Peripheral blood smear from a patient with chronic myelomonocytic leukemia. This illustration is taken from the perspective article by Reiter and co-workers on page 1634.

**Editorials and Perspectives**

**1631** Serum hepcidin: a novel diagnostic tool in disorders of iron metabolism
Gaetano Bergamaschi and Laura Villani

During the last few years new methods for the measurement of hepcidin concentration have been developed. In this perspective article, Drs. Bergamaschi and Villani examine the potential clinical usefulness of serum hepcidin determination. See related paper on page 1748.

**1634** Molecular basis of myelodysplastic/myeloproliferative neoplasms
Andreas Reiter, Rosangela Invernizzi, Nicholas C.P. Cross, and Mario Cazzola

The World Health Organization classification of tumors of hematopoietic and lymphoid tissues includes within myeloid neoplasms the category myelodysplastic/myeloproliferative neoplasms. In this perspective article Drs. Reiter, Invernizzi, Cross and Cazzola discuss our present knowledge of the molecular basis of these disorders. See related paper on page 1676.

**1639** New flow cytometry in hematological malignancies
Jan Cools and Peter Vandenberghe

The complex and heterogeneous biology of acute lymphoblastic leukemia is unfolding as more experimental approaches such as expression profiling, DNA sequencing, and high resolution genomic arrays continue to unveil new recurrent alterations. In this perspective article, Drs. Cools and Vandenberghe examine new diagnostic applications of flow cytometry. See related paper on page 1767.

**1641** The significance of monoclonal gammopathy of undetermined significance
Robert A. Kyle and Shaji Kumar

Since it is now well established that all patients with multiple myeloma have a preceding monoclonal gammopathy of undetermined significance (MGUS), identification of potential risk factors for the progression becomes most important. In this perspective article, Drs. Kyle and Kumar highlight the need for a better understanding of the etiology and biology of MGUS. See related paper on page 1714.

**Original Articles**

**Hematopoietic Stem Cells**

**1649** Generation of mesenchymal stromal cells in the presence of platelet lysate: a phenotypic and functional comparison of umbilical cord blood- and bone marrow-derived progenitors
Maria Antonietta Avanzini, Maria Ester Bernardo, Angela Maria Cometa, Cesare Perotti, Nadia Zaffaroni, Francesca Novara, Livia Visai, Antonia Moretta, Claudia Del Fante, Raffaella Villa, Lynne M. Ball, Willem E. Fibbe, Rita Maccario, and Franco Locatelli

Umbilical cord blood is an attractive source of stem cells for several cell-based therapies. In this paper, it is shown that umbilical cord blood-derived mesenchymal stroma cells, cultured in the presence of platelet lysate, have an increased proliferative potential but comparable immunomodulatory functions relative to their bone marrow-derived counterparts.

**Aplastic Anemia**

**1661** Granulocyte transfusions in severe aplastic anemia: an eleven-year experience
Karen Quillen, Edward Wong, Phillip Scheinberg, Neal S. Young, Thomas J. Walsh, Colin O. Wu, and Susan F. Leitman

Although they have been used for over 40 years, the value of granulocyte transfusions is controversial. This paper reviews outcomes in patients with severe aplastic anemia given such transfusions at the NIH. See related perspective article on page 1644.

**Chronic Myeloid Leukemia**

**1669** High rates of durable response are achieved with imatinib after treatment with interferon α plus cytarabine: results from the International Randomized Study of Interferon and STI571 (IRIS) trial

Imatinib is the standard of care for patients with newly diagnosed chronic-phase chronic myeloid leukemia. This is the largest analysis to date describing the efficacy of imatinib in patients who have received prior therapies for chronic myeloid leukemia and it demonstrates excellent responses to imatinib in this context.
1676 Myelodysplastic/Myeloproliferative Neoplasms

TET2 gene mutation is a frequent and adverse event in chronic myelomonocytic leukemia
Oliver Kesmider, Véronique Gelsi-Boyer, Marion Ciudad, Cindy Racouër Valérie Jooste, Norbert Vey, Bruno Quenel, Pierre Fenaux, Jean-Noël Bastie, Odile Beyne-Rauzy, Aspasia Stamatoulas, François Dreyfus, Norbert Ifrah, Stéphane de Botton, William Vainchenker, Oliver A. Bernard, Daniel Birnbaum, Michéla Fontenay, and Eric Solary on behalf of the Groupe Francophone des Myéloïdysplasies

Acquired somatic deletions and loss-of-function mutations in one or several codons of the TET2 (Ten-Eleven Translocation-2) gene were recently identified in hematopoietic cells from patients with myeloid neoplasms. This study shows that TET2 mutations are more frequent in chronic myelomonocytic leukemia than in other subgroups of myeloid neoplasms studied so far.

