Cover Figure
Platelet adhesion to immobilized human fibrinogen. This illustration is taken from the original article by Gresele et al. on page 663.

Editorials and Perspectives

599 Close to unraveling the secrets of congenital dyserythropoietic anemia types I and II
Achille Iolascon, and Jean Delaunay
The congenital dyserythropoietic anemias are rare recessive disorders characterized by erythroblast multinuclearity, ineffective erythropoiesis, anemia and iron overload. In this perspective article, Drs. Iolascon and Delaunay examine genetic and clinical aspects of these inherited disorders. See related paper on page 659.

602 Clinical relevance of extra-hematologic comorbidity in the management of patients with myelodysplastic syndrome
Matteo Giovanni Della Porta, and Luca Malcovati
Myelodysplastic syndromes occur mainly in older persons, and such subjects are likely to have comorbidities that significantly worsen their survival. In this perspective article, Drs. Della Porta and Malcovati examine the relevance of comorbidities for clinical decision making in patients with myelodysplastic syndromes. See related paper on page 729.

606 The molecular basis of familial chronic lymphocytic leukemia
Dalemari Crowther-Swanepoel, and Richard S. Houlston
The genetic basis of chronic lymphocytic leukemia is only just beginning to be understood. This perspective article by Drs. Crowther-Swanepoel and Houlston provides an up-to-date review of the molecular epidemiology of chronic lymphocytic leukemia, with emphasis on the integration of biology and genomics. See related paper on page 647.

610 Clinical and laboratory versus molecular markers for a correct classification of von Willebrand disease
Augusto B. Federici, and Maria T. Canciani
von Willebrand disease is the most common inherited bleeding disorder. In this perspective article, Drs. Federici and Canciani review how correlating the clinical, laboratory and genetic features of von Willebrand disease has led to improved understanding of its pathophysiology. They show how this has rationalized classification, which in turn can be used to improve treatment of these patients. See related paper on page 679.

Original Articles

615 Factor IX and deep vein thrombosis
Gordon Lowe
Elevated levels of several coagulation factors have been found to be associated with an increased risk of thrombosis. In this perspective article, Dr. Lowe examines the implications of the report by Bezemer and co-workers in this issue for our understanding of the mechanisms involved and how they should direct future research. See related paper on page 693.

Hematopoietic Stem Cells
Preferential expansion of human umbilical cord blood-derived CD34-positive cells on major histocompatibility complex-matched amnion-derived mesenchymal stem cells
Tomomi Mizokami, Hiroko Hisita, Satoshi Okazaki, Takashit Takaki, Xiaoli Wang, Chang-Ze Song, Qing Li, Junko Kato, Naoki Hosaka, Munen Inaba, Hideharu Kanzaki, and Susumu Ikehara
In vitro expansion of human hematopoietic stem cells has remained cumbersome. This paper demonstrates that umbilical cord blood-derived lineage negative/CD34-positive cells can selectively expand in vitro when cultured on autologous amnion-derived adherent cells.

618 Codanin-1, the protein encoded by the gene mutated in congenital dyserythropoietic anemia type I (CDAN1), is cell-cycle regulated
Sharon Noy-Lotan, Orly Dgany, Roxane Lahmi, Nathaly Marcoux, Tanya Krasnov, Nissan Yissachar, Doron Ginsberg, Benny Motro, Peretz Resnitzky, Isaac Yaniv, Gary M. Kurfer, and Hannah Tamary
Codanin-1 is a ubiquitous protein of unknown function, encoded by the gene mutated in congenital dyserythropoietic anemia type I. The findings of this study show that codanin-1 is active in the S-phase of the cell cycle. See related perspective article on page 599.

