with 24 hemophilia B patients diagnosed in his department at a time prior to the availability of clotting factor concentrates.[1] Quick's suggestion has been supported by some more recent data. In a preliminary Canadian report, adult severe hemophilia B patients were found to have had 35% fewer bleeds than severe hemophilia A patients,[2] while a second Canadian study, on virtually the whole of the Canadian hemophilia population, reported that significantly more severe hemophilia A patients used prophylaxis (69%) compared with severe hemophilia B patients (32%). The effect was most pronounced in those under 2 years of age but was noted at every age group, including those over the age of 50.[3] A higher bleed frequency for hemophilia A and subsequently hemophilia severity score was also observed by Schulman and colleagues in Sweden, but the number of severe patients in the derivation cohort was relatively small at 43 individuals.[4]

The study by Tagariello et al in this issue describes a 3-fold higher frequency of joint arthroplasty in patients with hemophilia A compared with hemophilia B of the same severity, defined as a coagulation factor level of < 1 U/dL. This difference was not due to confounders such as age, HIV or hepatitis C infections, or the presence of an inhibitor.[5] The data reported were retrospective but covered the whole of the Italian hemophilic population, a major strength of the study. The authors also performed a systematic review of published hemophilia arthroplasty series and found that in the 7 other series, 147 (91.3%) of the 161 patients with hemophilia undergoing joint arthroplasty had hemophilia A. Although these other series did not report the total number of patients registered in their centers, this proportion is significantly higher than expected from the proportion of hemophilia A patients in the large comprehensive registries (84% in Canada, the United Kingdom, and Italy).[5]

A potential criticism of this study is that joint arthroplasty is an end-stage event and a surrogate of severity. The frequency of bleeds would have been a better variable to compare in the 2 hemophilias, but this information was not available. Heterogeneity in the treatment of bleeds or referral for arthroplasty could have influenced the results, but it is not obvious why these would have varied by hemophilia type. Furthermore, it is not known if the lack of FVIII (compared with IX) results in more bleeds, if the bleeds respond less well to treatment, or if the bleeds are more severe or more destructive.

An important issue that could potentially explain the results is that severe hemophilia A and B are currently defined on the basis of a clotting factor level of < 1 U/dL[6] and not on the phenotype. The accuracy of the commonly used clotting assays at these low levels has been questioned.[7] It is also well recognized that patients with "severe" disease with clotting factors of < 1 U/dL show heterogeneity in the phenotype in terms of bleed frequency as well as in their thrombin-generating capacity.[8] It is likely that the group of < 1 U/dL patients contains individuals with truly no VIII/IX activity, as well as some with low but detectable activity. If the proportion of these was different for the 2 hemophilias, it could have influenced the results. Tagariello et al tried to address this issue by comparing the patient groups with genetic defects likely to result in absent clotting factor and those with less disrupting defects but found no difference in the arthroplasty rate.

At present, it is reasonable to conclude that when defining the 2 severe hemophilias in the same way as < 1 U/dL level, there appears to be a difference in the bleeding phenotype. The Tagariello study does not give us the definitive answer but does suggest that the observation is true. This will undoubtedly be the start of a new avenue to firstly reproduce and confirm these findings in other cohorts and to try to explain the pathophysiology of this observation.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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● ● ● IMMUNOBIOLOGY

Comment on Beq et al, page 816

Where have all the T cells gone?

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In this issue of *Blood*, Beq and colleagues describe the massive yet transient exodus of T cells from peripheral blood to lymph nodes, skin, and gut lymphoid tissue after in vivo IL-7 administration to healthy Rhesus macaques.[1] This dramatic brief T-cell lymphopenia has previously been described in both cancer and HIV clinical trials of rhIL-7.[2,3] Tissue redistribution of T lymphocytes had been invoked to explain this unusual occurrence but there was no data supporting this hypothesis until now.

Beq et al follow healthy Rhesus macaques after administration of recombinant simian (rs) interleukin (IL)–7 with repeat sampling of peripheral blood and tissues, measuring apoptosis, expression of chemokine receptors in CD4 and CD8 T-cell subsets, and chemokine levels in tissues and plasma. Their results show lack of increased apoptosis after rsIL-7 administration but significant up-regulation of homing chemokine receptors on T cells including CXCR4, CCR6, and CCR9 coupled with increased chemokine levels in

tissues (CCL19, CCL20, CCL21, and CCL25) and plasma (CCL3, CCL4, and CXCL12). The physiologic significance of these observations was demonstrated by T- lymphocyte infiltration in lymph nodes, gut and skin lymphoid tissue. T-cell cycling, a known outcome of IL-7 administration, was noted in these same tissues prior to detection of cycling T cells in the peripheral blood.