1682 Pediatric Leukemias

Clinical characteristics and outcome of children with biphenotypic acute leukemia
Amal S. Al-Seraihy, Tarek M. Owaidah, Mouhab Ayas, Hassan El-Solh, Mohammed Al-Mahr, Ali Al-Ahmari, and Asim F. Belgaumi

This study from Saudi Arabia found that 4% of 633 cases of pediatric acute leukemia were biphenotypic. The authors describe the clinical features of these patients and their response to treatment including stem cell transplantation.

1691 Malignant Lymphomas

Sperm quality before treatment in patients with early stage Hodgkin’s lymphoma enrolled in EORTC-GELA Lymphoma Group trials
Marleen A. van Echten-Arends, John M.M. Raemaekers, Caroline Bonmati, Michel Henry-Amar, José Thomas, Houchingue Eghbali, Pauline Brice, Caroline Bouman, Michel Henry-Amar, and Hanneke C. Kluin-Nelemans

Although widely recommended, cryopreservation of sperm is sometimes not performed for patients with Hodgkin’s lymphoma because of presumed poor sperm quality related to the disease. In this large study of males with Hodgkin’s lymphoma, 90% had good or intermediate sperm quality, indicating that in most patients with early-stage Hodgkin’s lymphoma sperm quality before treatment is good enough for future fatherhood.

1698 Chronic Lymphocytic Leukemia

Akt inhibitors induce apoptosis in chronic lymphocytic leukemia cells
Merce de Frias, Daniel Iglesias-Serret, Ana M. Costalís, Loren; Coll-Mulets, Antonio F. Santidrián, Diana M. González-Gironés, Esmeralda de la Banda, Gabriel Pons, and Joan Gil

Chronic lymphocytic leukemia (CLL) is now divisible into subsets with distinct clinical behaviors. The biology underlying these differences appears to include signaling pathways through the B-cell receptor and other receptors. The phosphatidylinositol-3-kinase/Akt pathway is important, raising the possibility that inhibitors could have therapeutic potential. Encouragingly, two inhibitors were found to induce preferential apoptosis of CLL cells, irrespective of TP53 status, with increases in NOXA and PUMA protein levels and a decrease in MCL-1.

1708 Monoclonal Gammopathies

Timing of acquisition of deletion 13 in plasma cell dyscrasias is dependent on genetic context
Laura Chieccio, Gian Paolo Dagdrada, Ashraf H. Ibrahim, Elizabet Dachs Cabanas, Rebecca K.M. Protheroe, David M. Stockley, Kim H. Orchard, Nicholas C.P. Cross, Christine J. Harrison, and Fiona M. Ross, on behalf of the UK Myeloma Forum

Monoclonal gammapathy of undetermined significance (MGUS) and smoldering myeloma (SMM) are characterized by an expansion of monoclonal plasma cells and can progress to symptomatic multiple myeloma. This study assessed the incidence and the association of monosomy 13 with IgH translocations, pancytopenia and deletions of 16q23 and TP53 in a large series of MGUS and SMM patients.

1714 Monoclonal Gammopathies

Patterns of survival and causes of death following a diagnosis of monoclonal gammapathy of undetermined significance: a population-based study
Sigurdur Y. Kristinsson, Magnus Björkhöhn, Therese M-L Andersson, Sandra Eloranta, Paul W. Dickman, Lynn R. Goldin, Cecilie Blimark, Ulf-Henrik Mellqvist, Anders Wahlin, Ingemar Turesson, and Ola Lundgren

There are limited data on survival patterns among patients with monoclonal gammapathy of undetermined significance (MGUS). In a study of 4,259 MGUS patients, the authors found that individuals diagnosed with MGUS in a clinical setting had a significantly reduced life expectancy. See related perspective article on page 1641.

1721 Blood Coagulation

Species-specific anticoagulant and mitogenic activities of murine protein S
José A. Fernández, Mary-J. Heeb, Xiao Xu, Itender Singh, Berislav Zlokovic, and John H. Griffin

Mice and other animals have proved extremely useful testing grounds for hypotheses and for potential therapies. However, significant interspecies differences can confound correct interpretation and attempts to extrapolate results to man. In this study Fernández and co-workers demonstrate that the human and murine protein C-protein S systems function in a similar way but do not interact efficiently with one another.
Aplastic anemia

1732 Unrelated donor stem cell transplantation in acquired severe aplastic anemia: a systematic review
Frank Peinemann, Ulrich Grouven, Nicolaus Kröger, Max Pittler, Beate Zschorlich, and Stefan Lange

Acquired severe aplastic anemia is a rare disease characterized by an immune-mediated functional impairment of hematopoietic stem cells. Transplantation of these cells from unrelated donors is a treatment option frequently offered to patients after failed immunosuppressive therapy. This systematic review indicates that unrelated donor hematopoietic stem cell transplantation in patients with acquired severe aplastic anemia after failure of immunosuppressive therapy is a valid treatment option.

