The sacroiliac joints (SIJ) are initially a normal articulation, and in spondyloarthropathy (SpA) it is of interest to different anatomical structures. To learn about the pathogenesis of enthesitis and ankylosis in SpA, and this is similar for anterior and posterior sacroiliac joints in patients with AS we investigated the efficacy of this treatment also in these patients.

**Patients and methods**—Eleven patients with AS (mean age 36 years, range 27–56; 10 male, 1 female; mean disease duration 5 years, range 0.5–13) with active disease were included in an open study. Three treatment cycles (weeks 0/2/6) with anti-TNFα (Remicade) in a dose of 5 mg/kg were given. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), BASFI (functional index), BASMI (metrology index), pain on a visual analogue scale (VAS), and C reactive protein (CRP) were measured over 12 weeks.

**Results**—Dramatic improvement (BASDAI improvement >50%) starting on the day after the first infusion was seen in 10 patients; treatment of one patient was discontinued because of a rash. Improvement persisted until week 12 in 9/10 patients. In the direct comparison between week 0 and week 12 all parameters improved significantly (Wilcoxon test). The median of scores and values for weeks 0, 2, and 12 were: BASDAI from 6.5 to 2.8 (p=0.001) and 2.4 (p=0.004; fig 1), BASFI from 5.3 to 2.0 (p=0.002) and 2.4 (p=0.008; fig 2), BASMI from 3.0 to 1.0 (p=0.031) and 1.0 (p=0.008); VAS for pain from 7.8 to 2.0 (p=0.002) and 2.5 (p=0.004); CRP from 15.5 mg/l to persistently normal (p=0.008 at week 12; fig 1).

**Discussion**—The results of this open study showing a dramatic improvement in over 90% of patients justify the conduction of a controlled study. Anti-TNFα treatment seems to be effective in active AS.

**Enthesitis and ankylosis in spondyloarthropathy (SpA)**

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The sacroiliac joint is centrally involved in SpA. Furthermore, peripheral and spinal enthesitis are characteristic and special features of SpA, and this is similar for anterior uveitis.

Dynamic magnetic resonance imaging (MRI) has proved helpful in early diagnosis of sacroiliitis. Similarly, MRI of the spinal column can also identify active inflammatory lesions such as spondylitis and spondylodiscitis—at a time when conventional x-rays are still normal. Thus our ability to screen and quantify early active disease has significantly improved. This will be of major relevance for clinical studies. From MRIs of two patients with very early SpA who were affected. To determine the exact localisations of sacroiliitis in early disease stages dynamic MRIs of 56 patients with SpA (112 SIJ) were retrospectively analysed. Of those, 43 were classified as undifferentiated SpA (including patients with early AS who progressed to AS in the further course of disease) and 13 as differentiated SpA (5 reactive arthritis, 4 psoriatic arthritis, 4 arthritis associated with inflammatory bowel disease). The mean (SD) age was 32 (12) years (range 16–57) and the mean (SD) disease duration 1.2 (1.3) years (0.3–7).

Only patients with x-ray stages <2 bilaterally were included: 50% of the patients were normal, 33% were graded as grade I, and 17% showed grade II changes unilaterally. In contrast, MRI detected 36 SIJ as normal, 35 had grade I, and 41 grade II changes according to the MRI criteria proposed; 60% showed strong gadolinium enhancement (grade b), 17% moderate enhancement (grade a), and 23% were normal (opposite sites).

The following anatomical structures were distinguished: joint space, joint capsule, entheses, ligaments, subchondral bone, and the bone marrow; ventral and dorsal involvement was differentially assessed. The differentiation between enthesal and ligamentous structures proved difficult. The joint capsule was commonly affected: the ventral capsule showed enhancement in 49% and the dorsal capsule in 75%; isolated enhancement was found most often in both, the ventral and the dorsal part. Enhancement in the joint space was detected in similar frequency: in 75% in the ventral and in 63% in the dorsal part. Involvement of entheseal structures was seen in 53% of the cases; in 32% extended enhancement of the dorsal intersosseous ligaments was seen. The iliac juxta-articular subchondral bone was affected in 75% of the cases, similarly often in the ventral (53%) and dorsal (68%) part. Diffuse enhancement in the bone marrow was seen in 47% and circumscribed in 24% of the cases.

These data show that all structures examined are more or less involved in SpA associated sacroliliitis, with involvement of the joint capsule and subchondral bone being most common.

