Thursday May 11, 2000 Lectures

Endocrinology in rheumatology — State of art lectures — Therapy of rheumatoid arthritis — Rheumatoid arthritis — Bone and joint decade — Health professional

The hypothalamic-pituitary-adrenal and gonadal axis in rheumatoid arthritis

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The hypothalamic-pituitary-adrenal (HPA) and the hypothalamic-pituitary-gonadal (HPG) axes involvement or response to immune activation, seems crucial for the control of excessive inflammatory and immune conditions such as autoimmune rheumatic diseases, including rheumatoid arthritis (RA).

However, female patients seem to depend more on the HPA axis, whereas male patients seem to depend more on the HPG axis. In particular, hypoandrogenism may play a pathogenetic role in male RA patients since adrenal and gonadal androgens, both products of the HPA and HPG axes, are considered natural immunosuppressors. A significantly altered steroidogenesis of adrenal androgens (i.e. dehydroepiandrosterone sulfate =DHEAS and DHEA) in non glucocorticoid-treated premenopausal RA patients has been described. Of course, altered adrenal androgen levels represent only one of the factors involved in the pathogenesis of RA, other factors might include genetic components. In particular, the CYP17 gene polymorphism, coding for the cytochrome P450c17α that mediates steroid enzyme activities considered key points in human steroidogenesis, seems involved in some RA cases of low gonadal androgens.

The menopausal peak of RA suggests that estrogens and/or progesterone deficiency also play a role in the disease, and many data indicate that estrogens suppress cellular immunity, but stimulate humoral immunity (i.e. deficiency promotes cellular Th1-type immunity).

A range of physical and psychosocial stressors are also implicated in the activation of the HPA axis and related HPG changes. Chronic and acute stressors appear to have different actions on immune mechanisms with experimental and human studies indicating that acute severe stressors may be even immunosuppressive, while chronic stress may enhance immune responses. Recent data, indicate that gonadal and adrenal steroid deficiency (altered HPA/HPG axis), plus prolactin increase (i.e. breastfeeding), probably facilitates the expression of Th1-type immunity, which is now considered to be critical in the pathogenesis of RA.

The interactions between the immunological and neuroendocrine circuits is the subject of active and extensive ongoing research, and might in the near future, offer highly promising strategies for hormone-replacement therapies in RA.

COMPARISON OF HORMONE LEVELS IN BLOOD PLASMA AND JOINT SYNOVIAL FLUID

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Several hormones (gonadal steroids, corticosteroids, prolactin, CRH) have been shown to have immunomodulatory action, in particular through influencing local production of cytokins and the function of synovial cells at the site of the inflammatory process. Aimed at finding out whether hormone levels in the knee joint exudate could be modified by changing their plasma levels, blood plasma and knee joint exudate hormone levels were compared. Synovial exudate from the knee joints of 10 patients with active form of rheumatoid arthritis and 5 patients with osteoarthrosis (control group with exudate of non-inflammatory origin) was taken for determination of the levels of gonadal steroids estradiol (E), progesterone (PRG) and testosterone (TE), as well as those of dehydroepiandrosterone (DHEA), cortisol (C), prolactin (PRL), aldosterone (ALD), and insulin using radioimmunological methods. Catecholamines were determined using radioenzyme method. Hormone levels in the exudate were compared with those measured in the plasma.

The preliminary results showed the presence in the exudate of all the hormones measured. Prolactin, progesterone and testosterone levels in the exsudate were shown to be similar as in the plasma (the exudate/plasma ratios were 0.98; 0.94; and 1.02 respectively). The levels of DHEA and E were lower in synovial fluid than in the plasma (0.62 and 0.60 respectively), whereas ALD and IRI levels were higher in the exudate than in the plasma (1.66 and 6.26 respectively). The exudate cortisol content was in average half that of the plasma levels, and catecholamine levels were markedly lower in the exudate.

A significant direct correlation could be established between progesterone (r=0.941), testosterone (r=0.899), estradiol (r=0.865), prolactin (r=0.916), and cortisol (r=0.699) levels in the knee joint exudate and the plasma. This suggests that the concentrations of the above hormones in the synovial fluid, and thus also their local inumunomodulatory action, might be modified by changing their levels in the plasma. Insulin and aldosterone concentrations in the plasma and the exudate did not show any significant correlation. The high contents of immunoreactive insulin in the exudate is noteworthy, and further investigations are required to clarify the origin of IRI and to find out the significance of its local action, in particular on synovial cells.

Adrenal secretion of cortisol in patients with rheumatoid arthritis

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In 1990 our group published (1) plotted circadian rhythms of plasma cortisol and ACTH in untreated RA patients with different inflammatory activities (ESR<40 mm/h, low; 40-80 mm/h, medium; >80 mm/h, high). In patients with low to medium disease activity, circadian extremes of cortisol occurred earlier in the day to normal controls. Patients with low level disease activity had a lower cortisol profile, while in patients with high disease activity cortisol secretion was elevated with loss of circadian rhythm. Regression analysis of the arithmetic mean of the cortisol values of the 24h cycle related to the parameter of inflammation ESR proved a highly significant correlation. But compared to values of healthy controls only patients with high inflammatory activity had higher cortisol values than the healthy controls. So it seems to be that in patients with low to medium disease activity cortisol production in RA was inappropriate low.

