site is prepared as for surgery (Fig. 4). The joint is entered with a 20- or 22-gauge needle attached to a 2 ml syringe and synovial fluid is carefully aspirated. In normal joints the yield of synovial fluid is very small. Aspirates may be contaminated with blood because of damage to intra-synovial blood vessels during arthrocentesis.

Fig. 4. Aspiration of synovial fluid from the hock of a Labrador cross with immune-mediated polyarthritis type I: yellowish turbid synovial fluid of low viscosity.



Fig. 5. Preparation of a synovial smear immediately after aspiration.



Contraindications for arthrocentesis such as periarticular infections or haemostatic disorders are rare.

The following synovial fluid parameters are routinely examined: Volume, macroscopic appearance (clarity and colour), viscosity, number of nucleated cells with a differential cell count, and protein concentration. In cases of suspected bacterial infective arthritis, synovial fluid should be submitted for aerobic and anaerobic culture. False negative results can occur, however, since culturing bacteria from synovial fluid is difficult.

Normal synovial fluid is colourless to slightly yellow, transparent, non clotting on exposure to air, and of high viscosity. Viscosity can be subjectively assessed by allowing a drop of synovial fluid to fall from the end of the needle, the length of the string is normally  $> 2.5$  cm. The protein concentration (measured by a refractometer) is below 2.5 g/dl and the nucleated cell count below approx. 1000/ $\mu$ l. The predominating cells are large mononuclear cells and lymphocytes, the percentage of neutrophils is  $< 5\%$ . Based on evaluation of direct synovial fluid smears the number of nucleated cells can be roughly estimated (2 – 3 cells/400X magnification are normally found) (Fig. 5, Fig. 6). If sufficient synovial fluid is available, the cell count can be determined with the aid of a haemocytometric chamber

(Neubauer improved) [17, 18]. In immune-mediated arthritides synovial fluid volume is often increased; it is generally turbid, discoloured, of decreased viscosity, may clot, and the protein and nucleated cell content are increased (nucleated cell count often  $> 5000/\mu$ l). The neutrophil counts are increased to 15-95% and are often  $> 70\%$  [3, 8, 19] (Fig. 7).

Rheumatoid factors may be determined, however, the test is not specific for rheumatoid arthritis and the result may depend on the test and the laboratory. Positive results may occur in different chronic inflammatory diseases, e.g., leishmaniasis, pyometra. Therefore, the value of this test is questionable [8, 19, 20]. Further diagnostic testing depends on the history, clinical signs and suspected underlying diseases: antinuclear antibody titre, serology / PCR testing for borrelia, ehrlichia, anaplasma and leishmania, cerebrospinal fluid analysis, muscle biopsy, platelet bound antibodies, direct antiglobulin test, skin biopsy, cytology of lymph nodes, etc. If endocarditis is suspected echocardiography and a blood culture are indicated.

In some cases a definitive diagnosis can only be established by synovial membrane biopsy (histopathology, microbiologic culture).

## Therapy

In IPA type II – IV treatment is primarily directed against the underlying disease if possible. In some cases analgesic/anti-inflammatory drugs or corticosteroids are indicated. As any drug may potentially trigger immune-mediated disease all drugs should be withdrawn except the ones absolutely required to treat a life-threatening condition.

If RA, IPA type I or a vaccination reaction is suspected analgesics (e.g., meloxicam 0.1 mg/kg SID, carprofen 2-4 mg/kg SID, metamizole 20 mg/kg BID-TID) and often doxycycline (5 mg/kg BID) are given till all test results are available. Spontaneous recovery is possible in vaccination reactions and in some dogs with IPA type I [8, 10]. In most cases of IPA type I immunosuppressive therapy with prednisolone (initial dose 1 – 1.5 mg/kg BID) is necessary [2, 3, 7, 8, 19]. Glucocorticoids should not be combined with NSAIDs because life-threatening gastrointestinal ulceration might occur. High prednisolone doses are given for 2 weeks and then the dose is gradually reduced (approx. 1/4 - 1/5 every 2-3 weeks) and changed to an alternate-day-therapy over the next months. Because of the potential for gastrointestinal ulceration with high-dose glucocorticoid therapy, gastrointestinal protectants such as sucralfate and/or H2 receptor antagonists or proton pump inhibitors are administered.

