before and after 9 months of regular transfusion in a 7-year-old with SCD.

At some point between 190 cm/sec and 240 cm/sec, probably depending on several variables, it becomes likely that a magnetic resonance angiogram will indicate significant arterial stenosis.[5]

Hydroxyurea (HU) is an antimetabolite chemotherapeutic agent known, among other effects, to stimulate fetal hemoglobin production. In the current study, this drug was used in a prospective phase 2 design (no control group) to determine the effect of HU given at maximum tolerated dose (MTD) on TCD velocities. The authors treated 37 children with elevated (> 50th percentile TCD values at baseline), 6 with abnormal TCD velocity who declined to accept the recommended therapy of chronic transfusion and 31 whose TCD velocity did not dictate a therapy based on current evidence. At an MTD of about 27 mg/kg/day, an approximate decrease of 26 to 31 cm/sec was observed at a median 8 months. With therapy, total hemoglobin increased 20%, fetal hemoglobin more than doubled, and overall TCD velocities dropped by about 17%. Although the authors state that there was no correlation between the magnitude of the TCD velocity decrease and the hematocrit increase, this is likely a result of the small sample, as a large body of evidence links TCD velocity to total hemoglobin or hematocrit in healthy or anemic patients.

This study is an important addition to a growing body of work that paves the way toward less invasive or intensive options (than bone marrow transplant or indefinite regular transfusion) for stroke prevention, at least for some patients. Although the STOP study suggested that regular transfusion lowered TCD velocity *out of proportion* to the increase in total hemoglobin that accompanied the transfusion protocol, this has been hard to determine with certainty, and the precise mechanisms whereby transfusion reduces stroke risk are still not known.

Likewise, from the current and other studies with HU, we do not yet know if HU lowers TCD velocity and, by inference, stroke risk beyond that expected from the increase in hemoglobin. In the end, it may not matter if it can be shown in a randomized controlled trial that, with HU therapy and the accompanying increase in hemoglobin (and fetal hemoglobin), along with a substantial decrease in TCD velocity, the stroke risk also goes down. The study by Zimmerman and colleagues advances the field and helps set the stage for a needed test of HU for primary stroke prevention in a randomized clinical trial, ideally with stratification based on baseline TCD velocity.

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

REFERENCES

1. Fullerton H, Johnston SC, Zhao S, Adams RJ. Declining rates in Californian children with sickle cell disease. Blood. 2004;104:336-339.
2. Nichols FT, Jones AM, Adams RJ. Stroke Prevention in Sickle Cell Disease (STOP) Study Guidelines for Transcranial Doppler Testing. J Neuroimaging. 2001; 11:354-362.
3. Adams RJ, Brambilla DJ, McKie VC, Hsu L, Files B, Vichinsky E, et al. Transfusion Prevents First Stroke in Children with Sickle Cell Disease: The "STOP" Study. N Engl J Med. July 1998;339(1):5-11.
4. Adams RJ and Brambilla DJ for the: Optimizing Stroke Prevention in Sickle Cell Anemia Investigative Team (STOP 2). Discontinuing Prophylactic Transfusion to Prevent Stroke in Sickle Cell Disease. N Engl J Med. 2005 Dec 29;353(26):2769-78.
5. Abboud M, Cure'J, Gallagher D, Hsu L, Wang W, Zimmerman R, et al. Magnetic Resonance Angiography (MRA) in Children with Abnormal Transcranial Doppler (TCD) Velocities in the STOP Study. Blood. 2004; 103:2822-2826.

IMMUNOBIOLOGY

Comment on Obata et al, page 913

What does a basophil do?