Since the pioneering publication of Hench and coworkers (2) which demonstrated the anti-inflammatory effects of cortisone in rheumatoid arthritis (RA) the question arose whether the glucocorticoid therapy was successful because it was replenishing an underlying deficiency of endogenous cortisol production. However, the results of a number of studies of the next decades proved disappointing. Determining cortisol in blood or urine showed conflicting results finding cortisol secretion elevated, normal or decreased. Regarding our own results HPA axis reactivity in RA seems to be viewed differentiated: there seems to be an increase of cortisol related and probably caused by the immunological activity mediated by cytokines but which was starting from an inappropriate low level of activation of the HPA axis.

Indeed further studies showed a correlation of cortisol to cytokines especially IL-6 in RA patients, reflecting a stimulation of the HPA axis by IL-6 via the neuroendocrine immune loop (3).

Very recent findings proved the observation that rheumatoid factor (RF) positive RA is quite different to rheumatoid factor negative RA with respect of the cortisol leveling. RF-negative RA patients had significant higher cortisol levels than the RF-positive RA patients of comparable disease activity (ESR, CRP) with additionally significant higher levels of soluble interleukin-2 receptor (sIL-2R) in the RF-positive RA group whereas sIL-2R levels in the RF-negative RA group were not different from the healthy control group (4).
This RA form seems to be not T-cell mediated because of low normal sIL-2R levels. RF positive RA is T-cell mediated because of high levels of sIL-2R. In RF-positive RA the increase of cortisol related to inflammatory activity is weaker possibly caused by a defective neuroendocrine immune loop. It is to discuss whether these findings contribute to a worser course of RF-positive RA.

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Pregnancy as friend or foe? Possible mechanisms of the different responsiveness of rheumatoid arthritis, systemic lupus and ankylosing spondylitis to pregnancy.

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Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and ankylosing spondylitis (AS) differ in their response to pregnancy. RA disease development is mitigated by estrogens and pregnancy typically suppresses disease activity. RA is regarded a T cell mediated and TH1 response driven disease. A change to the antiinflammatory and immunosuppressive TH2 cytokines as well as an inhibition of proinflammatory cytokines by soluble cytokine receptors may contribute to gestational disease amelioration.

SLE tends to flare during pregnancy and may be aggravated by high doses of exogenous estrogens. Some manifestations of SLE are linked to a particular TH response and accordingly pregnancy with its shift to a TH2 response may improve some symptoms, but aggravate others. In addition, the hyperprolactinemia of pregnancy could be involved in lupus flares. Studies of murine lupus showed that physiologic hyperprolactinemia induced by pregnancy, suckling or pseudopregnancy exaggerated clinical disease and stimulated antibody formation.

AS is generally not influenced by pregnancy or alterations of circulating female sex hormone levels. Several extra-articular manifestations occur in AS and it is possible that some are more linked to a TH1 than a TH2 immune response. This could then result in subsidence of some symptoms during pregnancy as described for anterior uveitis and peripheral arthritis.

Provided that TH1/TH2 response patterns indeed distinct diseases like RA,SLE and AS, the pregnancy-induced shift to a TH2 immune response may explain some of the differences in their responses to pregnancy.

PLASMA CATECHOLAMINES AND GENE EXPRESSION OF BIOSYNTHETIC ENZYME IN RATS WITH DIFFERENT SENSITIVITY TO DEVELOP THE ADJUVANT ARTHRITIS

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It has been shown that the adjuvant arthritis (AA) is easily induced by administration of Freund's adjuvant in rats of Lewis strain. Susceptibility to the arthritis in these rats is thought to be related to a defect in the hypothalamo-pituitary-adrenocortical axis (HPA). There is, however, growing evidence that the sympathoadrenal system (SAS) influences the immune responses.

The aim of the present work was to examine the SAS activity at control conditions and during stress exposure in Lewis rats and compare it with Fischer-344 rats (resistant to AA). Plasma epinephrine (EPI) and norepinephrine (NE) levels were measured at control conditions and after exposure to stressors - handling (1min) and immobilization (IMO, 5-120 min). Gene expression of tyrosine hydroxylase (TH), the rate-limiting enzyme of CA biosynthesis, was evaluated by TH mRNA levels in the adrenal medulla of control and immobilized rats, and of adjuvant treated rats of both strains. Lewis rats seemed to have lower plasma EPI and NE baseline levels and responses to handling than did Fischer rats. During exposure to IMO stress plasma catecholamine increases were significantly lower in Lewis compared to Fischer rats. Basal levels of plasma corticosterone were lower in Lewis rats but stress responses were similar in both strains. Control levels of adrenal TH mRNA were a little higher in Lewis animals but the IMO-induced increases were similar in both strains. Adjuvant treated animals of both strains exhibited significantly elevated adrenal TH mRNA levels.

