ed: non-steroidal anti-inflammatory drugs (NSAIDS) and corticosteroids (CS) are prescribed for most patients, and methotrexate (MTX) is recommended against refractory forms. We describe an ASD patient in whom a prolonged response was obtained with anti-tumor necrosis factor-α (TNF-α) biotherapy, in this case infliximab.

A 28-year-old woman suffering from ASD had taken CS and MTX for 10 years. The osteoarticular involvement consisted of bilateral carpal joint inflammation of the capital bone, without fusion or clear-cut ankylosis, and distal interphalangeal involvement, and was associated with a quasi-constant pseudo-urticarial skin eruption. Episodes of joint inflammation occurred every 2 to 3 years, requiring pulse CS and/or intravenous immunoglobulin injections. The patient is HLA-DR4-negative. Her plasma and intralymphocyte TNFα concentrations were low. During the last attack in 2001, the clinical picture associated debilitating inflammatory polyarthritis of the small- and medium-sized joints, fever (40°C) and aggravation of the pseudo-urticarial eruption on the trunk. Despite several CS pulses and intensification of the MTX dose, no attenuation of the manifestations was obtained.

Infliximab (3 mg/kg) was prescribed (on days 0 and 15, at 6 weeks and every 8 weeks thereafter) in combination with MTX (15 mg/week). The symptoms stabilized during the 2 weeks following the first administration, and one month later all signs had completely regressed except the skin lesions, which disappeared after the addition of dapsone. Forty-five months after starting infliximab, the patient remains totally asymptomatic, with an erythrocyte sedimentation rate of 5 mm/1st h. She continues to receive infliximab every 8 weeks. No dysimmunity or infectious complications have been observed.

TNFα receptors are expressed at the joint cartilage-pannus junction and, pertinently, the intra- articular TNFα concentration is elevated in infantile and adult rheumatoid arthritis (2). Infliximab is a chimeric monoclonal antibody that binds to TNFα with high affinity and thereby neutralizes its biological activity. Etanercept is a TNFα-receptor blocking agent; able to act at several levels, these antibodies block intra-articular receptors, decrease the *in vivo* production of other cytokines, lower the expression of endothelial cell-adhesion molecules, prevent mononuclear cell infiltration of the joints (3), and reduce the serum vascular endothelial growth factor level, which is associated with less angiogenesis (2).

The first reported cases of severe, chronic juvenile arthritis resistant to standard therapies but responding to infliximab appeared in 1997 (4); since then these initial observations have been confirmed (5, 6). Five years ago, publications based on 30 cases argued for the use of biotherapies to treat patients with ASD resistant to conventional treatments (7-10). Infliximab has been the form used most often, at concentration ranging from 3 to 5 mg/kg, infused on days 0 and 15, at 6 weeks, and then every 4-8 weeks. The largest series included only 12 patients who were primarily given etanercept. The main results were rapid efficacy with clear regression of the clinical symptoms in patients with systemic manifestations, normalization of the biologic parameters, and good safety.

However, unlike adults, children with Still's disease showed poor long-term control. The mean treatment duration in reported studies was 12-24 months (7,8). Our patient responded rapidly and completely after the second infliximab infusion associated with MTX, with excellent tolerance. We observed no side effects and no dysimmunity. Addition of dapsone led to the disappearance of skin lesions. Today, 45 months after starting infliximab, her ASD is completely controlled and she has developed no signs of relapse.

Acknowledgments. We thank Janet Jacobson (Scientific Communications) for editorial assistance.

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Late onset of long-lasting fever as a sole complication of treatment with anti-TNFα

Sirs,

Several clinical trials and the experience drawn from the 5-year use of chimeric monoclonal antibody to tumor necrosis factor-α (anti-TNFα) allow the evaluation of its therapeutic value and most of its side effects (1-3). However, long-term clinical use is essential for the complete understanding of the effects of the drug. This letter concerns a patient who, after receiving anti-TNFα (Infliximab-Remicade, Schering-Plough), presented with long-lasting high fever, probably associated with the medication itself.

A 65-year-old woman with a 14-year history of rheumatoid arthritis (RA) had been treated with corticosteroids and methotrexate in the past, which were discontinued because of serious side effects. Exacerbation of RAnecessitated treatment with anti-TNFα. After a negative screening for infections (including PPD-testing, chest x-ray, and screening for common viral infections) she was given two doses of Infliximab (3 mg/kg per dose i.v.), 6 and 3 weeks before admission, without any immediate adverse effect. Twenty-one days after the second infusion, the patient presented with high fever (39.5°–41.5°C) accompanied by daily severe attacks of rigor. No relief of the symptoms was noted after the administration of *per os* antimicrobial agents (amoxycillin for 2 days and then cefaclor for 2 days).

