ASH KICKS OFF 50TH ANNIVERSARY

NOTES FROM THE EDITOR-IN-CHIEF

PETER EMANUEL, MD

Dr. Emanuel is Executive Director of the Arkansas Cancer Research Center.

Next year marks the 50th anniversary of the American Society of Hematology. In the months leading up to 2008, you will hear about the many ways ASH is celebrating its 50th anniversary. This all culminates with the annual meeting celebration in San Francisco in 2008. 

One way The Hematologist is kicking off the anniversary is by spotlighting leading American hematologists of yesterday. Dr. Frank Bunn, Marshall Lichtman, and Wendell Rosse, on behalf of the 50th anniversary committee, will be profiling some of these “giants of hematology” in every issue of The Hematologist through 2008. We are starting off this series with profiles on William Bosworth Castle and James H. Jandl on page 5.

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VISION FOR FUTURE

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With this issue, Karen has already demonstrated her ability to come on board with considerable speed and effectiveness.
Editor’s Note: The Centers for Medicare and Medicaid Services (CMS) released a national coverage determination (NCD) for coverage of erythropoiesis-stimulating agents (ESAs) for non-renal uses on July 30. In response to recommendations by ASH and other organizations, the NCD does not exclude coverage of ESA therapy for patients with myelodysplasia (MDS). The new policy does not include MDS, which means that ESA treatment for Medicare beneficiaries with MDS continues to be covered without any conditions or limitations. Local Medicare carriers, however, may continue to make local coverage decisions that are not included in this NCD. As an expert in MDS and as Chair of the NCCN Panel on MDS, Dr. Peter Greenberg was asked to provide comments on the controversy surrounding the use of ESAs. This information may be useful to hematologists if local carriers require information and references in order to support the coverage of ESAs for MDS.

In March 2007, the FDA announced alerts and strengthened safety warnings for the use of erythropoiesis-stimulating agents (ESAs), predominantly recombinant human erythropoietin and darbepoetin. They noted that increased mortality, possible tumor promotion, and thrombotic/vascular events were observed in patients receiving ESAs when dosing targeted hemoglobin levels >12 gm/dL. These studies were performed in patient groups with chronic kidney failure, head and neck cancer receiving radiation therapy, or in other patients with cancer not receiving chemotherapy, and in those patients undergoing orthopedic surgery. As a result of these statements, the Centers for Medicare and Medicaid Services (CMS) opened a National Coverage Analysis to evaluate the use of ESAs in all non-renal disease applications. Although the prompt response of CMS to the FDA-issued warning was commendable, as it was aimed at protecting patients, the broad-based language of the FDA warning created an unfortunate dilemma.

In addition to patients with renal disease, cancer patients with symptomatic anemia resulting from chemotherapy, and patients infected with HIV who are taking zidovudine, there are many other patients with symptomatic anemia who clearly benefit from the use of ESAs when used in a responsible and appropriate manner. One group of patients potentially most urgently affected by the FDA alert and the possible non-coverage by CMS were patients with myelodysplastic syndromes (MDS) who receive ESAs for their refractory anemia. Patients with MDS are generally elderly and many are eligible for Medicare coverage. ESAs in these patients often have not only a positive effect on their quality of life, but data have also recently indicated beneficial effects on their survival and risk of progression to AML. As part of the process that CMS went through in the National Coverage Analysis, data were presented to CMS arguing for the efficacy of ESAs in patients with MDS. ESAs have been used safely in large numbers of adult patients with MDS and have become important for symptomatic improvement of those affected by the anemia caused by this disease, often with a decrease in RBC transfusion requirements. Published data on the safe and effective use of ESAs in patients with MDS that span more than a decade are available. Prior National Comprehensive Cancer Network (NCCN) MDS Practice Guidelines Panel recommendations for use of ESAs in MDS have evolved from these and more recent data (NCCN MDS Practice Guidelines v.1.2007; see algorithm on MDS-6, www.nccn.org).

Regarding the potential impact of recombinant human erythropoietin (Epo) on clinical outcomes in MDS, data have been reported in several recent abstracts and in one paper that bear on this subject. Studies in MDS patients with ≤10% marrow blasts or those in the International Prognostic Scoring System (IPSS) Low/Int-1 risk categories assessing the long-term use of Epo with or without granulocyte-colony stimulating factor (G-CSF, lenograstim) compared to either randomized controls or historical controls have shown no negative impact on survival or AML evolution of such treatment. In addition, reference 3 indicated improved survival in lower-risk MDS patients with low transfusion requirements treated with these agents. Reference 4 demonstrated improved survival and decreased AML progression of IPSS Low/Int-1 MDS patients treated with Epo plus G-CSF compared to historical control patients in the International MDS Risk Analysis Workshop (IMRAW) database (patients were from reference 5). Thus, these data do not indicate a negative impact of these drugs for treatment of MDS.

In addition to the potential impact on survival and transformation to AML, accumulating data in MDS indicate that debilitating fatigue and transfusion dependence significantly and negatively impact patients’ quality of life.

A major aim in management of MDS patients having symptomatic anemia is to decrease the need for RBC transfusions. The potential negative consequences of recurrent RBC transfusions are well recognized: iron overload, viral infections, transfusion reactions, iso-osensitization to platelets, and negative impact on quality of life. These problems are added to the potential negative impact on national blood supply resources.

A coalescence of challenging and often interlocking co-morbid conditions occurs with aging—including the association of the refractory anemia of MDS and congestive heart failure (CHF). Both illnesses are predominantly disorders of the elderly. Extensive data in non-MDS patients have shown critical negative interactions between anemia and CHF, demonstrating an independent association between anemia in CHF and increased mortality. Effective treatment of the anemia (predominantly with Epo) in patients with CHF improved their cardiac function and quality of life. In a cohort of RBC transfused and non-transfused MDS patients, the major cause of non-leukemic death was cardiac failure (in 51 percent of patients) and it was significantly more frequent in the transfusion-dependent patients. The contribution to poor survival of transfusions (with associated iron overload and consequent cardiotoxicity) or from the anemia per se requires further study. Clearly, effective management of symptomatic anemia in these patients is vital.

The NCCN MDS Practice Guidelines Committee has endorsed and reiterated prior recommendations for ESA use in the management of appropriately selected symptomatic anemia in MDS patients (NCCN MDS Practice Guidelines v.1.2007), albeit with a change in the target hemoglobin—i.e., to aim for a target hemoglobin of up to 12gm/dL (v.1.2008). The NCCN guidelines recommend that MDS patients with symptomatic anemia and with serum epo levels ≤500 who are iron replete and have no other known causes for their anemia would be candidates for ESA therapy. Dosing of epo for appropriate patients with MDS is recommended as 40,000-60,000 IU/week subcutaneously for a period of six to eight weeks, continued so long as response occurs and possibly tapered as indicated by response. If response has not occurred by that time, the drug should be discontinued, or addition of G-CSF or use of other agents should be considered, depending on the clinical subset of MDS patient being treated (for example, addition of G-CSF is often particularly beneficial for those with the refractory anemia with ringed sideroblast subtypes).