Red Cell Disorders
Inhibitors of poly-ADP-ribose polymerase (PARP) induce apoptosis of myeloid leukemia cells: potential for therapy of myeloid leukemia and myelodysplastic syndromes
Terry J. Gaymes, Sydney Shall, Lee J. MacPherson, Natalie A. Twine, Nicholas C. Lea, Farzin Farzaneh, and Ghulam J. Mufti
Hematopoietic cells from patients with acute myeloid leukemia and myelodysplastic syndrome often have defects in DNA repair processes. This study shows that these defects make the cells susceptible to induction of apoptosis by poly ADP-ribose polymerase (PARP) inhibitors.
**Chronic Lymphocytic Leukemia**
Elevated risk of chronic lymphocytic leukemia and other indolent non-Hodgkin’s lymphomas among relatives of chronic lymphocytic leukemia patients
Lynn R. Goldin, Magnus Björkholm, Sigurdur Y. Kristinsson, Ingemar Turesson, and Olaf Landgren

Previous studies have shown increased familial risk for chronic lymphocytic leukemia. This study by Goldin and colleagues examines the risk of lymphoid cancer development in first degree relatives of these patients. The data provide a compelling argument for focused studies of germline susceptibility genes and SNP associations in this at-risk population.

See related perspective article on page 606.

**Chronic Lymphocytic Leukemia**
Qualitative and quantitative polymerase chain reaction monitoring of minimal residual disease in relapsed chronic lymphocytic leukemia: early assessment can predict long-term outcome after reduced intensity allogeneic transplantation
Lucia Farina, Cristiana Carniti, Anna Dodero, Antonio Vendramin, Anna Raganato, Francesco Spina, Francesca Patraruca, Franco Narni, Fabio Benedetti, Attilio Olivieri, and Paolo Corradini

Allogeneic stem cell transplantation is being considered as a potentially curative treatment for patients with chronic lymphocytic leukemia. The findings of this study suggest that relapsed patients can achieve molecular remission after reduced intensity conditioning and allogeneic stem cell transplantation.

**Platelet Disorders**
Dominant inheritance of a novel integrin β3 mutation associated with a hereditary macrothrombocytopenia and platelet dysfunction in two Italian families
Paolo Gresele, Emanuela Falchetti, Silvia Giammini, Pio D’Adamo, Angela D’Eustacchio, Teresa Corazza, Anna Maria Mezzasoma, Filomena Di Bari, Giuseppe Guglielmini, Luca Cecchetti, Patrizia Noris, Carlo L. Baldiuni, and Anna Savoia

Glanzmann’s thrombasthenia is a bleeding disorder caused by mutations in the ITGA2B or ITGB3 genes. This paper describes two Italian families with moderate thrombocytopenia with large platelets, defective platelet function and moderate/severe mucocutaneous bleeding, transmitted as an autosomal dominant trait and associated with a novel mutation in the ITGB3 gene, encoding the integrin β3 chain. This report adds to previous studies of mutant alleles which illustrate the importance of signaling via this integrin for platelet function as well as for platelet formation.

**Hemostasis**
Storage and regulated secretion of factor VIII in blood outgrowth endothelial cells
M. van den Biggaart, E.A.M. Bouwens, N.A. Kootstra, R.P. Hebbel, J. Voorberg, and K. Mertens

In this study, the authors explored the feasibility of blood outgrowth endothelial cells as a cellular FVIII delivery device with particular reference to long-term production levels, intracellular storage in Weibel-Palade bodies and agonist-induced regulated secretion. The findings of this ex vivo study open a new avenue towards gene therapy for hemophilia A.

**Disorders of Hemostasis**
Autosomal dominant c1149r von Willebrand disease: phenotypic findings and their implications
Almudena Pérez-Rodríguez, Aranzazu García-Rivero, Esther Lourès, María Fernanda López-Fernández, Angela Rodríguez-Trillo, and Javier Batlle

The classification and even the diagnosis of von Willebrand disease continue to evolve. In this paper, the authors show how a detailed examination of difficult cases using clinical laboratory and molecular analyses can be used to reach a clinically useful conclusion. See related perspective article on page 610.

