Introduction. Among the systemic, primarily non-join diseases, arthritis is frequently found in patients diagnosed with psoriasis. Psoriatic arthritis (PSA) is characterized by radiographic evidence of periarticular bone erosions and, in some cases, joint destruction. Importantly, PSA is accompanied by pitting and deformities of nails and hyperkeratosis of the affected fingers. In contrast to the frequent association of seropositive rheumatoid arthritis with HLA-DR4, or ankylosing spondylitis with HLA-B27, the HLA association of PSA is less distinct and shows overall tendency towards an association with HLA class I antigens. Here we describe a novel, spontaneously developing toe inflammation resembling human PSA in human MHC class II transgenic mice lacking their own, endogenous mouse MHC class II.

Material and method. Five different MHC-transgenic lines, lacking their own endogenous MHC class II molecules (H2-Ab0, -DR3.Ab0, -DQ6.Ab0, -DQ8.Ab0 and -DR4.Ab0). Genomic DNA of all mice was screened for the presence of their own endogenous MHC class II molecules (H2-Ab0) were generated and used in these experiments (HLA-DR2.Ab0, -DR3.Ab0, -DQ6.Ab0, -DQ8.Ab0 and -DR4.Ab0). Genomic DNA of all mice was screened for the presence of the human MHC class II transgene and for the presence of neomycin resistance gene (used to disrupt mouse H2-IA locus) using PCR. Cell surface expression of human MHC class II antigens was confirmed by flow cytometry using leukocytes from peripheral blood. Mice were inspected for the development of disease twice a week for a period of 8-14 months. Mice were considered “arthritis” when they developed a swollen digit or exhibited skin-thickening with alopecia and nail deformities on at least one toe. Mice were sacrificed at various time points up to 14 months of age. Paws and other skeletal tissues including spine, hip and sacroiliac joints, sterno-costal junctions, and skin of different areas, were fixed in 10% buffered formalin, skeletal tissues decalcified, embedded in paraffin, sectioned and stained with hematoxylin and eosin.

Results. Transgenic mice, expressing HLA class II showed normal healthy phenotype during the first six months of age (Fig. 1A). After six months, some animals of four HLA-transgenic lines began to develop toe inflammation spontaneously, with the appearance of “sausage-like” fingers (Fig. 1B). HLA-DR4.Ab0, -DR2.Ab0, -DQ6.Ab0 and -DQ8.Ab0, but not HLA-DR3.Ab0, transgenic mice developed progressive inflammatory changes in the toes (i.e. progressive bone resorption and remodeling (Fig. 2B), hyperkeratosis, alopecia, loss of nails, shortening and thickening of the distal phalanges of all toes) resemble those described for human psoriatic arthritis. The massive bone resorption and granulomatous tissue accumulation resulted in significant thickening and some shortening of the distal portion of the toe. Thickening of the epidermis due to gradually increasing hyperkeratosis and parakeratosis was also observed. This osteo-degenerative disease manifests only at advanced ages (7-12 months) affecting 70-100% of the mice, with female preponderance. None of the serum samples, either from affected or normal mice, contained antibodies against viruses or pathogenic bacteria when tested with a standard antibody panel by Charles River Laboratories.

In order to assess the relative contribution of the HLA transgene to the disease development we compared female mice from the most affected transgenic line (HLA-DR4.Ab0) to the corresponding animals shown on Fig. 1. The defomed distal phalanges of mice at advanced age (B).

Discussion/conclusion. In rodents only few spontaneous joint diseases have been reported, none of which showed any similarities to those found in the aging HLA transgenic mice; and the few rodent models for psoriasis did not describe joint involvement either. Here we describe an inflammatory toe disease with progressive resorption and remodeling of the distal phalangeal bones accompanied by pitting and frequent loss of nails, and hyper- and parakeratosis in the epidermis in mice lacking the expression of their endogenous MHC class II molecules. The clinical appearance of the disease, histopathology and radiographic changes indicate a high resemblance to human PSA. The only common property of the five transgenic lines was the absence of the endogenous class II, and the only difference between the four susceptible and one resistant transgenic lines was the relatively lower HLA transgene expression (associated with lower numbers of CD4+ T cells) in the disease-resistant HLA-DR3.Ab0 line.

This observation suggests that a non-physiological interaction between the human MHC and the mouse T cell receptor through an insufficient signaling mechanism and the low number of CD4+ T cells in susceptible, versus high HLA expression (and higher CD4+ cell ratio) in the resistant HLA-DR3.Ab0 line.

Fig. 1. Macroscopic pictures of mouse hind paws in a 6-month-old normal (A) and a 12-month-old affected (B) HLA transgenic mouse. The loss of the nails, the alopecia and the thickening of the distal phalanges were characteristics of mice at advanced age (B).

Fig. 2. Radiographic images of normal (A) and arthritic (B) toes from the corresponding animals shown on Fig. 1. The deformed distal phalanx (B) suggests vigorous bone resorption and remodeling. **Department of Immunology, Mayo Clinic Foundation, Rochester, MN 55905.