Citing information such as that indicated above, a number of established clinical groups (including ASH, ASCO, NCCN, and the MDS foundation, along with the combined input from the Leukemia Committees of EOCG, CALGB, and SWOG) strongly advocated to CMS to continue to permit the use of ESAs for treating appropriate patients with MDS according to well-established management guidelines.

Following this input, the CMS decision memo of July 30, 2007, (CAG-00383N) has narrowed the scope of their final decision regarding use of ESAs in cancer and related neoplastic conditions to make no national coverage determination (NCD) on the use of ESAs in MDS (i.e., not restricting ESA use in MDS through the NCD). Local Medicare contractors may continue to make reasonable and necessary determinations on uses of ESAs that are not determined by the NCD. Given that controversy surrounding the use of ESAs is likely to continue, it was felt that it would be beneficial to arm clinicians with the above data about the efficacy of ESAs in MDS, such that clinicians can be well informed as they discuss this topic with their patients or other groups.


The ASH-ASCO 2007 Clinical Practice Guideline Update on the Use of Epotin and Darbepoetin will be published soon. We will feature a story on the guideline update in the next issue of The Hematologist. There will also be a discussion of the guidelines and the latest regulatory issues surrounding ESA coverage at the Practice Forum, on Saturday, December 8, at 6:00 p.m. during the 2007 ASH Annual Meeting.
ASH Introduces a New Late-Breaking Abstract Deadline

ARMAND KEATING, MD

The ASH Program Committee recognizes that the results of some exciting research may not be available by the abstract submission deadline.

This year, ASH offers a new late-breaking abstract deadline of October 9, 2007, for abstracts that highlight novel and substantive studies of high impact. The late-breaking abstract submission program will be available October 1 through October 9 on the ASH Web site (www.hematology.org).

The selection process will be competitive; no more than six abstracts will be selected for oral presentation in a late-breaking abstracts simultaneous session on Tuesday morning of the ASH annual meeting. Late-breaking abstracts will not be eligible for oral presentation in the usual simultaneous sessions, nor will they be eligible for poster presentation.

Late-breaking abstracts will not be chosen from among the abstracts submitted by the general submission deadline, but all other ASH policies stated in the general submission Call for Abstracts still apply. Only the accepted late-breaking abstracts will be published online and in the On-Line Program Book.

Examples of suitable late-breaking abstracts might include the results of a practice-changing prospective clinical trial or the discovery of a mechanism underlying or characterizing a disease process (such as the JAK2 mutation in myelodysplastic disorders) that were not fully available by the general abstract submission deadline. The late-breaking abstract deadline is not intended to be merely an extension of the general submission deadline and will focus on capturing abstracts with ground-breaking and novel data that otherwise could not be presented at the annual meeting. Investigators with data that are substantive and novel and available earlier must submit their abstract by the general submission deadline.

If you have questions about the late-breaking abstracts deadline, please contact Melissa Connolly, Annual Meeting Program Specialist, at mconnolly@hematology.org.
FY 2008 Budget Process: ASH Continues to Advocate for Larger Increase for NIH

As congressional leaders maintain their intention to adjourn for the year by late October, Congress is continuing the process of drafting the bills that will fund federal departments, agencies, and programs for fiscal year (FY) 2008. Over the summer, the House and Senate Appropriations Committees proposed funding levels for various federal programs, including the National Institutes of Health (NIH). The House version of the FY 2008 Labor-HHS spending bill provides a net increase of $549 million (1.9 percent) over FY 2007 for NIH. Meanwhile, the net increase proposed for the Senate for the NIH budget in its draft bill is $797 million (2.6 percent) over FY 2007. As this issue of The Hematologist went to press, President Bush indicated his intention to veto the bill due to its cost, and it appeared that full Senate passage may not come until October. Many in Washington are expecting that agreement between the House and Senate will be unlikely, which would necessitate an omnibus spending bill.

It is important to note that both the Senate and the House proposed funding levels for NIH in FY 2008 essentially represent a cut in NIH funding, since the small increases they provided do not keep pace with the projected 3.7 percent increase in biomedical inflation for 2008.

ASH will continue its advocacy efforts supporting increases for NIH on Capitol Hill throughout the remainder of the FY 2008 budget debate. With a very tight year expected for the entire federal budget and many domestic programs facing cuts or minimal increases, significant cuts to NIH funding is critical to gain any further traction for increasing NIH funding in the budget process. Please see the “Take Action” box on this page to learn how you can help influence the budget process, and, for the most up-to-date information about NIH funding and ASH’s advocacy efforts, visit the ASH Web site at www.hematology.org. President Vetoes Stem Cell Research Bill; Congressional Leaders Continue the Fight to Expand Federally Funded Stem Cell Research

As expected, President Bush vetoed the Stem Cell Research Enhancement Act (S. 5) in late June. While congressional leaders hope to override the President’s veto, it is unlikely that the bill has the two-thirds majority support in either the Senate or the House necessary to override the veto.

Additionally, in response to President Bush’s veto of the bill, Senate Labor-HHS Appropriations Subcommittee Chairman Tom Harkin (D-IA) and Subcommittee Ranking Member Arlen Specter (R-PA) have included a provision in the Senate version of the FY 2008 Labor-HHS Appropriations bill that would essentially overturn the President’s recent decision and make more embryonic stem cell lines available for federal funding. The language inserted by Senators Harkin and Specter, the chief Senate sponsors of the Stem Cell Research Enhancement Act, would allow research funding on stem cell lines derived prior to June 15, 2007; current Bush Administration policy allows for federal funds to be used only for research on embryonic stem cell lines derived prior to August 9, 2001.

Because similar language was not included in the House version of the FY 2008 Labor-HHS Appropriations bill, it remains unclear as to whether the stem cell language will be included in a final version of the bill that would be submitted to the President.

For the most up-to-date information on the stem cell research debate, please visit the ASH Web site at www.hematology.org.

Medicare Agency Proposes Physician Fee Schedule for 2008; Physicians Face 9.9 Percent Cut Unless Congress Acts

CMS published its Proposed 2008 Medicare Physician Fee Schedule Rule on July 12, and as expected the Agency proposed reducing physician payments by 9.9 percent beginning January 1, 2008. CMS has been working with Congress to avert these drastic cuts. For the past five years, estimated cuts to the Medicare physician payment rate have been temporarily avoided through legislation. Currently, congressional committees in the U.S. House of Representatives are working on legislation to address Medicare physician payment. However, even with congressional action, the best scenarios would be a .5 percent increase or a freeze in the 2007 conversion factor in 2008.