There is generally a marked improvement within a few days, but maintenance therapy is important to prevent relapses. Constant low-dose prednisolone is sometimes necessary to keep the animal in clinical remission. Repetition of the arthrocentesis is helpful to assess response to therapy and is indicated if relapses occur. A fall in the total cell count and a reduction in the proportion of polymorphs are good prognostic signs [19, 21].

Other immunosuppressive therapy is warranted when prednisolone fails, only controls the disease at persistently high doses, causes unacceptable side effects or if a relapse occurs. Other agents are generally used in combination with prednisolone. There are no controlled studies to show that one cytotoxic drug is better than another [7, 8, 19]. Some

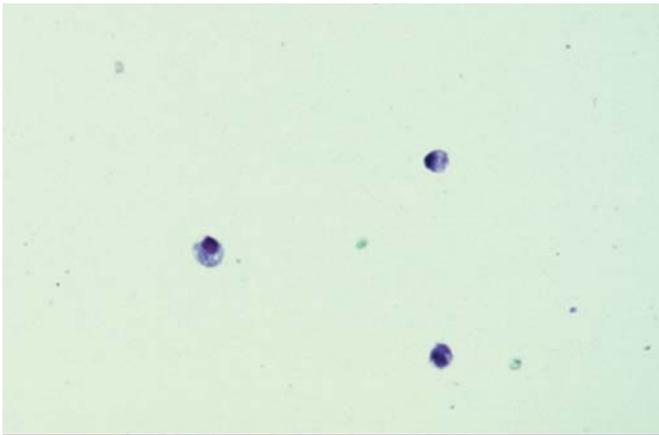


Fig. 6. Smear of synovial fluid from a healthy dog; few mononuclear cells (Pappenheim, 400 x)

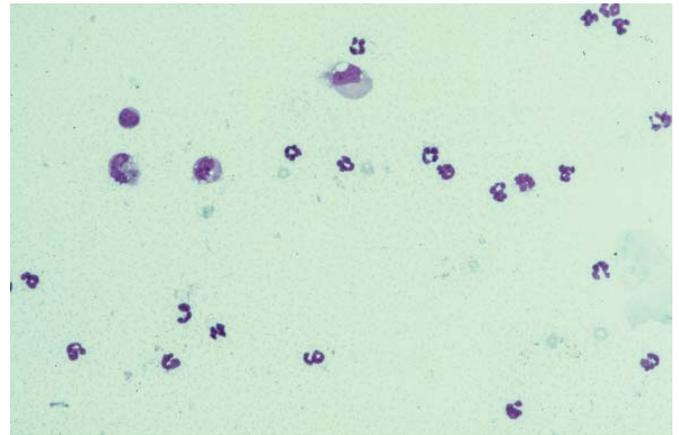


Fig. 7. Smear of synovial fluid from a dog with idiopathic immune-mediated polyarthritis type I; greatly increased nucleated cell counts (Pappenheim, 400 x).

authors recommend cyclophosphamide (50 mg/m<sup>2</sup> 4 days/week). Side effects are sterile haemorrhagic cystitis and bone marrow suppression. If cytotoxic drugs are given a complete blood count every 1-2 weeks is indicated. If the WBC count falls below 6000/ $\mu$ l or the platelet count below 125,000/ $\mu$ l, the dose should be reduced by 1/4; if the WBC count falls below 5000/ $\mu$ l (neutrophils < 2500/ $\mu$ l) the drug is discontinued for 1 week and then recommenced at 1/2 the initial dose. Cyclophosphamide should not be used for more than 3 – 4 months because of increasing risk of bladder toxicity. Chlorambucil can be used instead of cyclophosphamide or cyclosporin (initially approx. 5-10 mg/kg PO SID) or azathioprine (initially 2 mg/kg PO for 2 weeks, maintenance dose 0.5-1 mg/kg every other day alternating with prednisolone) can be tried. In addition new immunosuppressive agents are being introduced such as leflunomide (4 mg/kg SID) [22]. Levamisole as an immunomodulatory drug has been described for canine polyarthritis (5-7 mg/kg every other day, maximum 150 mg daily) [3]. Omega-3-fatty acids can be given as supportive therapy. Patients receiving immunosuppressive therapy should be checked regularly for secondary infections (e.g., of the urinary tract).

