Iron is the 6th most abundant element in the universe comprising most of the constituents of the Earth (35%). Going from the big picture of the universe to the smaller theater of human life, iron is important in many biologic processes. Iron biology and potential implications of iron overload have not received much attention in hematopoietic stem cell transplantation (HSCT), largely due to the lack of practical ways to address excess body iron during the peritransplantation period. Consequently, there has been a discrepancy between the explosion of biologic and genetic knowledge and clinical application as it pertains to iron overload significance and treatment in HSCT.

Ferritin keeps iron in a nonreactive state, preventing the Fenton chemical reaction that leads to the formation of oxygen radicals. Although most ferritin is kept intracellularly, the circulating fraction is used as a surrogate for iron stores. Interestingly, little is known about the role of serum ferritin compared to transferrin. Moreover, ferritin is an acute phase reactant and may be elevated for a variety of reasons.

Maradei et al show that a pretransplant ferritin level above 1000 ng/dL is an independent risk factor for decreased 5-year survival and is associated with a high incidence of hepatic sinusoidal obstruction syndrome (SOS, also referred to as veno-occlusive disease or VOD), a poorly understood but often deadly complication of HSCT. Allogeneic transplantation, busulfan-based conditioning regimen, and use of imatinib before HSCT completed the list of SOS-associated risk factors identified by multivariate analysis.

The authors had pretransplant ferritin levels from most of the patients from their institution and used a standard clinical definition of SOS. No transfusion information was provided, and there were no other measurements of iron stores, such as MRI of the liver. The rate of SOS was high, a phenomenon frequently seen when busulfan is given orally without dose adjustments. The high rates of SOS likely allowed the statistical detection of the ferritin effect. The limitations in estimating the actual iron stores here raise an issue: If the ferritin elevation does not reflect iron stores, what does this association tell us? In addition, the increased risk of SOS with pre-SCT imatinib observation is potentially important (although based on a small subgroup), and deserves evaluation in larger cohorts.

SOS: too many irons in the fire!

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In this issue of Blood, Maradei and colleagues investigate the role of prehematopoietic stem cell transplantation hyperferritinemia as a risk factor for sinusoidal obstruction syndrome. They show that increased levels of ferritin (presumptively reflecting increased iron stores) increases the incidence of this complication after allogeneic transplantation.

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

REFERENCES
If iron overload jeopardizes transplant outcomes, will iron chelation be beneficial, analogous to what is observed in thalassemia? This is a complex question to study in a clinical trial. Chelation is not a quick process, which limits its use before transplantation for aggressive hematologic malignancies. Side effects and drug interactions will have to be considered as well, especially after HSCT where multiple medications are the rule. Another important issue is the extent to which the innate immune system is affected by excess iron or by pharmacologic treatment. Chelation may be feasible before HSCT for indolent malignant and nonmalignant conditions, although data supporting the efficacy of this approach are lacking in most diseases. A trial of post-transplantation chelation is unlikely to be effective in preventing SOS, which is an early complication of transplantation. Furthermore, proving that chelation will improve long-term survival will require large studies with extended follow-up. Until such prospective trials are completed, it seems prudent to include pre-HSCT ferritin level as a risk factor for patients undergoing allogeneic transplantation, as suggested by Maradei et al in this issue of Blood, or by Armand et al among others.5 Hopefully, the rapid advances in the field of iron biology will lead to new therapeutic/prophylaxis paradigms, which, in turn, will help us better understand hepatic toxicity in HSCT.

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Vascular Biology
Comment on Brooks et al, page 1276
Is Virchow’s triad complete?

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In this issue of Blood, Brooks and colleagues report on a thromboresistant phenotype of venous valve sinus endothelium as compared to vein luminal endothelium.

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Venous thrombi are formed in the setting of low flow and low shear stress and mainly consist of fibrin strands, red blood cells, and a few platelets. In 1856, Rudolf Virchow postulated that abnormalities in blood flow, hypercoagulability of the blood, and injury to the vessel wall are causally related to thrombus formation (see figure). Reduced venous blood flow during, for instance, immobilization, prolonged bed rest, limb paralysis, long-distance travel, or in obese or pregnant individuals, has been convincingly shown to increase the risk of deep vein thrombosis (DVT).1 In keeping with Virchow’s concept, alterations of the coagulation system that induce a hypercoagulable state also confer an increased risk of DVT. For example, patients with high clotting factor levels have an increased risk of both a first and a recurrent DVT.2,3 Alterations of the vessel wall that lead to plaque formation and plaque rupture play a key role in the development and progression of arterial occlusive disease. However, whether the vessel wall itself plays a role in the development of venous thrombosis is less clear.

In an elegant study, Brooks et al address this important aspect. They explored the procoagulant and anticoagulant properties of the venous valve sinus endothelium in comparison to the vein luminal endothelium.4 Compared with the vein luminal endothelium, expression of endothelial protein C receptor (EPCR) and thrombomodulin (TM) was increased in valvular sinus endothelium while the expression of von Willebrand factor (VWF) was reduced. In other words, what they found was an up-regulation of anticoagulant (EPCR, TM) and a down-regulation of procoagulant (VWF) properties of the valvular sinus endothelium. From this observation, they conclude that valve pockets have a more thromboresistant phenotype. Along this line, they speculate that variations of this valvular sinus endothelial thromboresistance may be associated with a propensity toward venous thrombosis. This would further support the common notion that in patients with DVT of the lower limbs, thrombus formation preferentially starts in the valve pockets of the veins of the calf and then extends to the proximal veins.5

These findings are intriguing as they bring alterations of the vessel walls into focus when considering the multiple pathomechanisms leading to venous thrombosis. Nevertheless, whether a shift in the procoagulant and anticoagulant balance of particular sections of the
SOS: too many irons in the fire!
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