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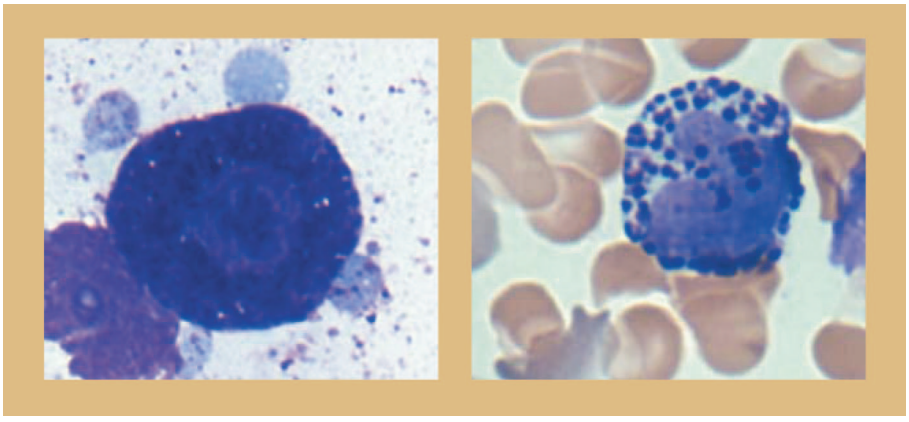
The absence of an animal model deficient in basophils has been a major obstacle in efforts to delineate the functional significance of basophils in health and disease. In this issue of *Blood,* Obata and colleagues describe a monoclonal antibody (Ba103) which selectively reduces the number of basophils in the peripheral blood and spleen in mice.

Basophils and mast cells share significant phenotypic and functional properties (see figure).[1] Both cell lineages possess metachromatic granules containing histamine and proteoglycans, and express the high-affinity immunoglobulin E (IgE) receptor through which they can be activated to degranulate and synthesize inflammatory mediators. These similarities have led many to consider these 2 cell types to have redundant functional properties. Experiments performed on mast-cell–deficient mice confirmed not only the essential role of mast cells in allergic inflammation, but also revealed their important contributions to a number of innate and acquired immune responses.[2,3] However, while mast-cell function in vivo can be studied by using mice displaying defective expression of KIT due to loss-of-function mutations in *c-kit*, a similar model has not been available for basophils. Development of the Ba103 antibody, which specifically depletes basophils, should therefore facilitate a



Photomicrograph of a human bone marrow mast cell (left) and a peripheral-blood basophil (right) stained with Wright-Giemsa. Images were acquired using an Olympus BX41 microscope equipped with a Planar 100×/1.25 oil lens and an Olympus Q Color 3 camera (Olympus America, Melville, NY) and were processed with Q Capture Pro version 5.1.1.14 software and Microsoft PowerPoint 2002 (Microsoft, Redmond, WA).

more complete understanding of the functional significance of this cell lineage.

A critical question pertinent to the study by Obata and colleagues, as raised by a recent commentary in *Blood*,[4] is whether the cells recognized and depleted by Ba103 antibody are really basophils. Ba103 recognizes a subset of mast cells as well as a second cell type that is increased by infection with the parasite *Nippostrongylus brasiliensis,* carries high-affinity receptors for IgE and IL-3 while lacking other lineage commitment markers, has the ultrastructural features of basophils, and expresses the basophil protease MMCP-8 while lacking other proteases characteristically associated with eosinophils and neutrophils. It therefore seems reasonable to accept the latter cell type recognized by the antibody as a basophil. When injected intravenously, the antibody selectively depletes basophils but not mast cells.

The experiments reported by Obata and colleagues, which compare and contrast mast-cell–deficient and basophil-deficient mice, reveal interesting clues about the contribution of basophils to various allergic reactions. Basophils have been suspected to contribute to IgE-mediated immediate hypersensitivity reactions including anaphylaxis. Interestingly, the authors show that, in contrast to mast-cell–deficient mice, basophil-deficient mice display no significant suppression of IgE-mediated systemic or local anaphylaxis. Perhaps less surprisingly, basophil-deficient mice also do not have any significant inhibition of delayed contact hypersensitivity.

Basophils have been considered to be important mediators of late-phase allergic reactions, based on their having been found in increased numbers after allergen challenge in tissues such as lung and skin.[5] Experiments by Obata and colleagues suggest that basophils play a more pivotal role in initiation rather than maintenance of IgE-mediated chronic inflammation, at least in the skin. Human counterparts of IgE-mediated chronic inflammatory processes may include such common disorders as atopic dermatitis and allergic asthma. The value of basophils as targets for future novel therapies for selected allergic disorders remains to be explored.