ASH has developed a detailed summary of the rule, including information about proposals to report anemia quality indicators, changes to the codes for medically accepted indications for off-label drug uses, the 2008 Physician Quality Reporting Initiative, payment for intravenous immunoglobulin (IVIG), and Average Sales Price issues, etc. This summary and ASH’s comments to CMS are available online at www.hematology.org/ policy/news/ proposed_PFS_rule_summary07.doc. The final rule will be published around November 1 and will go into effect on January 1, 2008.
James H. Jandl was one of the world’s premier experimental hematologists and a leading writer of hematology texts. His conduct of science set a standard that informed a generation of trainees who had the good fortune of working with him. His intellect was as deep as it was broad. He had unsurpassed insights into evolving biological mechanisms and, by a combination of reasoning and instinct, could design the experiment most apt to produce a conclusive result.

Jandl received his MD from Harvard Medical School in 1949 and, during his residency at Boston City Hospital, came under the aegis of William Castle, who served as his mentor for the next two decades, playing a critical role in developing and fostering his interest in the red blood cell.

Jandl took full advantage of the wealth of pathology at the Boston City Hospital and focused with laser-like intensity on inherited and acquired disorders of the red blood cell. He began studying patients with alcoholic cirrhosis and published definitive studies on red cell production and survival in chronic liver disease, as well as the impact of cirrhosis on folate acid metabolism. Thirteen years later, he and Richard Cooper showed that, in liver disease, the red cell membrane acquires excess phospholipids and cholesterol, leading to the formation of target-like and spiculated red cells.

Jandl devoted a large portion of his creative energy to studies of hematologic anemias. In a remarkably thorough and inventive series of studies, he explored the mechanism by which antibody-coated red cells are destroyed in the liver and spleen. He explored the use of radio-labeled erythrocytes to monitor cell survival and to identify sites of organ sequestration. Subsequently, he and his colleagues demonstrated that antibody-coated red cells attach to macrophages via the immunoglobulin FC receptor, forming flower-like rosettes. The macrophages nuzzle at the membrane of adherent red cells, transforming normal biconcave discs into spherocytes. This vivid morphologic observation provided an elegant explanation for the enhanced rosette formation of antibody-coated red cells, which contributes importantly to their destruction. In addition, he and his colleagues published definitive studies delineating the fate of free hemoglobin in the plasma and the process by which the kidney handles hemoglobin, as well as identifying organs of uptake.

Jandl made equally important contributions in other types of hematologic anemia. He and Harry Jacob showed increased cation leak and consequent high glucose consumption in red cells of patients with hereditary spherocytosis, providing a logical explanation for their demise in the unfriendly nutrient-depleted cots of the spleen. Jandl and Jacob also broadened our understanding of the nature of drug-induced oxidant hemolysis in individuals with glucose-6-phosphate dehydrogenase deficiency. Their experiments provided new insights into how oxidant stress can lead to denaturation of hemoglobin, resulting in the development of rigid inclusion-laden red cells. Jandl’s studies of red cell metabolism produced a coherent understanding of the mechanism by which deficiency in specific red cell enzymes, including pyruvate kinase, leads to a shortening of red cell lifespan.

These remarkably insightful and comprehensive studies of the hematologic anemias were accompanied, and perhaps trumped, by an equally thorough and groundbreaking investigation of the utilization of iron by erythroid cells. Jandl provided the first comprehensive understanding of the entry of iron into erythroid cells through iron transfers and its binding to specific receptors. He also developed the concept of the “iron transferrin cycle,” a process by which this iron-binding protein in the plasma efficiently transports a large amount of iron to the erythropoietic cells in the bone marrow sufficient to accommodate high-level hemoglobin production. These studies were among the very first to recognize the critical importance of receptors for specific biologic transport functions.

This brief summary of Jandl’s research accomplishments does not do justice to his stature and leadership in clinical investigation. His trainees learned that scientific truth is a very stern mistress, and that any presumption of discovery must pass the muster of rigorous self-criticism. To turn the English language, not only in his scholarly writing, but also in his lectures and in informal discussion. His remarkable effectiveness as a mentor came from a synergistic blend of these highly disciplined attributes with great personal modesty and an avuncular research style, stumpfend mentorial role model, one who attracted a legion of devoted disciples, among whom James Jandl was arguably primus inter pares.

2. Reminiscences of William Bosworth Castle (May 1953), on page 19 in a Columbia University Hospital History Office Collection.

James H. Jandl died on July 17, 2006, after a prolonged illness.
Was Mom Right About Eating Veggies? 

Fetal and Maternal Thrombophilia Genes Cooperate to Influence Pregnancy Outcomes

The Heart Outcomes Prevention Evaluation 2 (HOPE-2) trial was designed to evaluate the effect of lowering homocysteine on the development of arterial vascular disease. In this five-year study, a daily combination of folate, vitamin B12, and vitamin B6 was administered to 2,758 participants, while another 2,784 participants took matching placebos. In conjunction with this trial, separate analysis was done to determine whether decreasing plasma homocysteine levels reduced the occurrence of asymptomatic venous thromboembolic disease.

Of the 5,522 participants, 72 percent were from the United States and Canada where food is fortified with folate. Consequently, the mean plasma homocysteine level at entry into the trial was only 11.5 mmol/L. At the end of the trial, the mean homocysteine level decreased by 2.2 mmol/L in the treatment group and increased by 0.8 mmol/L in the control group. It is notable that in the treatment group, the mean homocysteine level decreased by 1.9 mmol/L in participants from regions with folate food fortification and decreased by 4.8 mmol/L in participants from regions that do not fortify food with folate. This suggests that patients in regions without folate-rich diets derive the most benefit from vitamin supplementation. Despite changes in plasma homocysteine levels, the treatment and the control groups had an identical number (44) of symptomatic venous thromboembolic events. Restricting the analysis to the 2,821 participants who had plasma homocysteine levels in the highest quartile (>13.8 mmol/L) still did not show a benefit for folate therapy.

Homocystinuria is a rare inborn error of metabolism associated with extremely high plasma homocysteine levels, premature cardiovascular disease, and developmental abnormalities of the ocular, skeletal, and nervous systems. Less significant elevation of plasma homocysteine is common and is not associated with developmental abnormalities. Analysis of patients and matched control subjects participating in the Leiden Thrombophilia Study suggested that plasma homocysteine levels above the 95th percentile in the control group (>18.5 mmol/L) is a risk factor for venous thrombosis. It is notable that there was a very high risk for thromboembolic events in participants with homocysteine levels greater than 22 mmol/L. Since modest elevations of plasma homocysteine to less than 18.0 mmol/L were not associated with any increased risk of thrombosis, data from the Leiden study suggested that there might be a threshold level when homocysteine may induce venous thrombosis.

