function? Although endogenous NO production from endothelial nitric oxide synthase (NOS) may be the major source of plasma nitrite, other sources should be explored. Macrophage NOS (iNOS) can be induced 2 to 3 orders of magnitude following inflammation. Are blood nitrite levels influenced by infection, cancer, or connective tissue disorders? Such information is highly germane to the issue of whether blood nitrite serves as an important source of NO for regulation of vasomotor tone.

The evolution of civilization has relied, in part, on the fixation of atmospheric nitrogen into nitrates and nitrites, enabling the development of a range of products including fertilizers and explosives. The process in which nitrite is "defixated," converted into biologically active NO, may also turn out to have important and widespread biologic significance. ■

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HEMATOPOIESIS

Comment on Kopp et al, page 505

Revascularization and hematopoietic recovery following myelosuppression are "Tied" together

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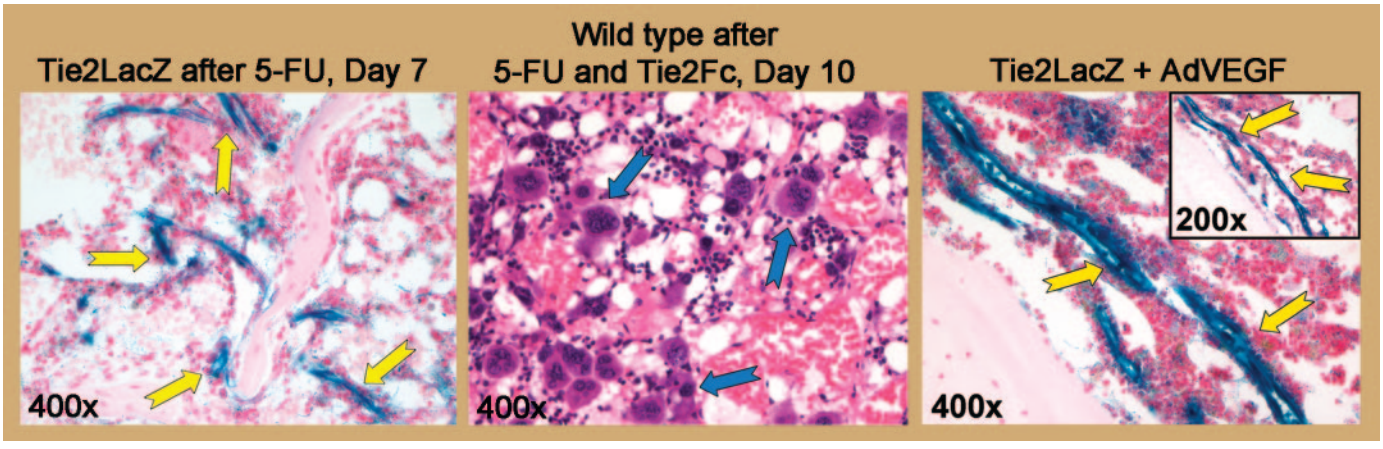
Hematopoietic recovery following chemoradiotherapy depends upon regeneration of the bone marrow microarchitecture; revascularization of bone marrow sinusoids with Tie2-expressing endothelial cells may constitute a defining event in this process.

The intimate association between hematopoietic and endothelial cells is both well established and incompletely defined. During early embryogenesis, the hematopoietic and endothelial lineages arise from a common precursor, the hemangioblast, and share expression of numerous "lineage-specific" molecules. In the adult, endothelial and hematopoietic cells play mutually supportive roles that are multifaceted. The study by Kopp and colleagues in this issue of *Blood* identifies one more facet, demonstrating that *Tie2* signaling plays a key role in neovascularization of bone marrow (BM) sinusoids and consequent hematopoietic recovery following myelosuppressive treatment.

Within the heterogeneous architecture of the BM, distinct "niches" support different stages of hematopoiesis,[1] from maintenance of hematopoietic stem cells (HSCs)/hematopoietic progenitor cells (HPCs) to expansion of progenitors, maturation of lineage-committed cells, and mobilization of mature cells to the circulation. Steady-state hematopoiesis requires the constant replenishment of mature blood cells, leading to a constant flux of cells between niches. In times of stress, the demands for rapid proliferation and maturation of appropriate hematopoietic lineages necessitate more dynamic changes within the marrow. Some of the most elusive aspects of hematopoietic regulation lie in the cellular and molecular signals that direct trafficking of HSCs and HPCs within the greater BM architecture and that support various aspects of hematopoiesis within distinct niches.

Using transgenic strategies and a model of chemotherapy-induced marrow injury, Kopp and colleagues provide new insights into the signals responsible for regeneration of the vascular niche and hematopoietic recovery in this setting. The data provide compelling evidence that Tie2 signaling is crucial for neovascularization and that interactions between hematopoietic and endothelial cells in the regenerating vascular niche promote thrombopoiesis. In the authors' model for hemangiogenic reconstitution, regression of BM sinusoidal vessels stimulates increased production of vascular endothelial growth factor A (VEGF-A), which up-regulates Tie2 expression on sinusoidal endothelial cells. The Tie2 ligand, angiopoietin-1 (Ang-1), further stimulates VEGF-A production and promotes proliferation and reassembly of the vascular architecture. It is



Vascular Tie2 expression is increased in a time-dependent manner after myelosuppression. See the complete figure in the article beginning on page 505.

interesting to note that Ang-1 also induces thrombopoiesis, even in thrombopoietin- and *c-Mpl*–null animals, perhaps by inducing migration and attachment of megakaryocytes to the neovasculature. Clearly, the physical association between megakaryocytes and regenerating vessels facilitates efficient production and release of mature platelets into the circulation; whether the cellular interactions between endothelial cells and hematopoietic progenitors also promote megakaryocyte maturation remains less clear.