Thus, the data obtained suggest that the basal values as well as the stress-induced changes in SAS activity are slightly reduced in Lewis rats when compared to those in Sprague Dowley or Wistar rats. The Fischer rats exhibit increased baseline levels and a significant catecholamine hypersecretion after the stress exposure. Stress-induced increases in adrenal TH gene expression are similar in both strains. Since catecholamines exhibit an antiinflammatory effect their reduced responses in Lewis rats might serve as one of the factors responsible for the increased sensitivity to develop the adjuvant arthritis.

Supported by Slovak Grant Agency for Science (2-610999) and VTP No. 21-06-01/1998.

HYPOACTIVITY OF MAJOR STRESS EFFECTOR SYSTEMS AND HIGH JOINT CRH CONCENTRATIONS: Important contributing factors to the pathogenesis of inflammatory arthritis.

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The hypothalamic-pituitary-adrenocortical axis (HPA) and sympathoneural and adrenomedullary systems are the major effector systems whose main function is to maintain basal and stress-related homeostasis. Central corticotropin-releasing hormone (CRH) is the potent regulator of the stress effector systems. Our recent research suggests that different stressors evoke different hypothalamic CRH responses whose activation occurs via stressor-specific pathways. Excessive CRH responses to inflammation can mimic the state of stress or hypercortisolemia and thus enhance resistance to inflammatory diseases. Conversely, defective CRH responses can mimic the glucocorticoid-deficient state and increases susceptibility to inflammatory disease. Whereas arthritis-resistant Fischer 344/N rats have normal stress-induced HPA axis responses, arthritis-susceptible Lewis rats are characterized by deficient central CRH responses to metabolic, inflammatory, or emotional stressors. Recent experimental studies also suggest that epinephrine has potent anti-inflammatory properties, reversible by β-receptor blockade or adrenal medullectomy. Our previous studies showed that Lewis rats have smaller sympathoneuronal but not adrenomedullary responses during the exposure to metabolic stress than do Fischer 344/N rats. In contrast to hypothalamic CRH, peripheral CRH has proinflammatory properties and Lewis rats that have impaired stress-induced activation of the HPA axis have increased frequency of inflammatory arthritis and other autoimmune diseases. Two mechanisms may contribute to these findings: impaired basal and stress-induced activation of the sympathoadrenomedullary and high peripheral (joint) CRH concentrations. In summary, defective responses of the HPA axis and adrenomedullary systems as well as abnormal joint CRH concentrations play an important role in the pathogenesis of inflammatory arthritis.

THE CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME : (CAPS) 2000 2nd SERIES

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A review of a new series of 50 patients subsequent to the 50 previously reported in 1998 is presented. The majority were females (35/50), SLE accounted for 23 patients, 21 with Primary APS (PAPS), one each with lupus-like disease, UCTD, Rheumatoid\SLE overlap, TIP/PAPS overlap, polychondritis and scleroderma. Previously APS manifestations were evident in 29/50 and these consisted of DVT in 12, arterial occlusions in 10, fetal losses in 5, thrombocytopenia (5), haemolytic anaemia 8. Two patients had a previous history of perforated nasal septum.

Precipitating factors were evident in 40 patients (80%)

Infections occurred in 27 (URI (12), urinary (7), infected leg ulcers (5), cutaneous (1), gastrointestinal (3), typhoid (1), cholecystitis (1). Other factors were sun exposure (1), needle-stick injury (1), fractures (2), biopsies (2), anticoagulation withdrawal (4), low INR (1).

CAPS occurred post-fetal loss in one patient and following HELLP syndrome in another.

Two patients suffered from a relapsing course unlike patients with TTP where this is frequent.

Large vessel venous occlusions (15), arterial occlusions (12) were evident in the CAPS patients (a minority). Renal involvement was seen in 42, pulmonary in 42, cerebral in 38, skin in 38, intestinal in 32, hepatic in 22, cardiac in 12 (ischemia). Involvement of parathyroid (1), thyroid (1), uterus (1), ovary (1), bladder (1) and bone marrow (3) were also encountered. The adrenal gland was affected in 6 patients : Transverse myelitis occurred in 1.

Valve lesions were evident in 17 (mostly MI)

28 patients survived and 22 died (44% mortality). In three patients amputation of the gangrenous limbs resulted in cessation of ongoing clotting.

A review of treatment will be given.

The loss of endothelium-dependent vascular tone control in systemic sclerosis (SSc)

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Vascular tone dysfunction is one of the main clinical aspects that testifies the early involvement of the endothelium in SSc. The working hypothesis is that continuous episodes of reperfusion injury and oxidative stress of the vascular microenvironment may induce the loss of the endothelium-dependent control of vascular tone in different organs. In the acral circulation in the early and advanced phase of SSc, the stimulation of endothelium-dependent vascular tone control with substance P did not result in a significant vasodilation. This demonstrates that the endothelium is deranged and that it cannot respond to the stimulation induced by peptides in order to produce a vigorous vasodilation. It is suggested that this impairment is due to the diminished release of nitric oxide by endothelial cells. In the lung it has been demonstrated an impairment of the vascular tone control. In the kidney, the ability to increase glomerular filtration rate in response to a protein or aminoacid load, defined as renal functional reserve (RFR), is severely impaired in SSc patients without clinical signs of renal involvement. In fact, the GFR increase after i.v. aminoacid load in 21 SSc patients was 2±19%, whereas it was 35±14% in 10 healthy controls ($p<0.0002$). Corresponding changes in total renal vascular resistance were 2.5±20% vs 18±6%($p<0.02$). The activation of the RFR depends on the vasodilation of the preglomerular vessels, and its absence indirectly demonstrates a vasodilating defect at kidney level. In conclusion, the endothelium-dependent vasodilation is significantly impaired in all organs in SSc and a protection of the endothelium is necessary in order to maintain the vascular tone control avoiding the breakdown of the vessel patency.