Finally, it could be predicted that the availability of a basophil-deficient animal model should lead to studies dissecting the role of basophils in innate immunity and other non-allergic inflammatory processes, ultimately shedding more light on the age old question of what a basophil does to contribute to healthy immunologic homeostasis.

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

REFERENCES

1. Galli SJ. Mast cells and basophils. Curr Opin Hematol. 2000;7:32-39.
2. Galli SJ, Kitamura Y. Genetically mast-cell-deficient W/Wv and Sl/Sld mice: their value for the analysis of the roles of mast cells in biologic responses in vivo. Am J Pathol. 1987;127:191-198.
3. Grimbaldeston MA, Chen CC, Piliponsky AM, Tsai M, Tam SY, Galli SJ. Mast cell-deficient W-sash c-kit mutant Kit W-sh/W-sh mice as a model for investigating mast cell biology in vivo. Am J Pathol. 2005;167:835-848.
4. Lee JJ, McGarry MP. When is a mouse basophil not a basophil? Blood. 2007;109:859-861.
5. Gibbs BF. Human basophils as effectors and immunomodulators of allergic inflammation and innate immunity. Clin Exp Med. 2005;5:43-49.

CLINICAL TRIALS AND OBSERVATIONS

Comment on Darby et al, page 815

An actuarial GPS for hemophilic longevity

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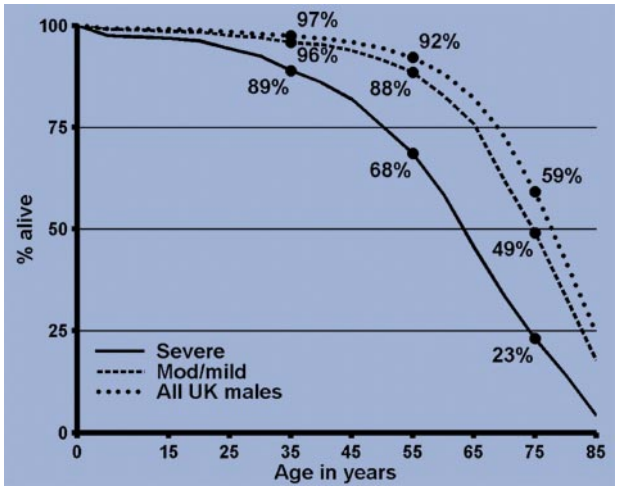
HIV as a transfusion-transmitted pathogen drastically reduced the lifespan of people with hemophilia beginning in the 1980s. The question of what would have been the expected lifespan in this chronic disease, had HIV not happened, has been the subject of previous epidemiologic reports.

Data from the large, well-characterized United Kingdom cohort of hemophilia patients described by Darby and colleagues in this issue of *Blood* provides the most complete picture to date of how long HIV-uninfected individuals live and what disease or injury states are most frequently associated with their demise (see figure). The vital status of 6018 HIV-uninfected hemophilia A and B individuals of all clinical severities was captured comprehensively, and causes of death for virtually all decedents were ascertained. Without the confounding of HIV for more than 2 decades (1977-1999), these findings provide confirmation of previously defined mortality risk factors for hemophilia, and also elucidate how the impact of certain of these risks have evolved over time.

For example, the investigators confirm hepatitis as a mortality risk factor, but its weighted impact is not as striking as previous reports have implied in patients with severe hemophilia A or B. Conversely, a protective effect of hemophilia against death from coronary heart disease/myocardial infarction is demonstrated, confirming previous observations.[1] Not surprisingly, intracranial hemorrhage (ICH) persists as a hemorrhagic mortality risk factor, particularly in children younger than 4 years of age. Over the 23 years assessed, however, the age of those infants dying from ICH became progressively younger, particularly among those with severe disease. As the authors suggest, this effect may result from the introduction of primary prophylaxis in the United Kingdom in the early 1990s, which typically begins at



Survival in men in the United Kingdom with hemophilia who were not infected with HIV and in the general male population of the United Kingdom in 1999. See the complete figure in the article beginning on page 815.