The results of the HOPE-2 trial failed to demonstrate a benefit for homocysteine lowering therapy in the analyzed cohorts. Does this mean that homocysteine is never a risk factor for thromboembolic disease, and patients with hyperhomocysteinemia will not benefit from folate supplementation? The patients enrolled in the HOPE-2 study, as well as the patients enrolled in the recently published VITRO study9, were selected for their overall cardiovascular risk, not their baseline plasma homocysteine levels. Consequently, there were very few analyzed participants with plasma homocysteine levels above the critical threshold as proposed by the Leiden Thrombophilia Study group. Therefore, it is still unclear whether the risk of thromboembolic events in patients with very high plasma homocysteine levels would be reduced by a combination of folate, vitamin B6, and vitamin B12.

What does all this mean for mothers (and physicians) who recommend eating lots of veggies? First, it emphasizes that food in the United States and Canada that is fortified with folate has made significant hyperhomocysteinemia a rare occurrence in these countries. Second, patients with mild hyperhomocysteinemia do not benefit from therapy designed to reduce plasma homocysteine. Third, it is still unknown whether the exceptional patient with a plasma homocysteine level greater than 22 mmol/L would still benefit from folate therapy, and this demands further study. However, given the available data and the minimal toxicity of therapy, it appears that treatment for these select few is for now still a worthwhile endeavor.


ROY SILVERSTEIN, MD
Dr. Silverstein indicated no relevant conflicts of interest.
New Insights into the Role of DNA Damage and Repair in Age-Related Changes of Hematopoietic Stem Cells


Normal hematopoiesis and peripheral blood counts are maintained throughout life. However, observations in mice indicate that lymphopoiesis declines with age and hematopoietic stem cells (HSCs) undergo numerical and qualitative changes, including telomere shortening, accumulation of DNA double-strand breaks, increased frequencies of long-term reconstituting HSCs (LT-HSCs), and reduced ability to self-renew under the proliferative stress of multiple serial transplantations. To better understand the mechanisms responsible for these alterations, Nijnik et al. and Rossi et al. characterized HSC subpopulations from young and old mice with defects in DNA repair pathways. The mouse strain used by Nijnik et al. contains a hypomorphic mutation in DNA ligase IV (Lig4Y288C), which specifically impairs non-homologous end-joining (NHEJ) repair of DNA double-strand breaks and recapitulates many features of the human DNA ligase IV syndrome. The Rossi group studied three genetically engineered strains of mice deficient in NHEJ repair (“Ku80”), nucleotide excision repair (“XPD”), or telomere maintenance (late-generation [G5] mTR-). With aging, the absolute numbers of LT-HSCs, short-term HSCs, and multipotent progenitors in Lig4Y288C mice decreased significantly, in contrast to the stable cell numbers maintained in older wild-type (WT) control animals. Marrow cell counts and erythrocytoid cell percentages were also reduced in older compared with younger mutant mice. HSCs from Lig4Y288C mice competed poorly in co-transplantation models, and progenitor growth in cobblestone-area-forming cell cultures was greatly compromised. These changes were not due to defective Lig4Y288C marrow stromal cells or macrophages. Double-stranded DNA breaks were more frequent in progenitors from 18-week-old Lig4Y288C mice than from young WT controls. Rossi et al. found that the numbers of LT-HSCs in older Ku80- , XPD-, and G5 mTR- mice were equivalent to WT controls. However, diminished frequencies of multipotent and oligopotent progenitor populations were observed in an age-independent pattern. Serial transplantation and competitive repopulation experiments revealed severe, age-dependent deficits in the self-renewal and proliferative capacities of LT-HSCs from each of these mouse strains, thus was associated with increased apoptotic activity in cultured progenitors. Age-related increases in DNA damage were observed in normal mouse HSCs and early multipotent progenitors, with the greatest increases in the LT-HSC population, thus suggesting that the more primitive, quiescent stem cells are less efficient at repairing genomic damage and/or better able to tolerate unreparable lesions.

These studies indicate that DNA repair mechanisms and telomere maintenance are important for preserving the functional integrity of LT-HSCs during the accumulation of genomic damage with normal aging and under the stress of proliferation and reconstitution. They complement previous observations that DNA damage response mediators, including p16 INK4a, p53, and ATM, also modulate autonomous HSC functions with aging and that age-dependent telomere shortening can reduce the supportive function of marrow micro-environmental stromal cells. Since genes involved in myeloid and lymphoid leukemic transformation are upregulated in LT-HSCs from older mice and the greatest accumulation of age-related DNA damage occurs in LT-HSCs and primitive progenitors, it is possible that abnormalities in DNA repair pathways could predispose older stem cells to oncogenic mutations. Studies to define the roles of age-related DNA damage and repair in human HSCs are needed to determine whether these or similar mechanisms might be responsible, at least in part, for the significantly increased incidence of hematologic malignancies in elderly men and women.

How Sweet Is It?

Diabetes is the fifth leading cause of death by disease in the United States. Diabetes also contributes to higher rates of morbidity — people with diabetes are at higher risk for heart disease, blindness, kidney failure, extreme amputations, and other chronic conditions. Direct medical and indirect expenditures attributable to diabetes in 2002 were estimated at $132 billion. Attributable and indirect expenditures resulting from lost workdays, restricted activity days, mortality, and permanent disability due to diabetes totaled $39.8 billion. When adjusting for differences in age, sex, and race/ethnicity between the population with and without diabetes, people with diabetes had medical expenditures that were 2.4 times higher than expenditures that would be incurred by the same group in the absence of diabetes. Clearly, diabetes is a major health problem. There are two broad types of diabetes, type 1 and 2.

Type 1 diabetes mellitus (DM) is an autoimmune disease resulting from an immune-mediated cellular attack on the pancreatic beta cells, which produce insulin. The beta cells are destroyed and thus insulin is no longer produced. At the time of clinical diagnosis, approximately 60 percent to 80 percent of the beta-cell mass has been destroyed. Therefore, preservation of the beta cells is an important target in the management of type 1 DM and in the prevention of its related complications.

The authors report in this manuscript the conduct of a study to examine the effect of high-dose immunosuppression followed by autologous nonmyeloablative hematopoietic stem cell transplantation (AHST) to preserve beta-cell function in 15 patients with newly diagnosed type 1 DM. During a seven-to-36-month follow-up, 14 patients became insulin-free (one for 35 months, four for at least 21 months, seven for at least six months, and two with late response were insulin-free for one and five months, respectively). Among those, one patient resumed insulin use one year after AHST. The only severe adverse effects were pneumonia in one patient and endocrine dysfunction in two others. Ninety-three percent of patients achieved different periods of insulin independence, and treatment-related toxicity was low, with no mortality.

What happened here? There are extensive data demonstrating the success of utilizing allogeneic hematopoietic stem cell transplantation in animal models and data in humans that type 1 diabetes could be transferred to allogeneic recipients, as well as reversed in allogeneic recipients. This study, however, uses the patients’ own cells, and it is important to note that these cells were not selected, that is, no T-cell depletion of the graft (to remove the autoreactive T cells) as is being done for the national studies on scleroderma and lupus. Moreover, the patients were all young, without an excessive body mass index (BMI), and selected to be very early in the onset of their disease. They were all intensively immunosuppressed with anti-thymocyte globulin and a large dose of cyclophosphamide.