IVIG - what is its role

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High dose γ-globulins were first employed in treating patients with immunodeficiencies. Following the observation of an increased number of platelets in a child with Wiscott-Aldrich syndrome treated with i.v. γ-globulin, the compound was used successfully in patients with autoimmune thrombocytopenia [idiopathic thrombocytopenic purpura (ITP)]. The positive results in ITP in children and adults prompted the introduction of this therapy in diverse autoimmune states including systemic lupus erythematosus (SLE), dermatopolymyositis, Guillain-Barre' syndrome, multiple sclerosis, rheumatoid arthritis and others.
Recently we showed the efficacy of human IVIG as a treatment for the murine experimental model of anti-phospholipid syndrome (APS) and SLE (1,2).: IVIG prevented fetal loss in APS and abrogated the clinical manifestations of SLE. The efficacy of IVIG in 20 patients with SLE was detailed recently (3) .
IVIG was found to affect autoimmune conditions through multifactorial mechanisms. These are divided into humoral mechanisms which include Fc blockade by the IVIG effects on autoantibody binding and production, via the idiotypic anti-idiotypic network, prevention of immune complex formation, and neutralization of microbial toxins. IVIG also exerts its effects via cellular mechanisms entailing immune modulation of T and B cell number and function, as well as inhibition of anti-inflammatory cytokine production.
Recently we have shown the efficacy of IVIG to prevent tumor metastases (4).
We will describe the additional potential of IVIG which is the human serum Ig fraction that is mainly composed of IgG prepared from plasma pools of over 15,000 healthy blood donors and is suitable for i.v. use.

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ANKYLOSING SPONDYLITIS AND RHEUMATOID ARTHRITIS ARE CAUSED BY *Klebsiella* AND *Proteus* INFECTIONS RESPECTIVELY: EARLY ANTI-BACTERIAL THERAPY REQUIRED

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The discovery that ankylosing spondylitis (AS) and rheumatoid arthritis (RA) occur more frequently in HLA-B27 and HLA-DR1/4 individuals has led to the discovery through molecular mimicry, that these diseases are caused by *Klebsiella* infection around the ileo-caecal junction and *Proteus* infection of the upper urinary tract, respectively.

Furthermore *Klebsiella* crosreact with collagens type I,III and IV found in the spine and large joints and *Proteus* crossreacts with type XI collagen found in hyaline cartilage of small joints,thereby explaining the predominant pathological sites of these diseases (Wilson et al.,Ann Rheum Dis 1995;54:216).

Elevated levels of specific antibodies to these bacteria have been found in England,Scotland,Ireland,France,Spain, Belgium,Netherlands,Norway,Germany,Finland,Slovakia, USA,Canada,Mexico,Australia,Turkey,Argentina,China , India and Japan (Ebringer et al.,Lancet 1985;ii:305).

The hypothesis is proposed that AS is a form of "*Klebsiella* reactive arthritis" whilst RA is a form of "*Proteus* reactive arthritis" and modalities of anti-bacterial therapy should be evaluated in prospective studies (Ebringer et al.,J Rheumatol 27:March 2000).

COMMENTS ON VISUAL/FINE ART PALEO-PATHOLOGY OF RHEUMATOID ARTHRITIS (RA)

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Several rheumatologists have recently been able to find convincing evidence for RA on some persons depicted by famous painters in their pictures of the art-historical period embracing renaissance, baroque, romantism, classicism and rococo. Thus, visual/fine art paleopathology succeded in proving existence of RA long before it was described in 1800 and later in the medical literature.
This new approach, that enriched history and origin of RA, has also brought some problems and questions which deserve to be discussed and answered.
In my opinion – as a rheumatologist as well as an active portrait painter – not all of the published findings can be considered to be acceptable, because it is hardly possible to believe that all of the depicted models, showing some swellings or deformities of hands or feet, would have really suffered from RA. It is first of all the master's painting style which is responsible for it and which can evoke such impression and consequent interpretation, as there is especially evident in several pictures by Rubens, Botticelli, and some others. The following, though confused polemics about the origin of RA (Europe? America?) seems to be an interesting result of this unusual approach linking fine arts and clinical rheumatology. For us, rheumatologists, looking at pictures illustrating persons might be not only a pleasure but also an expert activity – let's extend it to other master's works of art, too.

RHEUMATOID ARTHRITIS: A CONTROLLABLE DISEASE?