MRI can also detect spinal inflammation at early stages. Examples of patients with AS with early spondylitis anterior and posterior and spondylodiscitis were presented.

**Successful anti-TNFα treatment in ankylosing spondylitis (AS)**

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Background—Treatment with anti-tumour necrosis factor α (anti-TNFα) monoclonal antibodies has been successfully applied to patients with rheumatoid arthritis. Because TNFα has been detected in inflamed sacroiliac joints in patients with AS we investigated the efficacy of this treatment also in these patients.

Figure 1: Ankylosing spondylitis disease activity assessments. CRP and BASDAI before, during, and after treatment with 5 mg/kg anti-TNFα (arrows indicate the dates of infusion).
consecutively followed up we suggest that the event may take place in the joint capsule entheses.

By computed tomography guided biopsies of the sacroliliac joints the inflammatory lesions were characterized: CD4+ and CD8+ T cells and macrophages predominate; cytokines such as tumour necrosis factor α (TNFα), interleukin 6, and transforming growth factor β (TGFβ) have been detected at mRNA and protein levels. In earlier disease this is more TNFα than TGFβ, also in the proximal bone marrow. The degree of cellularity correlates with the enhancement of gadolinium in sacroliliac MRIs.

By enzyme linked immunosorbent assay (ELISA) and FACS techniques we have shown that low TNFα secretion is associated with more chronic disease in reactive arthritis. By detection of intracellular cytokines at the single cell level an enhanced immune reactivity (interferon γ secretion) to the aggrecan G1 domain—which can induce spondylitis in animal models—has been seen in patients with AS. When the same technique was used a decreased TNFα secretion after non-specific stimulation was found in patients with AS and also in healthy HLA-B27 positive controls. Of interest, after successful anti-TNFα treatment both immune reactions proved to be increased, suggesting that anti-TNFα treatment suppress immune reactivity in AS and arguing against a deleterious role of a high TNFα secretory capacity and against a pathogenic role of an autoimmune Th1 response to the aggrecan G1 molecule.

Role of enthesis in juvenile SpA

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Enthesopathy is one of the most important signs of disease in children with juvenile onset spondyloarthropathies (Jo-SpA). As part of the original description of seronegative enthesopathy and arthropathy syndrome and as part of the enthesitis related arthritis subgroup of childhood arthritides, enthesopathy is the distinguishing feature of Jo-SpA.

The single entheses most commonly affected are those of the lower extremities, particularly the plantar fascia and Achilles tendon attachments to the calcaneus.

In conclusion, we noted a significant oedema and inflammatory infiltrate in the enthesis bone marrow of patients with SpA, in comparison with patients with RA and OA, and the inflammatory cells were predominantly T lymphocytes, with a majority of CD8 lymphocytes. This result suggests that, at least in enthesis, CD8 cells have a predominant role in the inflammatory process of SpA.

Histopathology of ankylosing enthesopathy (ANKENT)

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ANKENT is a naturally occurring, progressive stiffening of the ankle and/or tarsal joints in mice. It occurs in up to 30% of adult male mice of C57 black background and is seen only in female mice. ANKENT usually starts at the age of 4–8 months, develops during a period of 2–4 weeks, and then remains stable.

Ankylosing enthesopathy was found to begin with a short phase of proliferative inflammation of the joints and adjacent tissues, with some fibrous exudation, some leucocytic infiltration, and slight bone erosion during the first 2–3 weeks. This inflammation is soon accompanied and followed by proliferation of cartilaginous cells at the bone insertions of joint capsule ligaments (entheses). Their articular cartilage itself shows only slight proliferation. Ossification of the cartilage proliferations and some demal ossification lead to large bone spurs (syndesmophytes) that inhibit mobility. Fusion of cartilage proliferations or of bone spurs from adjacent bones occasionally leads to spondylolisthesis or marginal ankylosis.

ANKENT in mice strongly resembles the condition seen in the spinal joints in ankylosing spondylitis (AS) in man: a short lasting, scarcely destructive inflammation at the entheses followed by proliferation of cartilage and bone, leading to ankylosis mainly the margins of the joint and leaves the central articular cartilage intact for a long time. In nearly 60% of Mexican mestizos with AS tarso-syndesmophytes occur. In AS affection of the spine is prominent, an involvement of an ever
increasing number of joints is usual, even though the disease often shows remissions and exacerbations. ANKENT seems to be limited to the tarsal/ankle region, and although several joints are affected, they are more or less at the same stage of pathology. The only place at which a second inflammation commonly occurs is the contralateral tarsal/ankle area. The spine is not affected in ANKENT. The histopathology of ANKENT has been published.