Bone Marrow Failure

1743 Changes in cytokine profile pre- and post-immunosuppression in acquired aplastic anemia
Carlo Dufour, Elisa Ferretti, Francesca Bagnasco, Oriana Burlando, Marina Lanciotti, Ugo Ramenghi, Paola Saracco, Maria Teresa Van Lint, Daniela Longoni, Giovanni Fernando Torelli, Marta Pilon, Anna Locasciulli, Aldo Misuraca, Milena La Spina, Andrea Bacigalupo, Vito Pistoia, Anna Corcione, and Johanna Svahn on behalf of the Marrow Failure Study Group of the AIEOP

Some patients with aplastic anemia respond to immunosuppressive therapy. Here the authors compare pre and post-immunosuppressive therapy levels of CD3/interferon-γ secreting cells in responders and non-responders.

Disorders of Iron Metabolism

1758 Results of the first international round robin for the quantification of urinary and plasma hepcidin assays: need for standardization

This study indicates that hepcidin levels reported by various methods vary considerably but analytical variance is generally low and similar for all methods. See related perspective article on page 1631.

Red Cell Disorders

1762 β-spectrinBari: a truncated β-chain responsible for dominant hereditary spherocytosis
Silverio Perrotta, Fulvio Della Ragione, Francesca Rossi, Rosa Anna Avvisati, Daniela Di Pinto, Giovanna De Mieri, Saverio Scanguglia, Silvia Mancusi, Luigia De Falco, Vito Marano, and Achille Iolascon

This report describes a β-spectrin variant, named β-spectrinBari, characterized by a truncated chain and associated with hereditary spherocytosis.

Chronic Myeloid Leukemia

1767 An accurate and rapid flow cytometric diagnosis of BCR/ABL positive acute lymphoblastic leukemia
Sara Raponi, Mariya Stefania De Propis, Hobert Wai, Stefania Intoppa, Loredana Elia, Daniela Diverio, Antonella Vitale, Robin Foà, and Anna Guarini

This report describes an accurate and rapid flow cytometric diagnosis of BCR/ABL positive acute lymphoblastic leukemia. See related perspective article on page 1639.
Gaucher Disease
Real-world clinical experience with long-term miglustat maintenance therapy in type 1 Gaucher disease: the ZAGAL project
Pilar Giraldo, Pilar Alfonso, Koldo Atutxa, María A. Fernández-Galán, Abelardo Barea, Rafael Franco, Dora Alonso, Alejandro Martín, Paz Latre, and Miguel Pocovi

There are few published data from real-world clinical experience with miglustat, an oral inhibitor of glucosylceramide synthase, in type 1 Gaucher disease. This study suggests that miglustat is an effective therapy for the long-term maintenance of patients with type 1 Gaucher disease previously stabilized with enzyme replacement therapy.

Letters to the Editor

Iron Overload
Early cardiac iron overload in children with transfusion-dependent anemias
Juliano Lara Fernandes, Antonio Fabron Jr, and Monica Verissimo

Thalassemia Syndromes
Improved survival in thalassemia major patients on switching from desferrioxamine to combined chelation therapy with desferrioxamine and deferiprone
Paul T. Telfer, Fiona Warburton, Soteroula Christou, Michael Hadjigavriel, Maria Sitarou, Anita Kolnagou, and Michael Angastiniotis

Acute Leukemia
What is the optimal treatment for biphenotypic acute leukemia? Authors’ reply
Jianmin Wang, and Xiaojian Xu

The targeting of the sole cyclin D1 is not adequate for mantle cell lymphoma and myeloma therapies
Guergana Tchakarska, Anne Le Lan-Leguen, Lucile Roth, and Brigitte Sola

Platelets
The GPIIbIIIa antagonist drugs eptifibatide and tirofiban do not induce activation of apoptosis executioner caspase-3 in resting platelets but inhibit caspase-3 activation in platelets stimulated with thrombin or calcium ionophore A23187
Valery Leytin, Asimuan Mutlu, Sergiy Mykhaylov, David J. Allen, Armen V. Gyulkhandanyan, and John Freedman

Continuing Medical Education

Biphenotypic acute leukemia in children

The implications of a diagnosis of monoclonal gammopathy of undetermined significance

TET2 gene mutations in chronic myelomonocytic leukemia

Granulocyte transfusions in severe aplastic anemia