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Treatment of rheumatoid arthritis (RA) has recently dramatically been influenced by new insights and developments, including the following:

- Joint damage occurs already early in the disease.
- Therefore early effective/aggressive treatment should be considered.
- the armamentarium of disease modifying antirheumatic drugs (DMARDs) has expanded, including drugs like sulphasalazine, methotrexate and leflunomide. These drugs have a faster mode of action that the "older" DMARDs (gold, hydroxychloroquine).
- DMARDs have been shown to retard progression of joint damage.
- Target-oriented therapies have been developed and shown effective. Relevant targets include TNF-alpha and COX-2
- Measures have been developed to minimize side-effects (e.g. combining methotrexate with folic acid; using COX-2 specific drugs).

Althoug T cells are considere to play a crucial role in RA pathogenesis, anti T cell therapies so far have not been consistently effective.
TNF-alpha blocking agents have a fast and impressive effect on RA disease activity and short term studies report retardation or arrest of joint damage . If these effects are maintained in the long term, RA may become a controllable disease. This would have profound impacts on rheumatology, rheumatologists and health care system, that will be discussed in this lecture.

TREATMENT OF RHEUMATOID ARTHRITIS WITH RECOMBINANT HUMAN INTERLEUKIN-1 RECEPTOR ANTAGONIST

K.PAVELKA

Objective: To evaluate the efficacy and safety of interleukin-1 receptor antagonist (IL-1Ra) in patients with rheumatoid arthritis (RA).

Methods: Patients with active And severe RA (disease duration < 8 years) were recruited into a 24-week, double-blind, randomised, placebo-controlled, multicenter study. Patients were randomised to 1 of 4 treatment groups: placebo or a single, self-administered subcutaneous injection of IL-1Ra at a daily dose of 30 mg, 75 mg or 150 mg.

Results: A total of 472 patients with active and severe were recruited. At enrolment, the mean age, sex ratio, disease duration, and percentage of patients with rheumatoid factor, clinical parameters of disease activity and erosions were similar in the 4 treatment groups. At 24 weeks, of the patients who received 150 mg/day IL-1Ra, 43% met the American College of Rheumatology criteria for response (the primary efficacy measure), 44 % met the Paulus criteria, and statistically significant improvements were seen in the number of swollen joints, number of tender joints, investigator's assessment of disease activity, patient's assessment of disease activity, pain score on a visual analogue scale, duration of morning stiffness, Health Assessment Questionnaire score, C-reactive protein level, and erythrocyte sedimentation rate. In addition, the rate of radiologic progression in the patients receiving IL-1Ra was significantly less than in the placebo group at 24 weeks, as evidenced by the Larsen score and the erosive joint count. IL-1Ra was well tolerated and no serious adverse events were observed. An injection-site reaction was the most frequently observed adverse event, and this resulted in a 5 % rate of withdrawal from the study among those receiving IL-1Ra at 150 mg/day.

Conclusion: This study confirmed both the efficacy and the safety of Il-1Ra in a large cohort of patients with active and severe RA and also beneficial effect on the rate of joint erosion.

Reference:

Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist.
B.Bresnihan, J.M.Alvaro-Gracia, M.Cobby, M.Doherty, Z.Domljan, P.Emery, G.Nuki, K.Pavelka, R.Rau, B.Rozman, I.Watt, B.Williams, R.Aitchison, D.McCabe, P.Musikič

PERIARTICULAR CORTICOSTEROID TREATMENT OF THE SACROILIAC JOINT IN NON-SPONDYLARTHRO-PATHICA PATIENTS

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Objective: To evaluate the efficacy of periarticular corticosteroid injection of sacroiliac joint (SIJ) in non-spondylarthropathic patients with pain in the region of SIJ in a double blind and controlled study.

Methods: Twenty-two consecutive non-spondylarthropathic patients with pain at least for one month in the region of SIJ entered the study. At the beginning of the follow-up one affected SIJ in 12 patients was treated with periarticular injection of 1.5 ml (40 mg/ml) methylprednisoloneacetate and 1.5 ml (20 mg/ml) of lidocaine (MP group) whereas 10 patients received 1.5 ml of isotonic sodium chloride and 1.5 ml (20 mg/ml) lidocaine (non-MP group). Clinical assessment at the start of the follow-up and after one month included visual analogue scale (VAS) and pain index (range 0-12) of SIJ which was the sum of tenderness of SIJ, Patrick test, Mennel test and thigh flexion test, each of them evaluated by scale of 0-3.

Results: At one month follow-up examination VAS ($p=0.04$) had improved significantly in the MP group compared with the non-MP group. Also pain index had improved more in the MP ($p=0.07$) group than in the non-MP group, but the difference did not reach statistical significance.

Conclusion: These preliminary results indicate that periarticular treatment of SIJ with methylprednisoloneacetate may be effective in non-spondylarthropathic patients with pain in the region of SIJ.