Will the hematopoietic cell transplant community be performing autologous rescue for diabetes? There are several caveats to the data presented. First and foremost is the known “honeymoon” period that many patients have in which patients have a relative remission after the onset of the disease. This period can be quite variable, and in this study, the potential spontaneous remission significantly confounds the results. The follow-up of the whole group is short and thus it is not known if there will be a lasting response. The authors concluded that continuing the immunosuppression might be beneficial for the patients, but one would predict that returning autologous immune cells back to the patient with the stem cell graft would return the autoreactive T cells as well, unless the preparatory regimen changed the presentation of autoimmunity. Finally, there is the possibility that there are “other cells” found in the marrow that could possibly repair the damaged pancreas. As the authors conclude, we will need a prospective randomized study to determine the utility of this approach.

This study is the first of what will be many different approaches of cellular therapy for diabetes and other autoimmune diseases. In addition to the use of hematopoietic cells, there is strong interest in regulatory T cells, umbilical cord cells, dendritic cells, mesenchymal cells, and embryonic cells, to name a few. Look more for the field of cellular therapy and regenerative medicine.
GVHD: Gene Profiling Comes of Age


Graft-versus-host disease (GVHD) continues to be the leading cause of non-relapse mortality following allogeneic stem cell transplantation. Although the underlying biology is a topic of intense investigation, what determines who will develop GVHD after matched allogeneic transplantation is not well understood. Although GVHD only develops if there are some mismatches in histocompatibility antigens between the donor and host, it does not inevitably develop. Until now, scientists have mainly investigated whether differences between AHCT recipients might explain this observation.

In this study, the researchers have examined the donors to see whether changes in their immune responses might make some donors stronger “responders” than others and consequently the likelihood of the recipient developing GVHD. They measured the gene-expression profiles of CD4 and CD8 T cells from 50 AHCT donors with microarrays. They noticed that gene-expression profiling segregates donors whose recipient suffered from GVHD. Using quantitative PCR, they confirmed that the differences were statistically significant. In addition, they found that for chronic GVHD, the “dangerous donor” trait (occurrence of GVHD in the recipient) is under polygenic control and is shaped by the activity of genes that regulate transforming growth factor-β signaling and cell proliferation. These findings strongly suggest that the donor gene-expression profile has a dominant influence on the expression of GVHD.

In microarray experiments, the donor-gene profile defined on day 0 showed exceedingly strong correlation with that of recipient CD4 and CD8 T cells harvested on day 365. For most genes tested by quantitative RT-PCR, differential gene expression between patients with chronic GVHD and those without was confirmed to be robust, on the basis of statistical analysis of multiple independent training-test datasets. They found that for chronic GVHD the “dangerous donor” trait (occurrence of GVHD in the recipient) is under polygenic control and is shaped by the activity of genes that regulate transforming growth factor-β signaling and cell proliferation. These findings strongly suggest that the donor gene-expression profile has a dominant influence on the expression of GVHD.

Prostaglandins Play a Role in Maintenance and Expansion of Hematopoietic Stem Cells


A chemical genetic screen for compounds affecting hematopoietic stem cell (HSC) survival/expansion has revealed that prostaglandin E2 (PGE2) promotes hematopoietic stem cell self-renewal and inhibits the activity of HSC-related drugs. Zebrabread were used because they 1) are transparent, allowing visualization of developing blood cells; 2) mature quickly with blood cells visualized within 1.5 days of fertilization; and 3) can be injected with blood, thus allowing compounds inhibiting HSC maintenance or differentiation to be assessed. The investigators previously showed that a line of flat-bottomed cells, a small cluster of hematopoietic cells can be visualized by probing for cells that co-express the zebrafish homologues of Runx1 (AML1) and cMyb. Zebrabread embryo were individually exposed to the compounds and HSC assessed by visualization of runx1+cMyb+ cells. Eighty compounds either increased or decreased HSC numbers, 10 of which will be used to further study the pathways. On closer analysis, chemicals enhancing PGE2 synthesis increased HSC numbers, and those blocking prostaglandin synthesis decreased stem cell numbers. Data were confirmed by functional analyses of zebrafish HSC. Similar data were obtained for murine HSC; PGE2 increased differentiation of murine embryonic stem cells, whereas prostaglandin inhibitors, such as aspirin or similar agents, are known to affect the prostaglandin pathway. On closer analysis, chemicals enhancing PGE2 synthesis increased HSC numbers, and those blocking prostaglandin synthesis decreased stem cell numbers. Data were confirmed by functional analyses of zebrafish HSC. Similar data were obtained for murine HSC; PGE2 increased differentiation of murine embryonic stem cells, whereas prostaglandin inhibitors, such as aspirin or similar agents, are known to affect the prostaglandin pathway.

PGE2 and prostaglandin synthesis inhibitors have been shown to affect hematopoiesis in human and mouse cells. Similar studies were reported previously; however, at that time, the data could not be interpreted because functional HSC assays were not yet well established. Addition of PGE to human bone marrow cells increased the number of CFU-GM and the proportion of cycling CFU-GM. It was proposed that PGE may have dual effects on hematopoiesis, limiting proliferation of CFU-GM at higher concentrations and promoting CFU-GM differentiation from earlier stem cell progenitors. In vivo studies, PGE enhanced proliferation of BFU-E and CFU-GEMM+. In vivo administration of PGE to mice resulted in a decrease in CFU-E, which, based on these new studies, could represent an effect on HSC self-renewal. The data reported by North and colleagues are very important as they suggest that BM expansion may be delayed by PGE2 inhibitors. Clinicians have routinely avoided prescribing NSAIDs or aspirin during engraftment or BM recovery due to the functional inhibition of already low numbers of platelets, and these new data suggest that specific cox2 inhibitors may need to be avoided as well. The data also suggest that stable effects of PGE2 or similar agents may enhance BM recovery following conventional-dose or high-dose chemotherapy. However, we need to take into consideration previous data showing that sustained administration of 16, 16 dimethyl PGE2 reduces restoration of hematopoiesis following cyclophosphamide administration. Additional studies are needed before we know for certain how to utilize the prostaglandin pathway for therapeutic manipulation of hematopoiesis.