Is inflammation the trigger for new bone formation in ankylosing spondylitis?

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Objective—To test the hypothesis that new bone formation in ankylosing spondylitis (AS), a member of the “family” of HLA-B27 associated diseases, is triggered by inflammation.

Methods—The study was based on light microscopic studies of tissue samples taken either at operations or as biopsy specimens from patients with AS and psoriatic arthritis (PsA). (Patients with AS—45 bone samples, 309 synovial tissue; patients with PsA—95 bone, 863 synovial tissue.)

Results—The typical formation of new bone in AS and PsA takes the form of desmal ossification: in the cambium layer, fibroblasts transform into irradiating type I collagen fibres, into pre-osteoblasts and osteoblasts. These subsequently form new, fibrous bone with no interference of any elements of inflammation.

Conclusion—Our study indicates that new bone formation in AS is a desmal ossification at the enthesic border of bone and that there is no evidence for inflammatory triggers. Analogous processes have been seen in transgenic (BMP-6) mice.

Pathology of peripheral joints in spondyloarthropathy

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Peripheral joint involvement occurs in approximately 30% of patients with ankylosing spondylitis (AS) and is often a presenting feature. Immunohistological studies of synovial membrane (SM) show an intense inflammatory infiltrate characterised by a thin lining layer, prominent aggregates of CD4+ >CD8+ T cells, and a large number of factor VIII+ blood vessels. In addition, in a disease not associated with autoantibody production, prominent aggregates of B cells and plasma cells are seen.

Features of AS SM are similar to those described in another spondyloarthropathy, psoriatic arthritis (PsA). Further studies in PsA have focused on vascular staining and on T cells. The SM in PsA is highly vascular, suggesting prominent angiogenesis. Of interest, PsA SM endothelial cells express both NURR-1, an early activation gene which may have a role in cell proliferation, and MMP-1, which may help breakdown surrounding collagen.

Whereas CD4+ T cells predominate in PsA SM obtained during active disease, CD8+ T cells outnumber CD4+ T cells by 2:1 in synovial fluid. Given the association of PsA with HLA class I antigens, we proposed a CD8+ mediated immune recognition event. Studies of T cell receptor (TCR) phenotype confirmed that the CD8+ T cells are clonally expanded as compared with peripheral blood, with smaller, but none the less significant, clonal expansions also occurring in the CD4+ T cells population. Of interest, although TCR phenotype studies of PsA SM obtained during active disease do indeed confirm a predominant non-specific influx of T cells, with metathexin induced disease remission, the clonal nature of the remaining, probably disease-pathogenic populations of CD8+ and CD4+ T cells is unknown.

Thus these studies strongly support the concept of a specific T cell mediated immune event occurring in PsA SM, probably involving CD8+ and CD4+ T cells as well as dendritic cells which express both class I and class II HLA molecules.

Axial pathology in ankylosing spondylitis (AS)

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This presentation is based on a systematic screening of 5000 intervertebral discs (5 biopsies and 7 necropies) of patients with AS at different stages of the disease and of 22 control necropsy cases. Furthermore, spinal material from 9 necropies of AS cases was studied.

In AS SI joints there is more frequent synovitis, pannus formation and superficial cartilage destruction, myxoid marrow, enthesis, intra-articular fibrous strands, new bone formation and bone ankylosis than in control cases (p<0.05). Cartilaginous fusion is seen in both groups, but occurred much earlier in AS. When a joint is ankylosed, no synovium remains.

Mild but destructive synovitis and myxoid subchondral bone marrow are the earliest changes identified. Destruction of adjacent articular tissues is followed by scarring by fibrous tissue, woven bone, and new cartilage. The original cartilages fuse and this is the predominant mode of early ankylosis. All cartilaginous tissues are replaced by bone. Active enthesitis and scars of presumed previous enthesitis are seen at all stages except the early one. Pathological bone is at first dense, but later becomes porotic.