As the authors suggest, it is intriguing to consider using angiogenic agents to stimulate recovery following myelosuppressive therapy in the clinical arena. However, some measure of caution may be warranted, as Ang-1–Tie2 signaling is not limited to the BM vascular niche and likely has context-dependent effects.[2] While initially described as an "endothelial" receptor tyrosine kinase (RTK) having an essential role in angiogenesis and vascular remodeling, Tie2 is also expressed by HSCs and has recently emerged as a critical regulator of HSC maintenance in the osteoblastic BM niche.[3] Furthermore, Ang-1 is also expressed by HSCs and HPCs, and these cells have been shown to promote migration and vascular remodeling by Tie2-expressing endothelial cells.[4] These observations raise questions as to the precise role(s) of Ang-1–Tie2 signaling within the osteoblastic and vascular niches—and in the cellular migration between them. The integration of conserved signaling pathways, with RTKs providing "stop" and "go" signals for proliferation and differentiation of progenitors along specific lineage pathways, is a recurring theme in the regulation of developmental processes.[5] If, in the BM, Tie2 provides a "stop" signal for HSCs in the osteoblastic niche and a "go" signal for endothelial cells in the vascular niche, stimulation of short-term revascularization and thrombopoiesis with Ang-1 might also delay long-term hematopoietic reconstitution. Thus, it might be wise to tie up some loose ends before embarking on a clinical path. ■

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CLINICAL OBSERVATIONS

Comment on Testi et al, page 447

APL treatment Italian style: is this the cure?

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In this issue of *Blood*, Testi and colleagues report the results of an Italian therapeutic trial for pediatric acute promyelocytic leukemia (Gruppo Italiano per le Malattie Ematologiche dell'Adulto–Italian Pediatric Hematology and Oncology Group [GIMEMA-AEIOP] ATRA and idarubicin [AIDA]). These remarkable results suggest that APL is now a totally curable disease for the vast majority of children with APL, but at a cost: late cardiac or marrow failure.

The treatment program for pediatric APL consisted of 3 phases: induction, consolidation (3 separate cycles), and maintenance. The unique features of this treatment include: very high-dose anthracycline induction (48 mg/m^2 idarubicin, which equals approximately 240 mg/m^2 daunorubicin) and consolidation (20 mg/m^2 idarubicin and 50 mg/m^2 mitoxantrone); use of different types of anthracyclines; use of lower doses of all-*trans* retinoic acid (ATRA, 25 mg/m^2 per day) than has been used in the United States (45 mg/m^2 per day); and bone marrow transplantation for molecularly defined persistent or recurrent acute promyelocytic leukemia (APL). No intrathecal therapy was given.

All evaluable patients (aged < 18 years) had molecular evidence of APL. From January 1993 to June 2000, 124 children from 42 different centers were enrolled. Induction of complete remission (CR) was achieved in 96% of all eligible patients (n = 110) and in 100% of those with a diagnostic white blood cell (WBC) count of 10 × 10^9/L (10 000/μL) or less (n = 72). The overall survival at 10+ years was 89%, with event-free survival at 76%. It was determined that no child experienced a chemotherapy induction failure. The patients who did not attain CR were all early deaths (days 1, 9, and 16 from intracranial hemorrhage; day 34 from infection), and all had WBC counts at diagnosis above 10 × 10^9/L (10 000/μL). Almost all relapses were seen in patients with diagnostic WBC counts of more than 10 × 10^9/L (10 000/μL), and there were no central nervous system (CNS) relapses. Overall survival for patients with a diagnostic WBC count of 10 × 10^9/L (10 000/μL) or less was 94%.

Given the total number of patients studied and the length of the follow-up, these results are the best reported to date in pediatrics. However, these results come at a price. Two patients developed myelodysplasia (MDS; at 36 and 80 months from initial diagnosis) and subsequently underwent transplantation. One has survived at 16 months from the MDS diagnosis. The other "cost" is cardiac health. Although the authors do not report any clinically significant cardiac effects, it appears that the collection of cardiac testing results in long-term follow-up has not been completed. Certainly congestive heart failure (CHF) and cardiac deaths are reported in APL patients following much lower total anthracycline dosing (patients fully treated by this regimen would get the equivalent of 650 mg/m^2 daunorubicin).[1,2]

The results of this trial for "good-risk" patients with APL suggest that their treatment could be reduced in the future, thereby possibly reducing the risks for MDS and/or cardiac damage. Agents that are more specific for APL and/or less globally cytotoxic, including arsenic trioxide and gemtuzumab ozogomycin, are already available.[3-5] Early reports of their use in newly diagnosed patients strongly suggest that these agents should be introduced earlier in the treatment of patients with APL. ■