The first objective of the rheumatologist will be to keep the natural skills: diagnosis and management of diseases and of painful and functional disorders of the musculo-skeletal apparatus. The core curriculum of UEMS for Continuing Medical Education and Professional Development could be a good objective: a thorough theoretical knowledge must be maintained of anatomy, biochemistry, physiology, biomechanics, pathophysiology of pain, and cellular and molecular biology and genetics relevant to the rheumatic diseases. "The general attitude should be maintaining clinical skills by regular contact with people with musculo-skeletal conditions, the indications and interpretation of imaging technique such as conventional X-rays, CT scans, ultrasonography and radioisotopes techniques in the diagnosis, assessment and monitoring of the rheumatic diseases":

- Degenerative disease of the joint and spine.

- Collagen vascular diseases (which must be considered as "rheumatology with systemic disorders" and not "internal diseases with rheumatological symptoms").

- Bone disease and calcium metabolism disorders, tumours.

- Inflammatory and metabolic arthritis.

- Soft tissues (tendons and muscle) and nervous disorders.

- Spine diseases and particularly low-back pain.

In that sense the rheumatologist must keep its place of orchestra director, to maintain close co-operation with profession allied in the management of rheumatic disorders.

Through these goals, rheumatologist should stay competent to indicate, interpretate and manage explorations: imaging, to avoid the gap between radiologists and rheumatologists and let open the dialogue between practitioners, but also bone measurement techniques. We would emphasise the necessary use of ultrasound in clinical practice. This imaging technique has to become a clinical tool, with the economic difficulties of the cost of the equipment.

Rheumatologist must stay performant in technics such as needle aspiration, bone or synovial biopsy, joint injection...at the least to be able to discuss indications.

In therapy, new biological development such as immunotherapy or molecular biology will be a major field of interest to avoid gap between clinical practice and biological tools, without neglecting more classical therapies such as rehabilitation.

The irruption of biomaterials and the development of percutaneous injections will change our way of therapy in a next future, sooner as we could expect, if we take into account the speed of development of biomaterial fabrication in industry project: artificial cartilage, bone replacement...

The rapid growth and ageing of the population will emphasise the necessary development of chronic disease coping and prevention and the sensibilisation of economic and political decisions (which is one of the goal of Joint and Bone decade. This means that the rheumatologist has to develop the maintaining quality of life, and not only the function. In that sense, development psychological interventions, prevention of pain and depression would be of benefit for rheumatologist. We have to prove that illness considered as benign are important for ageing population in terms of quality of life, but also economic expenses and prevention of severe complications.

Health economics will be a real problem. What is the real benefit of medical or surgical interventions: economic benefit of modifying drugs such as methotrexate in RA, bisphosphonate in osteoporosis, slow acting drug in osteoarthritis? The answer to these questions are crucial. The practical financial costs of treatment vis a vis the cost of surgical interventions are critical to understanding the necessities of prevention and treatment.

Epidemiologic and economic studies are important to develop in the next future.

Patients information will be another challenge in term of access to care: what will be the consequences of the non access to appropriate in term of medical responsibility? What are the good answers to people when we cannot give them appropriate care for economic reasons? What are the controls in term of experimental therapy or surgery or new medical developments? All these questions have to be compared to the growing knowledge of the patients with the quantity of informations obtained through the medias and internet, the best but also the worst.

Biologics in practice – Saturday 16 June, 10.00-11.45/Congress Hall

SP0097 MACROMOLECULES WITH ROLES IN CARTILAGE AND BONE HOMEOSTASIS

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The extracellular matrix of skeletal tissues contains molecules with key roles in tissue homeostasis. Particularly important are those that are part of the collagen network and maintains its integrity. Examples are members of the thrombospondin family, in cartilage particularly COMP, and members of the family of extracellular leucine rich repeat (LRR) proteins.

These proteins have key roles in the assembly of the collagen II fibrillar network and have the capacity to crosslink neighbouring fibrils by containing at least two functional domains, one binding to one fibril and the other binding to another fibril. An example is decorin showing an interaction site of the core proteins on one hand, while another being the dermatan sulfate side chain. Similarly fibromodulin contains structures with potential for interactions with different collagen fibrillar structures.

Current data indicate that an early event in osteoarthritis is the fragmentation of the binding proteins to separate the functional domains. This will result in an inability of the collagen network to prevent swelling of the tissue and maintain functionality.

The alterations elicit a response where molecules that have roles in catalysing collagen fibril assembly are produced. Such regulating proteins include COMP. This modular protein contains five identical subunits held together close to their C-terminus and having a C-terminal end globular domain that promotes tight binding to collagen. COMP appears to bring together the collagen monomers and catalyse the formation of early fibrils in a chaperon like mode. It is also present, apparently crosslinking completed fibrils by simultaneously binding several collagen IX molecules that are covalently bound on the surface of the collagen II/XI fibres.

Other matrix constituents like PRELP and chondroadherin bind to cell surface molecules, apparently involved in signalling to the cells. These two molecules also bind to collagens I and II.

Cell binding proteins have key roles in bone turnover. Examples are osteopontin, a protein binding the $\alpha\beta3$ as well as the $\alpha4\beta1$ integrin. The protein is produced by the osteoblast and binds to the bone mineralized surface. It then appears to have a central role in recruiting and promoting the development of osteoclast precursors to a fully functional cell. Osteopontin is

also expressed by a number of cells in the inflammatory system. It is likely that release of osteopontin in joint destruction will influence the inflammatory response.