In the spine the diarthrodial joints exhibit either synovitis or enthesitis with capsular ossification, myxoid bone marrow, chondroid metaplasia, synchondrosis, and ossification. Inflammatory changes are seen all along the annulus fibrosus, particularly at its chondroid enthesis, in the deeper perivertebral ligaments, and at their insertion by Sharpey's fibres. Chondroid metaplasia is seen, as well as fibrosis and tissue response which either ends chondral or woven. Replacement of inflammatory changes by bone leads to syndesmophytes. Inflammation sometimes occurs within the vertebral body (spondylitis) or disc (discitis).

In conclusion, in AS associated sacroilitis, synovitis and subchondral bone marrow changes explain the widespread destruction better than enthesis. An unusual form of chondroid metaplasia contributes to ankylosis. Enthesitis probably has a larger role in the spine, but otherwise spinal and SI changes are similar.

Possible role of TGFβ and BMPs in bone and enthesis pathology

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Bone morphogenetic proteins (BMPs), members of the transforming growth factor β (TGFβ) family, play a critical part in bone, cartilage and tendon formation during development of animals. Common e.

morphogens have been described for the process of bone healing; distinctive and unique characteristics may belong to individual BMPs in human development. Currently, few data are available on the role of these molecules in the physiology and pathology of adult tissues. The most common expected effect of ossification. However, in adults, bone and cartilage contain several of these morphogens physiologically without induction of pathological calcification.

Our data have shown that several BMPs and TGFβs are differentially expressed in synovial tissue of normal, acute and destructively inflamed joints. BMP-4, BMP-5, and, to some extent, GDF-5 were found suppressed, correlating with the severity and chronicity of the inflammatory process. In contrast, TGFβ2 seems to be upregulated early after trauma to counterbalance disruption. These data suggest an important role for BMPs and TGFβs in homeostasis and repair in adult skeletal tissues. This role of morphogens and growth factors obviously depends on the type and differentiation of cells, the expression level of specific receptors, the quality of inflammation, and the mechanical stress on bone, tendons, and joints.

Appropriate signals are given by BMP-2 and BMP-4 during callus formation in bone healing. BMP-2 also enhanced tendon to bone healing, whereas GDF-5 and GDF-6 enhanced healing of tendons. In contrast, BMP-7 is inappropriate for Achilles tendon repair and may induce an ossicle. Overexpression of certain BMPs may promote degenerative processes of the intervertebral disc or induce fibrodyplasia ossificans progressiva.

TGFβ may induce synovitis by chemotaxis, synovial cell proliferation and hyperplasia, and mediate angiogenesis by induction of vascular endothelial growth factor. TGFβ supports non-specific wound healing and fibrosis. Over time TGFβ may enhance osteoarthrosis.

In summary, TGFβ may provide protective signals early during the inflammatory process but induces non-specific fibrosis upon chronic disease progression. BMPs and TGFβ seem to have an important role in tissue homeostasis with an individual expression pattern depending on the type of tissue. Development of this pathway in two different pathological conditions: overexpression may induce pathological ossification; suppression, on the other hand, may give way to the dedifferentiating and destructive signals of inflammation.
Cartilage matrix molecular constituents and function

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Articular cartilage is a composite tissue with mechanical function. The composition and architecture of its matrix constituents differ between different sites in the joint. The tissue has to respond to changing functional requirements with age by adapting its structure via remodelling. The cells, chondrocytes, govern these processes. It is of key importance that they have the ability to monitor tissue function and structural integrity.

The tissue is composed of molecules assembled to provide structural features to give the essential properties. Major contributions come from the network of collagen fibres that provide essential tensile properties and the aggrecan assemblies providing an extreme density of negatively charged groups and ensuing osmotic pressure essential for retaining water and restricting water movement. Minor components have key roles in regulating the major constituents, in remodelling matrix assembly, and in signalling matrix conditions back to the cells. Because functional requirements vary with site and age the macromolecular assembly is variable, albeit the overall structure is rather constant. Thus in the superficial layer the structure is quite distinct from that at deeper layers. In each layer the organisation of the matrix close to the cells in the pericellular and territorial areas is quite distinct from that in the interterritorial area. Thus collagen fibre dimensions are essential for the tensile properties of the tissue, and abundance of collagen binding proteins differ between the various compartments. Also other constituents change with site in the tissue. Thus cartilage oligomeric matrix protein (COMP), a member of the thrombospondin superfamily, is particularly enriched in the superficial part of the adult articular cartilage, where it is found predominantly in an interterritorial location. Interestingly, the protein is in earlier stages of the joint development found primarily in a more pericellular location, where it is also particularly enriched in the growth cartilage. Aggrecan, aggregan (CILP), of M 92 kDa, is predominantly localised in the middle to bottom third of the articular cartilage, also enriched interterritorially. A family of leucine-rich proteins, including the collagen binding proteoglycans decorin, biglycan, fibromodulin, and lumican, seem to have major roles in the assembly of the collagen network and in maintaining its properties by interlinking collagen fibres. This family includes members not containing glycosaminoglycan chains, some of which promote cell attachment such as chondroadherin and osteoadherin, which are likely to have a key role in cell signals from matrix to cells important for tissue homeostasis.

