Clinicians are often unaware of the specific risks faced by survivors and without this knowledge may not screen for MS in young survivors, particularly in the absence of obesity. Despite a higher prevalence of obesity in ALL survivors, many develop 1 or more cardiovascular risk factors without actually being obese. In the French cohort described by Oudin et al, only 14.5% had an elevated waist circumference, while 25.3% were hypertensive and 31.8% had low HDL cholesterol. Appropriate early screening will facilitate intervention with lifestyle counseling focused on increasing physical activity, improving diet, and curbing risky behaviors such as cigarette smoking. When necessary, hypertension, dyslipidemia, and impaired glucose tolerance can be treated pharmacologically, but intervention at this late stage is not enough. Pediatric oncologists must find ways to interrupt the path between leukemia treatment and the cascade of behavioral and pathophysiologic consequences that lead to MS. Treatment modifications such as the elimination of cranial radiation from most ALL regimens will modify the risk, and multidimensional programs targeting lifestyle during ALL therapy are being evaluated in ongoing clinical trials. As health care practitioners who care for children during and in the wake of cancer therapy, our mission is to ensure that the excellent cure rate of childhood ALL translates into lives unbindered by the cost of that cure.

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Comment on Zhang et al, page 4569

Oxidative stress may cause ITP

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ITP has served as a model for autoimmune disorders with disturbances of the innate and adaptive immunity where targeted treatment with immunomodulation has proven effective. In this issue of Blood, Zhang et al report that these immune disturbances are triggered by oxidative stress. In addition, the molecular-based results indicate the possibility of distinguishing the transient, self-limited form of ITP from chronic, long-term ITP.

Confronted with a patient with newly diagnosed ITP, the physician cannot determine if the patient has a transient, self-limited disorder or long-term, chronic ITP. In children ITP is often present after an infection or vaccination. In adults, ITP is associated with helicobacter pylori, hepatitis C virus, HIV, and other viral infections, although the mechanism is not clear. It is unknown how platelets are targeted by the host’s immune system. Infection-related oxidative stress may induce disturbed immune response. (Auto)antibodies or immune complexes against platelets lead to early destruction of platelets by phagocytes or by cytotoxic T cells in predisposed individuals. The immune disturbances of ITP and

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of other autoimmune disorders have been indirectly documented by therapeutic immunomodulatory intervention such as intravenous human immunoglobulin concentrate, which targets the whole immune response,\textsuperscript{1} monoclonal anti-CD20 antibodies,\textsuperscript{2} by cyclosporine A, or by nonspecific immunosuppressants on an empiric basis.\textsuperscript{7,8} Zhang and colleagues report here on gene-expression and molecular-oxidative stress results as causative factors for chronic ITP in children.\textsuperscript{1}

With transcriptome cDNA microarray analysis of peripheral blood, the authors could show differences of clustering profiles among patients with transient, self-limited ITP and chronic, long-term ITP and control individuals. Overexpression of the gene vanin-1 (VNN1)—an oxidative stress sensor—was associated with chronic ITP only (see figure). VNN1 is characterized by its role in oxidative stress response, and it mediates production of inflammatory cytokines by antagonizing peroxisome proliferative-activated receptor $\gamma$ (PPAR$\gamma$). VNN1 is the only gene that was detected in chronic ITP. Exposure of human blood mononuclear cells to oxidative stress inducers (LPS, sodium arsenite) up-regulates VNN1. Quantitative real-time PCR measurement of VNN1 expression confirmed the oxidative stress events in peripheral blood cells. In addition, the ratio of reduced to oxidized glutathione—a parameter of the cellular redox state—was significantly down-modulated in children with chronic ITP in comparison to healthy controls.

In the present study by Zhang et al, the numbers of the patient/control groups are small, but ongoing oxygen stress is a significant factor in patients with chronic ITP. Chronic ITP is an autoimmune disorder where isolated low-platelet counts indicate the immune pathogenesis. In chronic ITP, clinical bleedings occur in some patients with very low platelet counts. Many other autoimmune disorders such as Guillain Barre syndrome, Kawasaki syndrome, lupus erythematosus, dermatomyositis, and dermatologic blistering disease have similar pathogeneses and respond to similar therapeutic interventions.\textsuperscript{3}

The demonstrated pathway should now be confirmed by a larger study including adults with ITP as well as in other autoimmune disorders.

From these new findings early prognostic estimation concerning transient or long-term disease may be possible. The pathophysiologic changes of the involved molecules in oxidative stress could create new therapeutic approaches and medications. The described triggering pathways of chronic autoimmune phenomena might provide earlier intervention in selected groups of an autoimmune disorder.

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