Mantle Cell Lymphoma: Quantifying Prognosis


Mantle cell lymphoma (MCL) is clinically heterogeneous; some patients demonstrate a chronic indolent course over several years, whereas others experience earlier progression and short survival. In order to better refine prognostic markers, Kienle and colleagues analyzed archival MCL samples obtained at the time of diagnosis by real-time quantitative reverse transcriptase PCR, targeting 20 genes previously associated with MCL pathology and prognosis. Although lymph node (n=65) and peripheral blood (n=13) samples were similar for overall tumor cell content, differing gene expression profiles were noted between these compartments, and correlative analyses were restricted to the lymph node cohort. CCND1, the gene encoding the hallmark MCL cyclin D1 protein, was verified to produce either a short or long variant transcript due to length of the untranslated region. Those patients with the short form [n=8] had higher CCND1 expression levels, higher proliferative rates, and a median survival of only 8.4 months, versus 45.1 month median survival for patients with the long variant. Immunosuppressing with Ki-67, a marker of proliferation, or stratifying patients into low- and high-risk groups. Those with more than 40 percent positive cells had a median survival of 17 months, versus 52.5 months for those with a lower percent positivity. Increased CCND1 expression levels and the short variant CCND1 correlated positively with Ki-67 index, whereas low expression of staxia telangiectasia gene (ATRX) and an antiapoptosis gene (MCL1), among others, had a negative correlation. In a multi-variate analysis of clinical and molecular parameters with decreased patient survival, significant positive correlations were found for Ki-67 protein expression, the presence of B symptoms, and gene expression of MYC, MDM2, EZH2, and CCND1.

MCL is among the most challenging subtypes of lymphoma, with no curative standard therapy approach yet identified. Molecular classification, however, reason for optimism that improved outcomes may be realized through novel agents now in clinical trials and by individualization of therapy based on molecular and proteotypic biomarkers. The present report verifies and extends earlier correlative work that defined markers of MCL pathology and prognosis; however, as noted by the authors, implicates the relevance of “gene dosage” for proliferation — promoting genes, proliferation inhibitors, and regulators of apoptosis. Although complex to orchestrate within prospective clinical trials, biomarker and bioinformatic analyses hold considerable promise for individualization of treatment and improved outcomes. Close collaboration between clinical and laboratory scientists in the design and conduct of therapeutic trials, and in prioritizing clinical studies of novel targeted therapies, will be critical to this process.
Is Transplantation for CML Dead?


Chronic myeloid leukemia (CML) is hardly a public health menace, yet it embodies the “bend to bedside” mantra that drives translational medicine. The discovery of the Philadelphia chromosome, the juxtaposition of the BCR and ABL genes to form the b(9;22), fostered understanding of aberrant signal transduction, targets for minimal residual disease monitoring by PCR, and ultimately “targeted” therapy by tyrosine kinase inhibitors (for example, imatinib). Prior to the advent of imatinib, biologic therapy with interferon was shown to lengthen the natural history of CML, and was deemed to be appropriate therapy for patients without an allogeneic transplant option. Transplantation has been considered a “-curative” therapy for CML, but not without the trade-off of considerable morbidity and mortality.

How to treat newly diagnosed chronic phase CML has changed dramatically with imatinib:

- Imatinib is remarkably effective for patients treated in chronic phase, as greater than 75 percent of patients obtain a complete cytogenetic remission (CCyR). In the IRIS trial, approximately 70 percent of cases remain in a CCyR at five years of follow-up. Treatment of advanced phase (accelerated blast disease) is associated with much poorer outcomes.
- Allogeneic transplantation is generally associated with 10-year survivals of 70 percent or better for patients in chronic phase, but survival likewise falls in accelerated or blast-phase disease.
- Relapse occurs for chronic-phase patients treated with imatinib, but outcome can be effectively monitored by sensitive RT-PCR assays.

Current recommendations from advisory panels, such as the European Leukemia Net and the National Cancer Care Alliance, state that all chronic phase patients start on imatinib therapy, but allow for consideration of transplantation based on the patient’s age, preference, and response to initial imatinib. The tacit assumption is that, given the excellent results of both imatinib and transplantation, a contemporary randomized trial comparing the methods would be very unlikely. This trial looked at 621 patients with chronic phase CML: of these, 354 were considered eligible for transplantation and "biologically randomized" based on the availability of a related donor. Of the 123 patients who received a transplant, the 10-year estimate of survival was 53 percent. Those 219 patients without a related donor who were treated with interferon until imatinib became available later in the trial. Imatinib was then offered to patients whose disease did not respond to interferon. The 10-year estimate of survival in this group was 52 percent. The survival curves of these two groups are shown in the figure above and show the not-surprising results: the transplant group suffers a higher early mortality, with a relative flattening of the survival curves, whereas group 2 has a better early outcome, with the survival curves continuing to drop. The cross-over of the curves comes at eight years. A statistical analysis showed that the survival rate of group 2 was significantly superior (though marginally, with a p=0.049). The authors conclude that transplantation can no longer be recommended as first-line therapy.

The undertaking of such a study is Herculean, but the conclusions deserve some scrutiny. First, the survival experience for group 2 was a blend of those who received interferon and (in some cases) imatinib, and those cases that went on to an unrelated transplant when a donor became available. The survival of those 122 patients in group 2 who only received interferon/imatinib was 50 percent; of the 97 patients who went on to receive an unrelated transplant, 65 percent survived. Moreover, it may be hard to translate this study to contemporary practice. Given the remarkable success of imatinib as first-line therapy, it would be expected that the survival curves for patients treated with transplantation would be superior to that of the interferon/imatinib group in this study. In addition, most transplant centers would be disappointed with the survival statistics in the transplant arm of this study of long-term outcomes (~50 percent).

Other studies have attempted to address the issue of up-front imatinib versus transplantation. One such study examined published survival data for patients who received a transplant and imatinib, modeling survival and life expectancy based on age, gender, and treatment strategies. In most models, survival and life expectancy worsen in the newly diagnosed chronic phase cases that initially received imatinib was superior compared with patients who initially received a transplant. The superiority of imatinib was greatest under the conditions of the low progression rate, older age, comparison of the CIBMTR transplant experience, and unrelated donor transplants. Transplantation appeared to be similar or somewhat superior to imatinib when one assumed better transplant outcomes, younger patient age, and higher imatinib relapse rates.

So, is transplantation for CML dead? Probably not. Given the ability to monitor imatinib response by sensitive RT-PCR techniques and mutation analysis, and the suggestion that prior imatinib therapy does not compromise later transplant results, it is reasonable to start most patients who have chronic-phase CML on imatinib, with consideration for transplantation for those candidates with sub-optimal or lost response. Waiting for frank progression to advanced-stage disease to move to transplantation is a strategy that may reduce the potential for cure and should be reserved for patients at high risk for transplant-related complications, whether they are from age or other health complications.


HEMATOLOGIST: ASH NEWS AND REPORTS

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Dr. Radich indicated no relevant conflicts of interest.
**Blood Public Access Policy Expanded to Include HHMI-Funded Authors**

Joel Anne Chasis, MD, and Eleonora Tapascott

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Ms. Tapascott is the Director of Publishing at ASH.