MICROCIRCULATION - THE ULTRASTRUCTURE OF LYMPHATIC CAPILLARIES IN THE SYNOVIAL MEMBRANE FROM PATIENTS WITH RHEUMATOID ARTHRITIS

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Lymphatics in human synovial tissue (normal knee joints, knee with osteoarthritis and rheumatoid arthritis) were demonstrated by enzyme-histochemical methods. However, the ultrastructure of lymphatic capillary walls in synovial membrane (SM) from RA patients was not described. The aim of our work was to demonstrate lymphatic capillaries (LC) in synovial membrane from RA patients and to visualize the ultrastructure of their walls. Light microscopy of serial semithin epoxy-resin sections and transmission electron microscopy (TEM) of ultrathin sections of synovial membrane obtained during synovectomy of knee joint from 3 patients fulfilling the ARA criteria for RA were used. In the light microscope the LC were found to accompany the postcapillary venules situated in the subsynovial connective tissue layer of the areolar SM. The shape of their lumens was irregular. In larger LC bicuspid valves were observed. LC were found also at the periphery of nodular lymphocytic infiltrate near high endothelial venules. Numerous mononuclear cells were observed in the connective tissue in the close vicinity of the LC walls but not in their lumens hitherto. TEM showed anchoring filaments attached to the abluminal surface of LC endothelium and discontinuous basal lamina. Between the endothelial cells of LC the intercellular junctions of the open type, consisting of overlapping endothelial flaps, were observed. The LC showed close morphological relationship with synovial connective tissue in which the tissue spaces were occupied by the inflammatory cells. The picture of infiltrated synovial interstitium was in contrast to empty lumens of LC. It is possible that inflammatory process in synovial joints might have impaired function of the intercellular junctions in the LC walls, deteriorated the absorbing function of these fine vessels and contributed to the development of chronic edema.

CHEMOKINE RECEPTOR EXPRESSION IN SYNOVIAL TISSUE FROM PATIENTS WITH RHEUMATOID ARTHRITIS

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Introduction: Rheumatoid arthritis is a destructive inflammatory disease characterized by the recruitment of different leukocyte populations to the arthritic joints. The molecular signals that control the extravasation and recruitment of leukocytes to these sites have not been fully characterized to date.

Objective: To identify chemokine receptor expression on infiltrating cells in the rheumatoid synovium.

Methods: Monoclonal antibodies (mAbs) to chemokine receptors CCR1, CCR2, CCR5 and CXCR3 (R&D *Systems*) were used to stain the synovial tissues from 10 RA patients, two osteoarthritic patients and two normal subjects. A battery of other mAbs was used to characterize the cell types in the tissues.

Results: A consistently strong expression of CXCR3 was observed in all the RA samples. CXCR3 positive cells were localized predominantly in the lining and sublining layers of the synovium with the strongest staining concentrated at the leading edge of the synovial pannus. Interestingly, in more than half of the RA-derived samples, we also observed a strong staining of the vascular endothelial cells (EC). The CXCR3 staining was polarized to the luminal surface of the EC, a pattern that was distinct from that obtained with the anti-CD31 mAb which labeled the entire cell surface. The majority of the T cell aggregates were positive for CXCR3, however in some aggregates, large areas of unstained cells were also observed. Anti-CCR5 mAb labeled a variable number of cells in the deeper layers of the synovium, presumably macrophages. T cell aggregates showed a weak and inconsistent CCR5 expression. Anti-CCR1 mAb stained few cells within and outside the T cell aggregates, and a slightly more pronounced signal in the same areas was obtained with the anti-CCR2 mAb.

Conclusion: CXCR3 is the predominant chemokine receptor expressed in the RA synovial membrane suggesting a possible role for CXCR3-expressing cells in the pathogenesis of RA.

J. Vencovsky's work is supported by grant NI/5369-3 from IGA MZ CR.

THE SIGNIFICANCE OF ANTIKERATIN ANTIBODIES, ANTI-PERINUCLEAR FACTOR, IGM RHEUMATOID FACTORS HLA SHARED EPITOPE AND CARTILAGE OLIGOMERIC MATRIX PROTEIN IN PREDICTION OF EROSIVE DISEASE IN EARLY RHEUMATOID ARTHRITIS.

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Objectives: To assess the contribution of selected laboratory examinations as prognostic markers of erosive disease in early rheumatoid arthritis (RA).
Patients and methods: One hundred and fourteen patients with disease duration less than 2 years after the onset of symptoms were investigated. Only patients who fulfilled the diagnostic criteria for RA either at the beginning of the disease or during the follow-up period were included. The antikeratin antibodies (AKA) and antiperinuclear factor (APF) were detected by indirect immunofluorescence, IgM rheumatoid factor (IgM RF) by ELISA and the presence of HLA shared epitope (HLA SE) by PCR with sequence specific primers. Plasma levels of cartilage oligomeric matrix protein (COMP) were measured by ELISA. Patients were divided into two groups based on the Larsen score for erosive or non-erosive signs at the end of at least 18 months of follow-up.
Results: Seventy-two (63.2%) patients developed erosions in their hands or/and feet whereas 42 (36.8%) remained without destructive changes. The initial AKA, APF, IgM RF and HLA SE were positive in 50 %, 46 %, 41% and 67% in erosive group, and in 16%, 24%, 24% and 58% in non-erosive group, respectively. The significant differences between erosive and non-erosive groups were detected for AKA ($p=0.002$) and APF ($p=0.047$) antibodies, whereas IgM RF and the presence of HLA SE did not significantly differ. Plasma levels of COMP do not statistically deffer between erosive a nonerosive groups.
Conclusions: The positivity of antikeratin antibodies and to less extent antiperinuclear factor are at the beginning of disease good predictors for development of erosions in patients with early rheumatoid arthritis. In contrast to published data the IgM RF positivity and the presence of HLA shared epitope did not contribute to prognostic assessment in our early patients. The value of anti-citrullinated peptide antibodies, which probably detect in a more sensitive and specific way antikeratin antibodies, is being evaluated in this group of patients as well.