This work is important for many reasons: (1) it provides us with data supporting tissue redistribution as the explanation of lymphopenia observed in recombinant human (rh) IL-7 clinical trials; (2) it shows potential mechanisms that could account for some of the side effects observed in preclinical and clinical studies of IL-7, specifically skin rashes, diarrhea, and possibly the elevation of liver enzymes (however, no liver biopsies were shown); (3) it gives insight into the homing of T cells in response to homeostatic cytokine signals that are relevant in both normal and lymphopenic conditions; (4) it shows that IL-7 induces T-cell cycling in lymph nodes, skin and gut, suggesting that the T-cell expansions seen in rhIL-7–treated subjects occur at the tissue level and are not due to redistribution; and (5) it suggests mechanisms that could explain lack of response to endogenous or exogenous IL-7 such as destruction of tissue or lymph node architecture or disruption of chemokine receptor-chemokine interactions. Finally, the study also highlights our shortcomings in assessing total body lymphocytes by demonstrating how peripheral blood T lymphocyte observations may not be representative and may even be misleading in disease states characterized by altered levels of cytokines, chemokines, and chemokine receptor expression.

Some questions remain: Why didn't CCR7 (an important molecule for homing to lymph nodes) increase on T cells? Why were there no increases of $CD3^+$ cells in lymph node biopsies at 24 hours despite demonstrable increases in Ki67 expression? Why were there significant differences in chemokine receptor expression between CD4 and CD8 T cells despite identical disappearance and recovery rates from the circulation? Nevertheless, this type of detailed work with frequent peripheral blood and tissue sampling would not be possible in a clinical study. Although the authors contrast their observations to the IL-2 effects, suggesting that apoptosis explained the lymphopenia induced by IL-2, one could argue that similar trafficking phenomena may also have occurred in IL-2–treated subjects, in addition to the enhanced apoptosis that followed the observed lymphopenia.[4]

Better understanding of the mechanisms of action of cytokines can help interpret clinical observations, improve future clinical study designs, ameliorate concerns about lymphopenia or other transient side effects, and further elucidate the role of cytokines in normal T-cell homeostasis and lymphopenia. Phase 1 clinical studies of rhIL-7 have shown significant expansion of both CD4 and CD8 T-cell subsets, suggesting a potential role for rhIL-7 in treatment of lymphopenic diseases such as HIV infection.[3,5] After the recent failure of IL-2 to show any clinical benefit in large phase III clinical trials in HIV infection[6,7] despite significant CD4 T-cell increases, it will be essential to demonstrate that cytokine-induced T-cell expansions in peripheral blood reflect a normal T-cell tissue distribution and function with a diverse T-cell repertoire.

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● ● ● PHAGOCYTES & GRANULOCYTES

Comment on Park et al, page 860

Efferocytosis: another function of uPAR

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uPAR, the receptor for urokinase plasminogen activator, is a regulator of the uptake by macrophages of apoptotic neutrophils (efferocytosis). Its role and mechanism appear to be complex and possibly controversial.

The urokinase plasminogen activator was originally thought to function primarily by concentrating urokinase-dependent proteolytic activity on the surface of cells, hence, increasing the potential of cells to move and migrate through barriers. Over the years, however, it has been firmly established that uPAR is also a signaling receptor, albeit missing an intracellular domain, therefore needing to interact with other extracellular/transmembrane proteins to activate signaling pathways. The development of uPAR Ko mice did not move the field forward initially because the mice appeared normal. However, a subsequent series of phenotypes have been reported on closer study, showing that uPAR is required in vivo for the homeostasis of a wide variety of cells including hematopoietic stem cells, osteoblasts, osteoclasts, macrophages, and others. uPAR Ko mice are deficient in a series of important functions (inflammation, bone homeostasis, kidney and hematopoietic stem cells mobilization and homing).[1-4] Some of these have been linked to human pathology.

uPAR is an adhesion receptor. It directly binds with high affinity to the extracellular matrix component, vitronectin, and this appears to be essential for uPAR dimerization and signaling.[5-7] A direct interaction between uPAR and different integrins has been suggested by many publications; however, in our opinion, while there is no doubt of a functional interaction, there is no real evidence that the link is direct.