SH recently reached an agreement with Howard Hughes Medical Institute (HHMI) to extend Blood’s Open Access option to HHMI-funded scientists. Blood’s Open Access option, recommended by ASH’s Journals Committee in July 2006 and approved by the Executive Committee, allows authors the option of having their articles deposited into PubMed Central immediately after publication in exchange for an open access fee. This option was developed as a strategy to accommodate public access requirements of funding groups, such as Wellcome Trust, and now HHMI, allowing articles in the journal’s 12-month embargo policy. As with all other open access options available through the journal, Blood will deposit the article into PubMed Central on the authors’ behalf, thereby removing the burden from authors to submit their articles.

HHMI’s new public access policy, which will go into effect January 2008, requires its scientists to publish their research and supplementary materials in journals that allow free access to the content in a public repository, such as PubMed Central, within six months of publication. The ASH Open Access option therefore exceeds the HHMI requirement by making the article immediately available, rather than at six months.

In line with Blood’s current business model, the journal’s 12-month publication embargo restricts non-subscribers’ access to an issue until 12 months after publication. However, in each new issue, five research articles and all Inside Hematology commentaries are immediately available to the public. Twelve months post-publication, all of an issue’s content is available to the public. Currently, more than 95 percent of Blood’s content is available to the public with no restrictions; it is free to the public.

Blood’s Open Access option for HHMI and Wellcome Trust works in conjunction with its publication in another public repository: the NIH-funded Archive Program. To date, Blood has deposited more than 600 articles and all are linked to PubMed Central through their PubMed citations as well. These public access strategies—including allowing authors to post copies of their articles on the author’s personal Web site, department Web site, and/or institutional intranet—emphasize ASH’s commitment to broad dissemination of content through processes that protect the integrity of the journal article of record and relieve authors from the burden of submitting manuscripts to various repositories while maintaining a sound business model for Blood.

The Open Access option will be available to HHMI authors on Blood’s online manuscript submission system effective October 1, 2007, well ahead of the HHMI deadline of January 1, 2008. Accordingly, HHMI will identify Blood as one of the journals that is compliant with its new, mandated public access policy.

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**Blood Now Scanning All Accepted Papers for Inappropriate Image Manipulation**

With the availability and sophistication of image-processing software, authors are frequently unaware of what is a common practice: it is unacceptable in a scholarly journal. Anecdotally, frequent case of the paper published in Science by Hwang et al. brought this issue to the attention of both the scientific community and the lay public. Blood, which started to screen some of the accepted papers in 2006 and now extends its policy to include all accepted papers, is among the first scientific journals enforcing new standards of what is permissible in image manipulation and digital image editing.

In his recent Editorial, Blood’s Editor-in-Chief, Dr. Sanford Shattil, defined the new policy in these words: “Our major goals are to educate our authors and readership about acceptable practices in preparing digital images for publication and to eliminate improperly processed images from our pages. While these are but two of many important goals of Blood’s editorial and publishing staff, we aim to make the digital images that we publish as pure and as eloquent as blood itself.”

From the pilot study in the fall of 2006 we learned that about 20 percent of the scanned papers contained at least one image that required further clarification from the authors. These preliminary results prompted the ASH Journals Committee to recommend incorporating image scanning into the Blood workflow and extending it to all accepted papers. The new process was fully implemented in June 2007.

Before implementation of the image scanning, it was necessary to make significant software changes to the Blood Bench>Press manuscript submission and tracking system. Blood is the first among more than 50 journals using Bench>Press to develop such a system.

The image scan is performed on accepted papers containing gels and/or micrographs; papers are not prepubished in First Edition or sent for production until all images pass inspection.

The editorial staff scans high-resolution images using Photoshop and contacts the author when signs of possible inappropriate image editing are found. Authors may be asked to explain discrepancies in the image background and/or supply the original experimental images for comparison. They may also be asked to alter an image and the corresponding legend in the interest of full transparency or to provide the original films for further evaluation. The final decision is in the hands of the Editor-in-Chief.

In addition to the introduction of the physical image scan, Blood has published a set of more detailed guidelines [http://Bloodjournal.hematologylibrary.org/authors/authorguide.php#man pussy under “Working with gels and micrographs”] for authors online; since then, the numbers of images rejected by the journal and the Editor as not compliant with appropriate image manipulation have decreased significantly. We expect that as our authors become more familiar with the requirements, the number of images that pass the image scan will increase.

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**IC-APL Members Report Outstanding Progress at EHA Meeting**

NANCY BERLINER, MD

Dr. Berliner is Chief of Hematology at Brigham and Women’s Hospital. She is also Vice President of ASH.

Members of the International Consortium on Acute Promyelocytic Leukemia (IC-APL) gathered in Vienna prior to the 2007 European Hematology Association (EHA) meeting to present an update on HHMI-fund researchers’ progress in developing a treatment for the disease and the role of the ASH umbrella, the IC-APL, in facilitating interactions between clinicians and researchers in developing countries, with the long-term goals of improving clinical care and creating the infrastructure for ongoing clinical trials and translational research in APL. APL was chosen as a model disease because of its prevalence in Latin America and the rapid progress that is being made in understanding its pathogenesis and in optimizing its therapy.

Representatives from the programs in Brazil, Mexico, and Uruguay reported on their progress at the meeting. Treatment has started at two centers under the auspices of clinical guidelines outlining standard of APL care developed by a subcommittee of the IC-APL. Brazil reported treatment results on its first 10 patients. Uruguay, who joined the project in December 2006, reported progress toward a national IRB approval to allow the accrual to start at several health centers.

Both the clinical results and the progress toward an interactive infrastructure supporting future research work were impressive. Clinical outcomes rival those in large clinical trials in developed countries, with a complete remission (CR) rate of 90 percent, with most patients in CR having evidence of molecular remission. (It is important to note that until a relapse treatment protocol is reported on their first 10 patients. Uruguay, who joined the project in December 2006, reported progress toward a national IRB approval to allow the accrual to start at several health centers.

Perhaps more impressive, the IC-APL has given rise to unprecedented cooperation between disparate centers in the respective countries, integrated through the active collaboration of St. Jude Children’s Research Hospital.

All centers are actively using the Pediatric Oncology Network Database (POND) and the Cure4Kids program for data management. Participants within each country and between countries have frequent teleconferences and regular face-to-face meetings to facilitate collaboration. The data manager from Uruguay has traveled to Sao Paulo, Brazil, to be trained in these programs. Although supported partly by ASH and partly by a grant from the Veronesi Foundation, much of the activity is being funded from local and national sources within the participating countries.

Discussion of future efforts focused on clinical modifications addressing the high incidence of ATRA syndrome and practical concerns about sample acquisition for central testing of coagulation parameters, as well as potential collaborative clinical-tranlational trials being initiated independently of the IC-APL umbrella.

In addition, several other countries are under consideration for inclusion in the IC-APL, and proposals from these countries will be discussed further at the December meeting prior to the ASH annual meeting.