Enthesitis: a broader definition

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Enthesitis is the characteristic primary lesion of ankylosing spondylitis (AS) and related spondyloarthropathies (SpA), starting with soft tissue inflammation, followed by the underlying bone marrow oedema with only occasional inflammatory cells. These changes predate the bone cortex erosion and new bone formation. Recent studies suggest that, unlike RA, where synovitis is the initial or primary lesion, the synovitis of SpA may be a secondary event, at least in some joints. A suggestion is made that we should broaden the definition of "enthesitis" so that it includes not only the bony attachment sites of tendons and ligaments but also the attachment sites of the articular cartilage at the end of the bone. Thus the chondral-subchondral junction of a bone is an enthesis where cartilage (rather than a ligament, capsule, or a tendon) attaches to the bone. The additional reasons for this concept will be discussed.

A plea is made that the investigators interested in enthesitis of AS and related SpA should also study the enthesitis and its evolution in African patients who have HIV associated SpA. SpA has markedly increased the prevalence of SpA (reactive arthritis (ReA), psoriatic arthritis, and undifferentiated SpA) in sub-Saharan Africa, where SpA was a rarity in the past. This is all the more remarkable given the almost complete absence of HLA-B27 in these populations, and the fact that the HIV associated ReA in white subjects, on the other hand, retains a strong B27 association.

Fusion of vertebral bodies and sacril靓丽 joints by cartilaginous tissue in B27 transgenic rats

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As described earlier, we have studied morphological alteration of joints of HLA-B27 transgenic rats by histological methods. Information about the histopathology of the spine in animal models and in man, characteristic of ankylosing spondylitis (AS), is limited. Therefore, the purpose of the study was to evaluate the pathology of the spine and other joints in these animals, which might serve as a useful model for this disease.

Rats from the 21–4H line were killed at 7 months of age. The spine was divided into four parts from the neck to the pelvis and examined together with the sacril靓丽 joints and histological sections of the knees and feet by haematoxylin and eosin staining.

Most prominently, all animals showed cartilaginous fusions of vertebrae (spondylothesis). Formation of syndesmophytes could be seen in small vertebral joints. One half of the animals had also spondylodiscs of the sacril靓丽 joint, in part associated with pannus-like lesions. In addition, some rats exhibited foci with an inflammatory cell enrichment in small vertebral joints. Pannus-like fibroproliferative tissue could be shown also in the knee joints. Most remarkably, deformities of the feet with immature cartilage and the formation of a pannus-like tissue was demonstrated. Furthermore, cartilaginous metaplasia could be detected in the patellar ligament. The data show for the first time the fusion of vertebral bodies by cartilaginous tissue in an animal model. It is postulated that cartilage fusion may be the initial process in AS as discussed in man and that the HLA-B27 transgenic rat is a most useful model for studying the pathology of this disease.

Enthesitis and reactive arthritis

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Enthesitis is a key feature of the spondyloarthropathies, and it has been suggested that it is associated with the pathogenesis of both peripheral arthritis and spinal disease. In SpA enthesitis is also common in patients with acute reactive arthritis, with reports of its incidence varying between 10 and 30%, usually associated with arthritis. However, recently, the term reactive enthesitis has also been introduced. Enthesitis can be the only reactive musculoskeletal symptom in about 5–10% of patients with reactive musculoskeletal complications. According to our previous studies with ultrasonography, enthesitis seems to be a frequent sign in patients with spondyloarthropathies, and seems to run a more chronic course than distinct arthritis. Patients with spondyloarthropathies have a high frequency of the HLA-B27 antigen. The importance of isolated reactive enthesitis has not been studied in detail, but the previous study1 and our own results favour a less significant association between HLA-B27 and reactive enthesitis.