This work was supported by a grant IZ/4354-3 from Internal grant agency of the Czech Ministry of Health.

OUR EXPERIENCE WITH CYCLOSPORIN A MICROEMULSION IN THE TREATMENT OF PATIENTS WITH RHEUMATOID AND PSORIATIC ARTHRITIS

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Improvement of the quality of life in patients with rheumatoid and psoriatic arthritis (RA, PsA) depends on the supression of inflammation activity and avoidance of joint destruction wich can be controlled by DMARDs such as cyclosporin A (CsA) microemulsion .
Aim : To assess effect of CsA in combination with other DMARDs and corticosteroids as well as evaluate the side effect of treatment with CsA.
Methods: The study population include 18 patients with severe or refractory RA and PsA. Each patient was treated by DMARDs and corticosteroids more than 3 months without sufficient effect. CsA microemulsion was added to the above mentioned treatment. The initial dose of CsA was 2,5 mg/kg/day which was increased to 3,5 mg/kg/day. When improvement of the clinical course of the patient had been noticed, the dosage of corticosteroids or NSAIDs has decreased. During the follow-up of 12 months, at the 6th and 12th mouths the treatment was assessed by ESR, CRP, articular index, index disability/HAQ, physician´s and patient´s global assessment of disease activity.
Results: The effects of combined therapy was assessed in 16 of 18 patients because of serious side effects in 2 patients in the first month of therapy (deterioration of renal function, increased activity of liver enzymes). Significant improvement was observed in the all parameters mainly at 6th months of treatment, which was not changed thereafter. HAQ disability index continuously improving throughout the whole time of investigation. None of the patients has achieved complete remission. In 7 patients not serious adverse events were noticed. (gastrointestinal intolerance (3), hirsutism (1), gingivitis (1) hypertension (5)). In our experience, long-term follow-up has shown that CsA is a effective second-line drug for RA and PsA and significantly improve the quality of life of patients with RA and PsA.

BONE AND JOINT DECADE 2000-2010

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The Bone and Joint Decade is a global initiative with the goal of improving the health-related quality of life for people with musculoskeletal disorders throughout the world. This goal is being achieved by raising awareness of the growing burden of musculoskeletal disorders on society; empowering patients to participate in their own care; promoting cost-effective prevention and treatment; and advancing understanding of musculoskeletal disorders through research to improve prevention and treatment. Osteoarthritis, rheumatoid arthritis, osteoporosis, back pain and musculoskeletal trauma are major causes of morbidity worldwide.

This initiative is in partnership with over 650 appropriate national and international professional and scientific organisations; research bodies; scientific journals and patient organisations, and working with governments and non-governmental organisations. It is supported by the United Nations and the World Health Organisation and over 20 governments at present..

Within each country, networks are being established consisting of the relevant organisations to develop national actions to achieve the goals of the *Decade*. There are at present 40 such national action networks, with the aim to achieve 100 by 2002. Initiatives vary from data collection of burden, developing evidence-based strategies and public and health professional educational initiatives.

A central activity of the Decade is a global health needs assessment for musculoskeletal conditions, the Bone and Joint Monitor Project. The first phase has been to identify the burden of musculoskeletal conditions in collaboration with the WHO Global Burden of Disease 2000 Group and international experts, and to establish agreed outcome measures so that the burden can be monitored in the future. This was the subject of a WHO Scientific Group Meeting in January 2000. The second phase will be to identify what can be done and what is being done, so that the gaps can be identified. Strategies and priorities relevant to the geographic and socio-economic settings can then be developed to close these gaps and improve the health-related quality of life for people with musculoskeletal disorders.

Activities of the Slovak orthopaedic and traumatologic Society in the Bone and Joint Decade.

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Shortly after iniciating the obovementioned decade by prof.Lars Lindren, the Slovak orthopaedic and traumatologic Society (SOTS) joined this program. The activitics of SOTS were directed towards 3 main problems:osteoarthritis, osteoporosis-and fractures in the elderly (geriatric fractures). In osteoarthritis we focused on degenerative changes on large weightbearing joints of the lower extremity (hip and knee) and their treatment mostly by joint replacement and on degenerative changes on the spine, aiming at a complex (also operative) treatment. In osteoporosis we stressed the importance of early, exact diagnosis (densitommetry) and complex treatment of complicating semipathologic fractures. In geriaatric traumatology we elaborated a modern strategy in the treatment of fractured necks of the femur, wherene succeeded mostly with joint replacements rather than osteosynthesis. All mentioned treatment strategies will be demonstred on instructive slides.

TEN YEARS OF THE LEAGUE AGAINST RHEUMATISM IN SLOVAK REPUBLIC.

