revealed pancytopenia [white blood cell count (WBC) 2.3 \times 10^3/mm^3, haemoglobin (Hb) 6.8 g/dl, haematocrit (Hct) 17.5, platelets 37 000/mm^3]. Prior to infliximab therapy her WBC was 8.0 \times 10^3/mm^3, Hb 11 g/dl, Hct 35 and platelet count 200 000/mm^3. She developed fever up to 102°F (38.9°C) and abdominal pain over the next 24 h, and ascitis was present. Peritoneal fluid was cloudy, with 322 red blood cells/mm^3, 4950 white blood cells/mm^3 and 96% neutrophils. Fluid cultures later grew Candida albicans. According to the patient’s wishes, only blood transfusions, antibiotics and supportive care were given, and she expired the next day. No autopsy was done.

Tumour necrosis factor (TNF) inhibitors are being investigated in the treatment of a variety of rheumatic disorders, including scleroderma [2, 3]. Early results with etanercept indicate marginal clinical improvement, especially of skin involvement. Due to the severity of the patient’s clinical picture, infliximab therapy was given. This was followed by pancytopenia and fungal infection. She was not receiving any other therapy that may have induced her haematological complication, which led us to implicate infliximab as an important contributor. This case should be added to the cases of existent pancytopenia already reported in association with anti-TNF-\alpha therapy [4, 5].

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Reply

We read with interest this letter from Menon et al. [1] reporting another case of pancytopenia following infliximab infusion, but this case was a bit different from ours. It concerned a patient with scleroderma (our patient was affected by rheumatoid arthritis), and the pancytopenia was strictly linked to infliximab treatment, whereas the bone marrow toxicity occurring after the infliximab infusion in our patient may have been partially due to the fact that he was being treated with methotrexate and allopurinol and had been receiving leflunomide until a few weeks before the infliximab treatment. As it was not clear which drug(s) or combination of drugs was responsible for the severe adverse reaction, we stressed the importance of careful patient monitoring when switching from one anti-rheumatic drug to another, especially in the case of the new and powerful immunosuppressive agents. It is interesting to note that both patients had impaired renal function and, although we cannot know whether this condition may be relevant in such cases, in our opinion it must clearly be kept in mind when starting infliximab therapy. At least one lesson that can be learned from these two cases of pancytopenia following infliximab infusion is that such powerful biological agents should be used with caution in rheumatic patients debilitated by other conditions and years of drug therapy.

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Fate of inflammatory neutrophils within the joint

Sir. We agree with Ottonello et al. [1] that the fate of neutrophils at inflammatory sites, especially within the rheumatoid joint, is an important issue which needs to be clarified. Their study, recently reported in this journal, is one of a very few which examines the influence of inflammatory synovial fluid on apoptosis in neutrophils [1, 2]. In their studies, joint fluid from eight of 11 RA patients produced inhibition of spontaneous and stimulated apoptosis in cultured neutrophils. Evidence is presented that this effect relates to adenosine levels within the joint fluids. The authors suggest that their findings support the view that, within the inflamed rheumatoid joint, synovial fluid factors (especially adenosine) tend to inhibit apoptosis and prolong neutrophil lifespan, thus maintaining the inflammatory response.

Their results appear to conflict with some of our own findings [2] in which we reported that synovial fluids from a variety of arthritic patients generally promoted neutrophil apoptosis, a finding at odds with
our own initial hypothesis. We demonstrated a clear dose–response effect using serial dilutions of joint fluid. We pointed out, however, the variability of individual responses between patient samples; indeed some synovial fluid samples caused inhibition or no effect rather than accelerated apoptosis. We studied more than 30 joint fluids and compared effects on autologous and heterologous peripheral blood as well as synovial fluid neutrophils. One important finding from our data, in keeping with other published work [3], was that rates of spontaneous apoptosis found in synovial fluid neutrophils were approximately double those of peripheral blood neutrophils. We interpret this as evidence to support the view that neutrophils within the inflamed joint cavity have been previously exposed to apoptosis-promoting influences, presumably contained in synovial fluid. (Others have shown that, following in vivo treatment of subjects with apoptosis-inhibiting cytokines, blood neutrophil cultures in vitro show retarded apoptosis [4].) Ottonello et al. provide no data in which quantitative comparisons are made of joint fluid and peripheral blood neutrophil responses to synovial fluid.

Our findings on the lack of correlation between cytokine levels and the effect of synovial fluid on neutrophil apoptosis are confirmed in the study of Ottonello et al. The differences between our results and those of Ottonello et al. may well be methodological in origin, reflecting differences in patient selection, drug treatment, sample preparation or neutrophil separation. Equally, they may reflect the variable capacity of synovial fluids to influence neutrophil cell death. This should not be surprising because, although the very fact that joint fluid can be withdrawn indicates inflammation, the process in a single joint may be moving towards either resolution or persistence. One would expect accelerated neutrophil apoptosis in resolving fluids and inhibition in persistently active fluids, given equally efficient macrophage clearance mechanisms. Alternatively, if one accepts that resolution of the neutrophil phase of inflammatory arthritis is mainly due to loss of cellular recruitment, then what happens to the neutrophils already in the joint? Death by necrosis (which ought to cause persistence of inflammation) or clearance through lymphatic channels (for which there is very little evidence) do not offer convincing explanations. We favour the view that rates of apoptosis in inflammatory neutrophils are being continually modulated by death and survival signals in the inflammatory milieu [3]. Clearly, a great deal more work remains to be done to clarify the role of neutrophil apoptosis in inflammatory arthritis.

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Reply

We fully agree with the remarks of Dr Bell and colleagues about the role of neutrophil apoptosis in the persistence and resolution of the inflammatory reaction. In particular, we concur with the concept of neutrophil apoptosis at sites of inflammation as a dynamic process modulated by opposite signals detectable in synovial fluids, either pro-apoptotic or anti-apoptotic [1–3]. Thus, it is conceivable that the differences observed between our studies [4, 5] may well reflect differences in the activity and/or phase of the disease and possibly the individual genetic pattern.

The fate of neutrophils at sites in the inflamed joint is also modulated by pro- and anti-apoptotic influences during the phase of cell recruitment, i.e. β2-integrin and selectin cross-linking during endothelial transmigration, and chemokine stimulation [3, 6, 7]. Thus, comparisons between the rates of apoptosis of neutrophils from the peripheral blood and synovial fluid may also reflect these factors, as well as the different age of circulating vs migrated cells. Although we did not provide data about this issue in our study, our observations are strengthened by the strict inverse correlation between the anti-apoptotic activity of synovial fluid and the number of neutrophils with morphological features of apoptosis in the same fluid.

Our data are in agreement with reports showing that biological fluids from pathologies characterized by neutrophilic inflammation have neutrophil anti-apoptotic properties. However, in order to clarify the points mentioned above there is a need for thorough investigation of the issue of neutrophil apoptosis in the resolution or perpetuation of the inflammatory response and the question of what local factors might influence these mechanisms.