Other bone proteins with a capacity to bind $\alpha v \beta 3$ include BSP and osteoadherin. Their role in bone turnover and interactions with other tissues remains to be elucidated, but available data indicate primary functions in bone formation.

SP0099 SYNOVIAL FIBROBLASTS DEGRADING CARTILAGE AND BONE

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The progressive destruction of cartilage and bone is one of the most characteristic features of rheumatoid arthritis (RA). It results from the concerted action of different cell types such as T cells, fibroblasts and macrophages that through direct contact as well as the release of cytokines form a cellular network in the inflamed synovium. Research of the last decade has provided evidence that RA synovial fibroblasts (RA-SF) contribute significantly to disease and play a major role in both initiating and driving the destructive process. It has been understood that intrinsic cellular *activation*, alterations in *apoptosis* and the *attachment* to cartilage and bone are critical prerequisites for the degradation of extracellular matrix.

The degradation of articular cartilage by activated RA-SF has been investigated in different *in vitro* and animal models. Among the latter, the SCID mouse model of RA has been used intensively to clarify the specific role of synovial fibroblasts in rheumatoid cartilage destruction. In this model, RA-SF are co-implanted with normal articular cartilage into severe combined immunodeficient (SCID) mice. As these mice do not reject the implants, the model allows studying the degradation of articular cartilage by RA-SF in the absence of human inflammatory cells. From the SCID mouse model it has been learnt that RA-SF maintain their activated phenotype in the absence of continuous inflammatory stimulation and progressively degrade cartilaginous matrix. As demonstrated by gene transfer experiments, modulation of intracellular signalling pathways such as the Ras-Raf-MAPK pathway, the NF-kappa B transcription factor and the p53 tumour suppressor gene alter the aggressive behaviour of RA-SF in the SCID mouse model of RA.

However, research has also demonstrated clearly that proinflammatory cytokines as produced by various cells in the rheumatoid synovium further enhance the aggressive potential of RA-SF. Apart from TNF alpha, IL-1, and IL-1 dependent pathways appear to play a central role.

It is now well established that RA-SF destroy the articular cartilage directly through the release of matrix degrading enzyme such as matrix metalloproteinases (MMPs), cathepsins and serine proteases. While several of these enzymes have been identified in the rheumatoid synovium and demonstrated to contribute to cartilage degradation, the specific role of individual members of these families is still poorly understood. In addition, despite a clear understanding of general mechanisms that regulate the

expression of MMPs and cathepsins, specific pathways by which these enzymes are upregulated differentially in the course of disease need clarification. Current efforts focus on the modulation of enzymes that apart from degrading extracellular matrix directly, play a major role in activating other matrix degrading enzymes. Membrane-type MMPs (MT-MMPs) as well as the Plasmin system appear promising candidates for such approaches.

So far, fibroblasts have been associated with bone resorption mainly by indirect mechanisms such as the release of factors that enhance osteoclast activity and facilitate the differentiation of macrophages into osteoclast-like cells. Thus, fibroblasts of the rheumatoid synovium constitute a major source of the osteoclast differentiating factor (ODF) that appears to play a central role in the differentiation and activation of osteoclasts. However, recent data indicate that specific populations of activated fibroblasts such as from the synovial like interface membrane around loose joint prostheses are also capable of resorbing bone *in vivo* without the help of osteoclasts. Upon stimulation, such fibroblasts release large amounts of acidic components that may account for their ability to decalcify bone prior to its degradation. Using RT-PCR, *in situ* hybridization and immunotransmission electron microscopy, we have been able to demonstrate that these cells express a vacuolar type ATPase (v-ATPase) on their cell surface that has been implicated in the H⁺ secretion by different cell types. It is concluded that subtypes of activated fibroblasts may not only enhance but also actively contribute to the bone resorption. The question of whether this applies also to RA-SF or is associated with different ways of cellular activation needs to be determined.

Review session N° 4: The kidney in systemic R. D. – Saturday 16 June, 10.00-11.45/ Forum Hall

SP0100 PATHOLOGIC CLASSIFICATION OF LUPUS NEPHRITIS

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A myriad of autoantibodies, particularly those against dsDNA, have been found to be involved in the production of a large heterogeneous set of immune complexes whose deposition in various organs, especially kidneys, appears to play a major role in triggering tissue lesions and an inflammatory response in systemic lupus erythematosus (SLE). In our series of 379 kidney biopsy and autopsy samples from SLE patients, immune deposits were demonstrated by traditional immunofluorescence in the glomeruli (99.0%) and characteristically also in the tubulo-interstitial compartment (57.4%) and extraglomerular vessels (64.4%).

Other pathogenetic immune mechanisms, e.g. anti-phospholipid antibodies and anti-neutrophil cytoplasmic antibodies, appear to be additionally involved, especially in triggering thrombosis and/or necrotizing glomerular lesions, respectively. Furthermore, nonimmune mechanisms, hyperperfusion and hyperfiltration associated with arterial hypertension and severe proteinuria as well as hyperlipidemia, play a more or less significant role in the progression of lupus renal disease. Several