Orlovská M., Masárová R., Hrčková L.
League against rheumatism in the Slovak Republic.

Panel to the 10. Anniversary of the foundation of the League against rheumatism in the Slovak Republic with the picture dokomentation of the activity during the past period.

INTIMATE PROBLEMS OF PATIENTS WITH RHEUMATOID ARTHRITIS AND JUVENILE CHRONIC ARTHRITIS

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Rheumatoid arthritis (RA) and juvenile chronic arthritis (JCA) with their chronic course substantially influence all activities of patients. They affect their ability of movement, working performance, economical independence, integrity in social environment and self-care.

Aim of the study: to evaluate how the individual handicap can reflect on the familial as well as intimate life of patients.

Methods: In a group of 29 patients (20 females, 9 males) aged from 19 to 70 years, from them 72% married and 62% actively working, the problems concerning familial, partner°s and social life were studied by means of questionnaire. Questions included 18 items and were oriented besides familial and intimate complications also to difficulties conditioned by disability.

Results: The loss of working ability was found in 69%, that was negatively effected in male by income dicrease and in female patients by limited social contacts. In more than 75% of patients individual disability clearly afflicted the personal working activities including hobbies. Most of patient stated to be affraid of future unpredictable resp. unfavourable development of his/her disease, loss of independence and self-reliance. Till 97% of patients expressed the positive and active attitude of their families despite of decrease in incomes. The family was shown to offer help to affected members in solving their personal problems. About one half of patients considered the help of psychologist for positive.

Conclusion: Dependence of our patients with RA and JCA on their families and positive relationship of their members in helping them was shown to essential result of this study, even though not enough professional attention is being devoted to this problem.

SOCIAL SITUATION OF RHEUMATIC PATIENTS IN THE SLOVAK REPUBLIC

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It was the aim of this work to find out the social situation of rheumatic patients in the Slovak Republic, who are the members of the civil association – the League against rheumatism in Slovakia.

In the time between November 1, 1998 – February 28, 1999 a standard questionnaire was sent to 3000 patients of the League against rheumatism in the Slovak Republic.

The questions in the questionnaire dealt with social and economic conditions and family relations. Out of this number were filled out and sent back 964 (32,1%) forms, of these were 242 (25%) men and 722 (75%) women in the age between 19-88 years.

The division of the group according to the education and employment is in accordance with the demographic characteristics of the population in the Slovak Republic. The division as per diseases doesn't follow their prevalence in the population. The inquiry was responded more often by patients with inflammatory rheumatic diseases (55%) less with the degenerative diseases (18%).

Alarming is a low ratio of the employed probands 170/964 (18%) in comparison with the invalid ones 387/964 (40%) in this group. Surprising is a low ratio of a partial invalidity 44/964 (5%) of the group members, out of who only one half are employed in a part time employment 21/964 (2%). For lack of the job opportunities, the partial invalid patients remain prevailingly unemployed 8/964 (0,8%) with a very low income level and therefore they change over into a full invalidity. This unfavourable situation is confirmed also by the fact, that in 427/964 (44%) the income for an individual family member reaches only a subsistence level. Due to a disease, the financial situation was markedly getting worse in 360/964 (37%). This fact has a negative influence upon the financial situation of the whole family as well, which as a consequence of the family member's disease is evaluated as unfavourable by 635/964 (66%) of responders.

The inquiry showed that the family relations provide a firm hinterland for patients, because they find confidence and understanding above all in the family 419/964 (44%). They expect from the family members mainly a psychical support 464/964 (49%) and an assistance at the personal service 272/964 (28%).

The inquiry results called attention to the very unfavourable economic situation of the rheumatic patients deteriorating considerably the quality of their life. They find the most important support in the family.

CYCLOSPORIN A IN THE TREATMENT OF JUVENILE CHRONIC ARTHRITIS: THE PAST AND THE FUTURE

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Juvenile chronic arthritis (JCA) is a chronic inflammatory, immune mediated disease in which the activation of T lymphocytes is central in the initiation and perpetuation of the disease. During the past few years cyclosporin A has come to represent a new direction in therapy of various autoimmune diseases including inflammatory rheumatic conditions. There are relatively limited experiences with long-term treatment of patients with JCA with cyclosporin A with special attention to systemic forms of this disease. History of cyclosporin A use in the treatment of JCA in Slovakia began before 10 years.

Specific questions of the use of cyclosporin A in the treatment of JCA are connected with selection of suitable patients, optimal dose, long-term monitoring of the treatment with reduction of adverse reactions and combination with other disease modifying drugs. There were observed significant inter- and intrasubject variations in systemic bioavailability. Selection procedures must consider also potential non-responders. A microemulsion-based formulation of cyclosporin A was developed in last years and possesses more predictable and improved systemic bioavailability with improved efficacy and safety profile.

Own experiences with long-term cyclosporin A treatment of severe systemic forms of refractory JCA are also presented with special attention to efficacy and safety of the treatment.

Despite new therapeutic modalities (including experimental approaches) cyclosporin A is still a good alternative in comparison to less selective immunosuppressants in selected patients with refractory forms of JCA.