The data presented at the meeting engendered great enthusiasm and energy. All of the leaders of the individual programs reported that the association with ASH in these activities has jumpstarted the high level of collaboration and interaction inherent in the IC-APL, and they are eager to continue to move things forward. The success of this venture is one in which the IC-APL should take considerable pride: the IC-APL provides a model for promoting the excellence of hematologic care and extending research.
Hematology Research at the NIDDK

(Cont. from Page 4)

We will also maximize our investments by supporting cross-cutting science that is broadly applicable to many disease-specific research issues. Examples of this research include identification of biomarkers and enabling technologies that can aid in the diagnosis of disease and in the assessment of new treatments in clinical trials. We will also support the development of cell-based therapeutic approaches for repairing damaged tissues. For example, insights gained from NIDDK-sponsored research on the regulation of fetal and adult globin gene expression in red blood cell precursors have provided a basis for the development of molecularly targeted agents. Successful development of such gene-targeting agents offers great promise for effective treatment of genetic diseases of hemoglobin, such as thalassemia and sickle cell disease. We will also continue to use cutting-edge research methods, such as high throughput analysis, for identification of biomarkers and enabling technologies that can aid in the diagnosis of disease and in the assessment of new treatments in clinical trials. We are continuing efforts to ensure that the science-based knowledge gained from NIDDK-funded research is imparted to health-care providers and the public for the direct benefit of patients and their families. For example, the NIDDK’s Hematopoietic Cell Lineage Genome Anatomy Projects were charged with developing protocols and reagents for characterizing cells in the hematopoietic stem cell lineage and their gene expression patterns using advanced technologies and bioinformatic techniques. The objective of the program was to create a nucleus for hematology research and promote the application of stem cell research to hematologic diseases and other health conditions.

We are encouraging minority investigators to apply for all of our research-training and career-development awards and support a Network of Minority Research Investigators to further their long-term academic research careers.

Promising postdoctoral fellows and junior faculty are encouraged to apply for one of the career-development awards supported by NIDDK for demonstrating awards for physician scientists, research scientists, patient-oriented researchers, and individuals wishing to pursue a career in quantitative research. Mid-career, patient-oriented investigators are encouraged to continue their mentoring activities and focus on their clinical research.

In addition, we encourage minority investigators to apply for all of our research-training and career-development awards and support a Network of Minority Research Investigators to further their long-term academic research careers.

Foster Exceptional Research Training and Mentoring Opportunities.

Maintaining an NIDDK-focused pipeline of outstanding investigators is critically important to our research progress against disease. We offer programs for individuals who are at different stages in their careers — ranging from those who have already attained advanced degrees to those who are very early in their educational development.

The National Research Service Award program of individual and institutional awards plays a critical role in fostering exposure to research environments and a commitment to a research career among individuals with doctoral degrees, medical degrees, or both. It also provides support for predoctoral fellows on institutional awards and for individual predoctoral students through the diversity fellowship program.

As a disease-focused Institute, the NIDDK needs to ensure a cadre of well-trained, subspecialty physician scientists. Special encouragement is given to individuals with medical degrees, and to medical students, to consider an academic research career. For example, the NIDDK provides short-term summer research training experiences through NIDDK-sponsored institutional awards. Another avenue is a program that provides support for a few medical students to take a one-year leave of absence from their studies to pursue a more in-depth research-training experience.

Ensure Knowledge Dissemination Through Outreach and Communications. We are continuing efforts to ensure that the science-based knowledge gained from NIDDK-funded research is imparted to health-care providers and the public for the direct benefit of patients and their families. For example, the NIDDK’s Hematopoietic Cell Lineage Genome Anatomy Projects were charged with developing protocols and reagents for characterizing cells in the hematopoietic stem cell lineage and their gene expression patterns using advanced technologies and bioinformatic techniques. The objective of the program was to create a nucleus for hematology research and promote the application of stem cell research to hematologic diseases and other health conditions.

Other examples are the Centers of Excellence in Molecular Hematology. The objective of these Core Centers is to bring together investigators from relevant disciplines to enhance and extend the effectiveness of research related to hematologic diseases and their complications. Clinical and basic science investigators are brought together in a manner that will enrich the effectiveness of hematologic diseases research. Each Core Center has a central focus of research investigation that is related to a hematologic research emphasis of the NIDDK.

Importantly, as we plan for the future, we will continue to seek and value external advice from investigators, professional scientific organizations, patient advocates, and the public. Key sources of input will continue to be our National Advisory Council, strategic planning processes, ad hoc planning groups, and scientific conferences and workshops. The Hematology Interagency Coordinating Committee provides a valuable forum to solicit stakeholder input regarding the setting of priorities and the planning of research goals. This input will provide a useful scientific guidepost as we make resource allocation decisions. Active collaboration with other components of the NIH and other federal agencies will also remain a cornerstone of NIDDK planning efforts. We will continue to seek and value such planning processes as we move forward.

Ever-increasing knowledge and the advent of new technologies bring new scientific opportunities for alleviating and conquering the many chronic diseases within the NIDDK’s mission. The continued goal will be to seize and maximize these opportunities to reduce the burden of disease and improve the public health. I look forward to working with the NIDDK’s many stakeholders in the hematology community now and in the future.
The ASH™ Web site offers a convenient way for ASH members to find information relating to upcoming Society events and provides easy access to the many valuable products and services offered by ASH. At www.hematology.org you can:

Check out the FDA DRUG ANNOUNCEMENTS (www.hematology.org/policy/resources/fda/index.cfm). The ASH Web site includes an archive of the FDA announcements about newly approved therapies for patients that are sent to members by e-mail. A link to the product label, which will provide the relevant clinical information on the indication, contraindications, dosing, and safety, is included in the announcement from the FDA.

Learn about PIMS (www.hematology.org/education/recertification/pims.cfm). Practice Improvement Modules (PIMs) are Web-based self-evaluation tools that guide board-certified physicians through chart abstractions and a practice system inventory to establish a robust multi-dimensional performance assessment for a chronic condition or preventive service. They can assist with Maintenance of Certification requirements.

Explore the ASH TEACHING CASES (www.hematology.org/education/teach_case/). These interactive cases, intended for medical students and hematology instructors, are designed to simulate the steps involved in diagnosing a patient, from taking the history and performing a physical exam, to ordering and interpreting lab tests, to making a final diagnosis and following the clinical course of the disease.

Browse the TRAINEE GRANTS CLEARINGHOUSE (www.hematology.org/education/training/grants_clearinghouse.cfm). This is an extensive list of hematology grant opportunities to aid trainees in their search for grant information. The list is updated bi-annually by the ASH Trainee Council at their April and December meetings.

Read THE HEMATOLOGIST ONLINE (www.hematology.org/publications/hematologist) and catch up on the latest news in the field of hematology right on your desktop.