Enthesitis in spondyloarthropathy

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Enthesal insertions are ubiquitous throughout the skeleton, and the term reactive enthesitis in the pathology of spondyloarthropathy (SpA) has long been recognised. Enthesitis is a prominent feature of spine, foot, and pelvis pathology in SpA and to a lesser extent in small joints, as in reactive arthritis. The recent use of fat suppression magnetic resonance imaging (MRI) techniques, which are optimised for showing sites of bone inflammation, has expanded our understanding of the enthesitis lesion.

The clinical concept of enthesitis is of a focal pathology at the insertion of a tendon, ligament, or joint capsule to bone. This is seen in MRI of the plantar fascia, but in many cases severe bone marrow inflammation (ostitis) affects much of the calcaneum. However, similar MRI findings are evident in patients with mechanical plantar fasciitis. This similarity between mechanical and inflammatory plantar fasciitis may suggest that biomechanical factors are also important in the pathology of SpA associated enthesitis. The structures which make up the enthesis (tendon, ligament, capsule, and periosteum) have a low water content and therefore are not well visualised by MRI and it is the adjacent soft tissue changes and bone changes that are the best appreciated. Interpretation of MRI scans for the presence of enthesitis in spondyloarthritis may therefore be difficult because of soft tissue changes related to synovitis. Nevertheless, many cases have diffuse bone oedema in knee joint synovitis in SpA. As assessed by MRI combined with

sonography most of these changes are associated with focal enthesis. The frequency and extent of enthesitis in synovial joints has implications for the mechanisms of synovitis in SpA and, possibly, synovitis may be secondary. The SpA are associated with an array of bone pathology, including SAPHO syndrome, arthritis mutilans, spondyloarthritis, CMRO, and others. Some authors have suggested that enthesitis is the primary lesion in this syndrome. The diffuse MRI changes in these conditions are highly reminiscent of enthesitis at other sites and an enthesitis associated pathology unifies these changes.

Classical pathological studies from the spine, and more recently the sacroiliac joints, have shown prominent inflammatory changes in the bone. Some have assessed the bone lesions from SAPHO and microbes have been recovered, but these are not universal. We have also noted that a lymphocyte infiltrate is not evident at the actual enthesis soft tissue insertion in early enthesitis, but changes are more likely in the underlying bone. Combined with recent histological studies suggest that SpA associated periostitis may be secondary to the diffuse enthesitis associated bone changes.

**Imaging of enthesitis**

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Enthesitis, the inflammation at sites of a tendon, fascia, ligament, or joint capsule attachment to bone, is a distinctive pathological feature of spondyloarthropathy. Peripheral extra-articular enthesitis is a clinical hallmark of spondyloarthropathy and may be seen in all forms, including the undifferentiated ones.

The imaging methods useful in studying peripheral enthesitis include plain film radiography, low kilovolt radiography, bone scintigraphy, diagnostic ultrasonography (US) and magnetic resonance imaging (MRI). Plain film radiography shows a combination of erosion and bone proliferation but only in the more advanced phases. In general, the bone proliferative changes of enthesitis of the bone are not universal. We have also noted that a lymphocyte infiltrate is not evident at the actual enthesis soft tissue insertion in early enthesitis, but changes are more likely in the underlying bone. Combined with recent histological studies suggest that SpA associated periostitis may be secondary to the diffuse enthesitis associated bone changes.

**Abstracts**

PREMALIGNANT BENIGN PAPILLOMATOUS MAMMARY NEUROFIBROMA  
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The occurrence of mammalian benign papillomatous neurofibroma as a premalignant condition is confirmed. The histological description of premalignant benign papillomatous neurofibroma of the breast is presented. The presented report showed that premalignant benign papillomatous neurofibroma of the breast occurs in women of all ages. The histological description of premalignant benign papillomatous neurofibroma of the breast is presented.

**Is there a unifying concept for the spondyloarthropathies?**

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Clinical, epidemiological, genetic, and animal data suggest that exposure to bacteria is crucial to the pathogenesis of the spondyloarthropathies (SpA). In reactive arthritis (ReA) this means in vivo persistence of ReA associated bacteria in the bone, in inflammatory bowel disease (IBD) breakage of tolerance to gut bacteria because of a damaged gut mucosa and, possibly, in psoriatic arthropathy a chronic stimulation of the immune system by bacteria such as streptococci, which might be responsible for both the skin and the joint manifestations. Primary ankylosing spondylitis (AS) and undifferentiated SpA are, by definition, not associated with any of these diseases, though they are the most common SpA subsets. However, in more advanced stages of ReA, patients with asymptomatic manifestation of IBD or an asymptomatic infection with one of the ReA associated bacteria might be present. Some of the SpA manifestations, such as peripheral arthritis, are only moderately associated with HLA-B27. However, others, such as sacroilitis/spondylitis, enthesitis, and uveitis, are strongly associated with HLA-B27.