In severe cases of RA gold preparations might be used (aurothiomalate 0.5 mg/kg IM once weekly for 6 weeks). A small test dose should be given before full treatment is begun to check for any adverse effects. Side effects are bone marrow depression, renal insufficiency, dermatosis, diarrhoea and corneal ulcers. Auranofin (0.05 – 2 mg/kg PO BID) is less toxic, but diarrhoea is a common side effect [3].

Surgical arthrodesis of diseased joints has been attempted with limited success but is very rarely necessary. Synovectomy might improve symptoms especially if a single joint is predominantly affected.

Cytokine studies in synovial fluid revealed that the cytokine patterns in canine PA and human rheumatoid arthritis or arthritis mouse models were similar. Immunomodulatory therapies already used in human medicine (e.g., TNF-alpha blocking agents) might be treatment options in canine polyarthritis in the future [23].

## Prognosis

IPA type I has a favourable prognosis and cure is possible. Mortality rate in two studies was 12.5 and 15%, respectively. Most dogs were euthanased due to insufficient response to immunosuppressive therapy or due to relapses. The rate of recurrence is high, (up to 44%) [8, 19] Some IPA cases may progress to the rheumatoid form.

The prognosis for vaccination reactions and IPA type II – IV is good if the underlying disease can be treated [3, 5, 10]. In SLE the prognosis is guarded, and in cases of renal involvement poor. In RA the prognosis is unfavourable if progressive joint destruction occurs. Dogs with SLE and RA usually need constant medication.

## References

- [1] BENNETT (D.), MAY (C.) - Joint diseases of dogs and cats. In: ETTINGER (S.J.), FELDMAN (E.C.) (eds.), Textbook of Veterinary Internal Medicine. Philadelphia: WB Saunders, 1995, 2032-2077.
- [2] PEDERSEN (N.C.), MORGAN (J.P.), VASSEUR (P.B.) - Joint diseases of dogs and cats. In: ETTINGER (S.J.), FELDMAN (E.C.) (eds.), Textbook of Veterinary Internal Medicine. Philadelphia: WB Saunders, 2000, 1875-1886.
- [3] BENNETT (D.) - Immune-mediated and infective arthritis. In: ETTINGER (S.J.), FELDMAN (E.C.) (eds.), Textbook of Veterinary Internal Medicine. Philadelphia: WB Saunders, 2005, 1958-1965.
- [4] BENNETT (D.) - Immune-based erosive inflammatory joint disease of the dog: canine rheumatoid arthritis. I. Clinical, radiological and laboratory investigations. *J Small Anim Pract*, 1987, **28**: 779-797.
- [5] KOHN (B.) - Immunbedingte (Poly-)arthritiden, immuninduzierte Arthritiden, immun-reaktive Arthropathien. In: SUTER (P.) & KOHN (B.) (eds.) Praktikum der Hundeklinik. Stuttgart: Parey, 2006, 988-993.
- [6] ARNETT (F.C.) - Revised criteria for the classification of rheumatoid arthritis. *Bull Rheum Dis*, 1989, **38**: 1-6.
- [7] BENNETT (D.) - Immune-based non-erosive inflammatory joint disease of the dog. 3. Idiopathic polyarthritis. *J Small Anim. Pract*, 1987, **28**: 909-928.
- [8] KOHN (B.), LÜBKE (S.), SCHMIDT (M.F.G.) & BRUNNBERG (L.)

