feasible, particularly for polymorphic antigens in into standard transfusion practices for related complication. Strategies to avoid or manage this risk are desperately needed.

Studies have demonstrated that antibodies against C, E, and Kell antigens account for >50% of alloantibodies identified in patients with SCD and that extended antigen matching to include C, E, and Kell can decrease the development of new antibodies in this population by 40% to 90%.2,4 Although academic medical centers are more likely to provide extended antigen matching,2 a recent North American survey indicated two-thirds of institutions continue to only match for ABO and D in nonalloimmunized patients with SCD.6 There are also significant global variations in transfusion practices in SCD.7,8

To date, this is the largest cohort of SCD patients who have been supported over an extended period almost exclusively with blood collected from self-identified African–American donors. Ethnic disparity has often been cited as the major contributor to alloimmunization in SCD throughout Europe and North America, where the donor population is predominantly nonblack. Diversity of the blood supply in an increasingly global, multiethnic nation is important, whether planning for national disasters or insuring safe and adequate resources for routine procedures.9 African Americans, in particular, continue to be underrepresented in community blood donation programs. Strategies to enhance matching by focused recruitment of African–American blood donors or establishing directed donor programs for children with SCD have long been advocated as potential solutions to this very serious transfusion-related complication.

The incorporation of DNA-based methods into standard transfusion practices for determining RBC genotype is becoming more feasible, particularly for polymorphic antigens in most blood group systems.8 The Rh system, however, has been a notable exception, primarily due to its complexities as demonstrated by Chou et al. The wide diversity of Rh variants among their patients (and presumably their donors) suggests that additional or alternate approaches may be needed to improve matching and reduce alloimmunization.

The authors identify a very relevant concern for hematologists and for patients with sickle cell disease. Racial differences alone do not explain the increased propensity of patients with SCD to develop allo- and autoantibodies. Patients with hemoglobinopathies and most non-European ethnic groups are among the populations that pose exceptional challenges in blood banking as identified by the 2007 National Heart, Lung, and Blood Institute Working Group on Transfusion Epidemiology and Recipient Outcomes Research and in whom more research is needed.10 The paper by Chou et al provides some very critical insights to a problem for which as yet there does not appear to be an easy solution.

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Hemoglobin disorders: a look to the future

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In this issue of Blood, Locatelli et al compare the results of histocompatible family donor bone marrow and cord blood transplants (BMT and CBT) for severe β thalassemia (SBT) and sickle cell disease (SCD) as experienced by the Eurocord and European Blood and Marrow Transplantation group and collaborating centers in the United States, Hong Kong, and Israel between 1994 and 2005.1 Obviously, many changes in medical care and particularly MHC typing occurred over that decade, so this retrospective represents a moving target, but some firm points can be made for which we are indebted to this excellent group.

In 1984, Thomas and Storb and their colleagues reported on the first 4 patients with SBT who were treated with histocompatible BMT in Seattle.2 Two years later, Johnson and Billings and their associates reported a successful transplant of a child
with leukemia and SCD who was apparently cured of both disorders, and Lucarelli and colleagues reported a much larger experience of the treatment of SBT with histocompatible family donors in their specialized unit in Pesaro, Italy. Their results were very good for that time and they have considerably improved. A few years later, the Belgian group led by Vermylen and colleagues reported astonishingly good results, first in 12 and then in 24 African patients with SCD. This stimulated Mark Walters (then in Seattle) and his coworkers to carry out a BMT trial for SCD in the United States. The trial evoked a very thoughtful editorial by Platt and Guinan, who pointed out the great difficulty faced by families of SCD patients if they roll the dice in favor of histocompatible family donor BMT.

The issue is highly complex. Conservative medical care is expensive and not curative but is steadily improving for patients with SCD and BMT. Though the future course of patients with SBT can usually be determined in the first year of life, patients with SCD are highly variable. Their futures cannot be securely predicted in the first years of life. Yet it is clear that decisions to move to a potentially curative transplant should be made early, before the organ-damaging effects of the diseases increase the risk of the transplant procedure. And the risks are significant. Though only 5% died in the Locatelli et al experience, another 10% or more developed severe chronic graft-versus-host disease. A surgical procedure with 5% mortality would receive very close scrutiny.

These dilemmas are further complicated by the comparison of BMT and CBT attempted by Locatelli et al. The CBT group was much smaller in number and size and considerably younger. Their doses of cord blood cells were much lower; they received thiopeta more often and less busulfan/cyclophosphamide, antithymocyte globulin, and methotrexate. It is very difficult to compare these groups, but the results speak for themselves. In the hands of this group, CBT patients did as well as one could hope for at this time.

Can we predict the future of management of SBT and SCD? BMT will surely be in the therapeutic arsenal. With better typing, more closely matched donors will be found. But unless we can conquer graft rejection and the dread chronic graft-versus-host disease, the detection of better donors will inevitably reduce the donor pool. Whether CBT will stay in use in the long term is questionable, because the low dose of repopulating cells in a CBT creates a very long period of susceptibility to infection. In contrast, encouraging BMT and even peripheral blood transplant results are being accumulated in several centers using adult haploidentical family donors. While CBT has been a useful stop gap, it may become unnecessary.

The key to less invasive and dangerous treatment of SBT and SCD may lie in replacement gene therapy or, more likely, in manipulation of the fetal switch. Gene therapy approaches have been proposed and actually carried out. Progress in that area is slow but demonstrable. Gene-editing efforts are also under close study. Perhaps the most promising idea is to suppress the fetal switch, an approach recently reviewed by Sankaran and Orkin. If successful, this method of therapy would cure both SBT and SCD.

The clinical application of these novel ideas lies in the future, but that future seems assured. Meanwhile, safer red cell transfusions, improved orally active iron chelators, control of infection (particularly in the newborn period), attacks on the inflammatory response in SCD, and far better psychosocial support will produce a much better quality of life for patients who are fortunate enough to be cared for in resource-rich environments.

Our greatest challenge is the hard fact that SBT and particularly SCD are scourges of poor countries. Can we really propose highly sophisticated and very expensive care in those settings? Perhaps a cheap and nontoxic pill will be found that reverses the fetal switch, but that nirvana seems quite distant.

Therefore, despite our cultural and religious differences, we must face the fact that these diseases are preventable. We will soon be capable of prenatal diagnosis of the major hemoglobin mutations from samples of maternal blood and can do so now routinely from chorionic villous biopsy specimens. Central laboratories can be established by the World Health Organization to provide the data, and local medical workers trained to understand the data can give the proper advice. These opportunities create difficult and contentious questions, but the task of modern medicine is to do the best we can for the most we can. To meet that challenge, we will have to consider the impact of our research in a world larger than our own.

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