From the Netherlands

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Rheumatology should take care not to be seen as a specialty limited to the care of patients with rheumatoid arthritis. Rheumatologists trained in internal medicine may provide optimal quality in the investigation and differential diagnosis of patients who present with signs and symptoms of the musculoskeletal system. Rheumatology is considered to be a part of internal medicine. Through education in clinical research, epidemiology, and clinical immunology the rheumatologist may function as the primary advisor in the first line of medical care for the treatment of pain syndromes or degenerative disorders and supervise the management of patients with systemic inflammatory diseases referred to the department of internal medicine. Research activities in the Dutch rheumatology community may reflect this view on the position of rheumatology in medicine. Projects were started on pain syndromes, osteoarthritis, osteoporosis, the efficacy of joint replacement, systemic vasculitis syndromes, and several other diseases.

The largest amount of research is directed, however, at the different aspects of rheumatoid arthritis. Most activities in this field are centred around the six divisions of rheumatology in university hospitals. In the next few years contributions can also be expected from a new research group on the psychosocial aspects of rheumatic diseases formed at the Technical University of Twente and headed by Hans Rasker.

Also new in Dutch rheumatology are groups of rheumatologists who collaborate in clinical research. These groups combine their efforts to find the optimum approach to the treatment of early arthritis with established drugs or combinations of drugs, study the natural history of chronic arthritis, and work on trials for new treatment modalities. This dispatch will focus on some recent research contributions to rheumatoid arthritis made by Dutch rheumatologists.

Res et al reported the presence of T cell reactivity against heat shock proteins in patients with arthritis and healthy control subjects. This work was stimulated by the observation that this T cell reactivity plays an essential part in experimental models of autoimmune disease. In reactive arthritis there is evidence for a direct stimulation of joint T cells by antigens of the organisms causing the infection which precedes the joint inflammation. The individual antigens of the triggering bacteria still have to be identified but the heat shock proteins may be of importance as these are the molecules recognised by synovial T cells in reactive arthritis. In rheumatoid arthritis T cells recognising heat shock proteins can also be found in the joint. The conclusions of the studies of Res et al, however, were that there is no indication for a specific part played by heat shock proteins in the pathogenesis of rheumatoid arthritis.

Despite intense research the (auto)antigens that incite synovial T cells are unknown. A recent study has raised new hopes for this field by showing reactivity of interleukin 2 responsive T cells in DR4 positive patients with rheumatoid arthritis against synovial fluid antigens.

Based on the assumption that the recognition of a limited number of autoantigens by T cells leads to an oligoclonal T cell response van Laar et al have addressed the issue of whether synovial T cell oligoclonality occurs in rheumatoid arthritis. They showed that expansion of in vivo activated T cells from synovial tissue yielded dominant T cell receptor β chain rearrangements as detected by Southern blot analysis, whereas their study on fresh, non-expanded, isolated synovial T cells pointed to a lack of oligoclonality. Further studies using the polymerase chain reaction to assess V region usage by synovial T cells also pointed to polyclonality.

van de Laar studied the part played by food allergy in rheumatoid arthritis. Based on the hypothesis that food intolerance can induce arthritis activity he conducted a double-blind clinical trial of allergen free feeding and a feeding that contained milk allergens and azo dyes in patients with rheumatoid arthritis. He reported no difference to the prejudice of these allergens but there was a subgroup of patients who reacted favourably to allergen restriction.

The speed of the clinical reaction, the high IgE levels, and the activated mast cells pointed towards an immediate immune reaction as the link between allergen exposure and arthritis activity.

Disease activity and outcome in rheumatoid arthritis was studied by van der Heyde et al. They tried to define a measure for disease activity and validated two methods for outcome variables. Subsequently they applied these outcome and process parameters in a prospective
follow up study of patients with recent onset rheumatoid arthritis. The disease activity score developed included the variables Ritchie articular index, number of swollen joints, erythrocyte sedimentation rate, and general health measured on a visual analogue scale. Outcome measures for radiographic progression and physical disability could be validated in a double blind controlled trial comparing hydroxychloroquine and sulphasalazine. Subsequently the validated outcome measures were used to compare the validity of disease activity measures in a prospective follow up study of patients with early rheumatoid arthritis. Most single disease activity measures correlated poorly with the outcome measures and showed limited discriminative power. The previously developed disease activity score was most valid in measuring disease activity.

Two groups of rheumatologists studied immunosuppressive drugs in rheumatoid arthritis. van Rijthoven et al studied cyclosporine and Jeurissen et al compared azathioprine with methotrexate. Cyclosporine at high (10 mg/kg) and low (2-5 mg/kg) doses induced a reduction of clinical activity parameters but the erythrocyte sedimentation rate did not improve. These workers also found serious toxic effects of cyclosporine at higher doses. It was concluded that only patients with normal renal function should be selected for cyclosporine treatment. The observed therapeutic effects make it worthwhile to investigate the value of cyclosporine in the treatment of patients who are in an early stage of rheumatoid arthritis. Jeurissen et al published the results of a double blind randomised 48 week trial comparing azathioprine (100–150 mg daily) with methotrexate (7-5–15 mg weekly). The main conclusions were: methotrexate has a superior clinical effect and the effect starts earlier compared with azathioprine in patients with rheumatoid arthritis refractory to treatment with gold or D-penicillamine; methotrexate causes less adverse reactions compared with azathioprine; patients with rheumatoid arthritis who begin treatment with methotrexate show significantly less radiological progression than patients who begin treatment with azathioprine. It was concluded that methotrexate is preferable to azathioprine to treat patients with rheumatoid arthritis because of the superior clinical effects.

Another Dutch contribution in the field of clinical research on rheumatoid arthritis is the work of Heurkens et al on rheumatoid vasculitis. They reported humoral immune mechanisms in the pathogenesis of rheumatoid vasculitis with special emphasis on the role of antibodies to endothelial cells. It was also reported that patients with severe systemic vasculitis could be managed with the combination of prednisone and azathioprine. Based on the results of a controlled trial comparing prednisone/azathioprine with the continuation of conventional disease modifying drugs in patients with cutaneous forms of rheumatoid vasculitis it was concluded that cutaneous vasculitis in rheumatoid arthritis should not be treated with immunosuppressive drugs specifically directed at the vasculitic process.

The work discussed here may be seen as a representative selection of the results of Dutch rheumatology research published in 1991. All the studies mentioned served as a thesis which had to be defended in public to obtain an MD or PhD degree. It is encouraging to observe that a growing number of rheumatologists in training take up this extra task and have the opportunity of finishing such a work. Most of these studies were financed by the Dutch League Against Rheumatism.