- Idiopathische immunbedingte Polyarthritis Typ I beim Hund: Inzidenz, Klinik, Laborbefunde, Therapie und Verlauf von 16 Fällen (1996-2000). *Kleintierprax*, 2005, **50**: 415-426.
- [9] DODDS (W.J.) - Vaccine-associated disease in young Weimaraners. American Holistic Veterinary Medical Association Annual Conference, Proceedings, 1994, 85-86.
- [10] KOHN (B.), GARNER (M.), LÜBKE (S.), SCHMIDT (M.F.G.), BENNETT (D.) & BRUNNBERG (L.) - Polyarthritis following vaccination in four dogs. *Vet Comp Orthop Traumatol*, 2003, **16**: 6-10.
- [11] DAY (M. J.) & BENNETT (D.) - Immune-mediated musculoskeletal and neurological disease. In: DAY (M.J.) (ed), *Clinical immunology of the dog and cat*. London: Manson Publishing, 1999, 126-145.
- [12] BELL (S.C.), CARTER (S.D.) & BENNETT (D.) - Canine distemper viral antigens and antibodies in dogs with rheumatoid arthritis. *Res Vet Sci*, 1991, **50**: 64-68.
- [13] OLLIER (W.E.), KENNEDY (L.J.), THOMSON (W.), BARNES (A.L.), BELL (S.C.), BENNETT (D.), ANGLES (J.M.), INNES (J.F.) & CARTER (S.D.) - Dog MHC alleles containing the human RA-shared epitope confer susceptibility to canine rheumatoid arthritis. *Immunogenetics*, 2001, **53**: 669-673.
- [14] WEBB (A.A.), TAYLOR (S.M.) & MUIR (G.D.) - Steroid-responsive meningitis-arteritis in dogs with non infectious, non-erosive, idiopathic, immune-mediated polyarthritis. *J Vet Intern Med*, 2002, **16**: 269-273.
- [15] DUNN (K.J.) & DUNN (J.K.) - Diagnostic investigations in 101 dogs with pyrexia of unknown origin. *J Small Anim. Pract*, 1998, **39**: 574-580
- [16] MILLER (B.J.) - Hyperthermia and fever of unknown origin. In: ETTINGER (S.J.) & FELDMAN (E.C.) (eds.), *Textbook of Veterinary Internal Medicine*. Philadelphia: WB Saunders, 2005, 9-13.
- [17] PARRY (B.W.) - Synovial fluid. In: COWELL (R.L.) & TYLER (R.D.) (eds.), *Diagnostic Cytology and Haematology of the Dog and Cat*. St. Louis: Mosby Inc., 1999, 104-115.
- [18] GIBSON (N.R.), CARMICHAEL (S.), LI (A.), REID (S.W.J.), NORMAND (E.H.), OWEN (M.R.), & BENNETT (D.) - Value of direct smears of synovial fluid in the diagnosis of canine joint disease. *Vet Rec*, 1999, **144**: 463-465.
- [19] CLEMENTS (D.N.), GEAR (R.N.A.), TATTERSALL (J.), CARMICHAEL (S.) & BENNETT (D.) - Type I immune-mediated polyarthritis in dogs: 39 cases (1997-2002). *J Am Vet Med Assoc*, 2004, **224**: 1323-1327.
- [20] CHABANNE (L.), FOURNEL (C.), FAURE (J.R.), VEYSSEYRE (C.M.), RIGAL (D.), BRINGUIER (J.P.) & MONIER (J.C.) - IgM and IgA rheumatoid factors in canine polyarthritis. *Vet Immunol Immunopathol*, 1993, **39**: 365-379.
- [21] PEDERSEN (N.C.), POOL (R.R.) & MORGAN (J.P.) - Joint diseases of dogs and cats. In: ETTINGER (S.J.) (ed.): *Textbook of Veterinary Internal Medicine*. Philadelphia: WB Saunders, 1989, 2329-2377.
- [22] GREGORY (C.R.), STEWART (A.), STURGES (B.), DE MANVELLE (T.), CANNON (A.), ORTEGA (T.), HARB (M.) & MORRIS (R.E.) - Leflunomide effectively treats naturally occurring immune-mediated and inflammatory diseases of dogs that are unresponsive to conventional therapy. *Transplantation Proceedings*, 1998, **30**: 4143-4148.
- [23] HEGEMANN (N.), WONDIMU (A.), KOHN (B.), BRUNNBERG (L.) & SCHMIDT (M.F.G.) - Cytokine profile in canine immune-mediated polyarthritis and osteoarthritis. *Vet Comp Orthop Traumatol*, 2005, **18**: 67-72.
-