There is now growing evidence that the main target is the enthesis, which might be primarily affected also in peripheral joints and the spine. Thus in B27+ patients the primary target might be the synovium while in B27+ patients it might be the enthesis. This hypothesis has to be proved in future studies. Evidence from studies in ReA and IBD associated arthritis suggests that only a limited number of bacterial antigens are seen by CD8 T cells, possibly presented by HLA-B27. Although some of the immunodominant antigens have been identified, no common bacterial antigen shared by different bacteria has been identified. It is clear that at least in ReA and IBD the peripheral arthritis is caused by the presence of bacteria. This is less clear for other manifestations, such as sacroilitis/spondylitis, enthesitis, and uveitis. No bacterial antigens have been detected in these structures and it seems unlikely that bacteria persist in such different structures. For these manifestations it is more likely that exposure to bacteria induces an autoimmune response to a crossreacting autoantigen. No such antigen has been identified to date. One interesting candidate antigen is proteoglycan, which is present in all structures, possibly affected in the course of disease such as entheses, uvea, and aorta. The G1 domain is immunodominant in animal models of AS. Based on current evidence it is suggested that bacterial antigens shared by different bacterial species induce an autoimmune response in HLA-B27+ patients and that the autoantigen is located in enthesis, cartilage, and/or bone. In HLA-B27+ patients the constant presence of bacterial antigens might be sufficient to explain the inflammation.

**Proteoglycan aggrecan in enthesitis: facts and concept**

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The inflammation of entheses attached to the axial and sacroiliac joints is a distinctive feature in spondyloarthropathies (SpA), typically seen in ankylosing spondylitis (AS). In SpA, the infiltration of proinflammatory lymphocytes and monocytes/macrophages in entheses and disc end plate indicates the involvement of immune and cytokine insults. Mice with H-2d genotype are susceptible to development of arthritis and spondylitis in response to repeated immunisation with proteoglycan aggrecan (PG). In contrast, the spondylitis is not seen in susceptible animal strains challenged with either type II collagen or link protein. The proteoglycan induced spondylitis is characterised by initial early mononuclear cell infiltration into the outer margins of the annulus in the enthesal insertions on the vertebrae, associated with angiogenesis and a progressive discitis, which lead to destruction of the nucleus and end plates as seen in human advanced AS. Injection of the aggrecan G1 domain (G1) alone also can induce the same spondyloarthritis, indicating that the pathogenic epitope(s) that cause spondylitis may located in the G1 domain. In humans an increase of immunity to proteoglycan aggrecan and the G1 domain is seen in the patients with AS. This supports the concept that the aggrecan G1 domain may serve as an autoantigen, which may play a part in initiating and sustaining the inflammation in spinal entheses leading to syndesmophyte formation.

Although little is known about the biochemical nature of the entheses, recent evidence shows that it contains molecules typically seen in cartilage, such as collagen type II and large proteoglycan aggrecan including the G1 domain. Because SpA is strongly associated with HLA-B27 and gut or unigénital pathology, immunity to an insult agent in gut or unigénital tract may break the immune tolerance to PG or G1 in an SpA susceptible (HLA-B27) population by molecular mimicry mechanisms. We can isolate G1-specific autoreactive T cell lines from patients with rheumatoid arthritis as well as from healthy subjects. These T cells can produce arthritis when they home in to knee joints in immunodeficient SCID mice. These PG or G1-specific auto-aggressive T cells may therefore expand and home in to PG-rich tissues (entheses, articular cartilage, spinal disc, etc), initiating inflammatory reactions, including mononuclear cell (monocytes and lymphocytes) infiltration and cytokine (interleukin 1α, interferon γ, transforming growth factor β, etc) secretion. G1-specific T cells may also attack extra-articular tissues, such as anterior uveal tract, heart, aorta, and brain, where aggrecan G1 and G1-related epitopes (versican G1 domain) are found and linked to arthritis.

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