The patient was admitted to hospital for further evaluation. Thorough investigations were negative, ruling out the possibility of tuberculosis (pulmonary and extrapulmonary) or other infection, bacterial or viral. There was also no evidence of any other disease that could present with fever, such as adult's Still disease. The high fever persisted for 13 days and was only partially relieved (by 2-3°C) by antipyrexials. On the 13th day, the fever subsided and 6 days later the patient became and remained afebrile. At present, 5 months after the episode, the patient is well although she is still suffering from RA symptoms.

A thorough consideration of this case, keeping in mind Miller's criteria (4), suggests a possible causal relationship between anti-TNFα and this febrile syndrome, i.e.:

1. The temporal association of events.
2. The lack of any other plausible etiologic explanation.
3. The spontaneous regression of fever.
4. After our failure to find a biologic etiology, we believe that the patient's fever may be attributed to either: i) the "profound control of TNFα in the periphery, which results in an enhancement of brain-derived TNFα and other cytokines" (5), or ii) a delayed hypersensitiv-

ity reaction, expressed only by fever. The patient, due to the episode described above, refused to continue treatment with anti-TNFα.

The hypersensitivity febrile reaction is a well known immediate adverse effect following infusion of anti-TNFα (6). A late-onset febrile reaction (after 14 days) has also been reported but was then associated with additional signs (7). This case is unique in that high and long-lasting fever was the sole manifestation. If evidence that this kind of fever is one of the side effects of treatment with anti-TNFα is confirmed, this should be taken into account in order to avoid a misleading diagnosis of infection, including tuberculosis, in patients receiving the drug.

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Prevalence of diffuse idiopathic skeletal hyperostosis in a female Italian population

Sirs,

Diffuse Idiopathic Skeletal Hyperostosis (DISH) is a skeletal disease characterised by calcification of the anterolateral aspect of the vertebral longitudinal ligament, with a wide spectrum of prevalence rates reported (1-7). In a previous report we showed that the prevalence itself might be of great interest (8). By serendipity we have seen female patients with DISH at our general outpatient clinic for rheumatic complaints. These random observations, as well as the absence of data in our female population, led us to assess the prevalence rate of DISH in an unselected sample representative of the general female population. The study formed a part of an epidemiological survey on rheumatic complaints in the population of the Neapolitan area (9).

165 Caucasian subjects were chosen as representative of the general female population. Eighty of them were selected from the employees of the National Agency for Electricity, and 85 from the members of a parish association. Among these subjects, 93 (mean age 57.9 years, range 46-79) agreed to undergo radiographs of the dorsal and lumbar spine in the lateral view (the overall participation rate was 56.4%) and were then enrolled for the evaluation of the prevalence of DISH. The patients who declined to participate in the study did not differ from the recruited subjects in terms of age, self-reported height and weight, and smoking habits. All participating patients gave their informed consent. The study protocol was approved by the local ethical committee.

Diagnosis of DISH was based on the modified Resnick's criteria for epidemiological studies (10). All radiographs were examined independently by three of the authors and contrasting results were resolved after group discussion.

DISH was found in 14 cases (mean age 65.6 yrs., range 54-79), with an overall prevalence rate of 15.1%. The rate increased with age, rising from 7.5% in the group of patients aged between 50-59 to 40% in the group of patients >70 years of age. No cases of DISH were seen in the group of patients aged below 49 yrs (Table I).

Table I. Prevalence rates of DISH in a female population, stratified by age.

Age (yrs)	Cases	No. of subjects	Prevalence (%)
40-49	0	20	0
50-59	3	40	7.5
60-69	5	18	27.8
> 70	6	15	40.0
Total	14	93	15.1

To date few epidemiological studies on the general female population have been performed. A Finnish study showed a prevalence of 2.6% in women with DISH, and the rates increased with age up to 6.7% in women older than 70 years (2). More recently, a survey of DISH in the Hungarian population was carried out and showed a prevalence rate in the female population of 12.8%, which is in line with our results, this rate increasing with age to 26% at age >75 (3). The prevalence of DISH among the women in our population was much higher than in Finland, with an age-adjusted rate ratio of 5.8 and a 95% confidence interval ranging from 3.4 to 9.8.

The paucity of epidemiological data on DISH could be explained by the fact that the diagnosis is exclusively based on radiographs and this could present a potential selection bias due to the low compliance of asymptomatic subjects in presenting for x-ray examinations.

In the present study we found a very high prevalence of DISH in an unselected female sample, the highest reported so far. The diagnostic criteria used in our study were a modification of the 1976 Resnick's criteria which are currently used for epidemiologic purposes (6-7, 10). Despite possible differences with the Finnish and Hungarian studies, the data obtained confirm a high DISH prevalence in our area. The use of age-adjustment with 95% C.I. intervals demonstrates that this high prevalence rate is due neither to age-confounding nor sample variability. Our data confirm the differences among prevalence rates in different countries, differences that could be explained by genetic and/or environmental factors.

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