**Disorders of Hemostasis**
Improved treatment feasibility in children with hemophilia using arteriovenous fistulae: the results after 7 years of follow-up
Maria Elisa Mancuso, Luisa Berardinelli, Claudio Beretta, Mauro Raiteri, Ermanno Pozzoli, and Elena Santagostino

Whilst the benefits of prophylactic replacement therapy for children with hemophilia and of immune tolerance for those with inhibitors are both generally accepted, venous access can be a limiting problem in their delivery. In this paper, Mancuso and co-workers report on their extensive experience using arteriovenous fistulae to deal with this problem and suggest they could be more widely adopted.

**Thrombosis**
F9 Malmö, factor IX and deep vein thrombosis

Despite evidence from two large studies that F9 Malmö is associated with an increased risk of venous thrombosis, the mechanism remains obscure. In this detailed study, the authors are able to exclude effects on levels of FIX protein and its procoagulant activity leaving the phenomenon more mysterious than before. See related perspective article on page 615.
Review Article

Thrombosis

700 Platelet receptors and signaling in the dynamics of thrombus formation
José Rivera, María Luisa Lozano, Leyre Navarrete-Núñez, Vicente Vicente

Platelet receptors are at the forefront of recent research and major advances have been made in understanding their molecular functions and their downstream signaling pathways. This review addresses the steps in the process of thrombus formation process in the arterial circulation, emphasizing our current knowledge on the role of platelet receptors and signaling.

Decision Making and Problem Solving

Aplastic Anemia

712 Hematopoietic growth factors in aplastic anemia patients treated with immunosuppressive therapy: systematic review and meta-analysis
Ronit Gurion, Anat Gafter-Gvili, Mical Paul, Liat Vidal, Isaac Ben-Bassat, Moshe Yeshurun, Ofer Shpilberg, and Pia Raanani

Immunosuppressive therapy is the treatment for patients with aplastic anemia who are ineligible for transplantation. The role of hematopoietic growth factors as adjunct to treatment in these patients is unclear. The findings of this study indicate that the addition of hematopoietic growth factors does not affect mortality, response rate or the occurrence of infections. These growth factors should not, therefore, be recommended routinely as an adjunct to immunosuppressive therapy for patients with aplastic anemia.

Brief Reports

Disorders of Iron Metabolism

720 A new mutation in the hepcidin promoter impairs its bone morphogenetic protein response an contributes to a severe phenotype in HFE related hemochromatosis
Marie-Laure Island, Anne-Marie Jouanolle, Annick Mosser, Yves Deugnier, Véronique David, Pierre Brissot, and Olivier Loréal

Bone morphogenetic protein (BMP) signaling activates transcription of the master iron regulator hepcidin in the liver. This study shows that a heterozygous mutation in the BMP-responsive element of the hepcidin gene promoter is associated with massive iron overload in a patient homozygous for the common HFE mutation, suggesting a new molecular mechanism of iron overload.

Myelodysplastic Syndromes

729 The hematopoietic stem cell transplantation comorbidity index is of prognostic relevance for patients with myelodysplastic syndrome
Esther Zipperer, Daniela Pelz, Kathrin Nachtman, Andrea Kaufeldgen, Cornelia Strupp, Norbert Gattermann, Rainer Haus, and Ulrich Germain

So far, in the prognostic evaluation of patients with myelodysplastic syndrome has been based mainly on disease-related parameters such as cytopenias, karyotype, or percentage of blast cells in the bone marrow. Patients’ characteristics reflecting comorbidities such as cardiovascular diseases and impaired renal or liver function have not taken into account. In this study, the authors found that the Hematopoietic Cell Transplantation Comorbidity Index (HCTCI) may be useful for patients with myelodysplastic syndrome receiving best supportive care only. See perspective article on page 602.

Myeloproliferative Neoplasms

733 Influence of the JAK2 V617F mutation and inherited thrombophilia on the thrombotic risk among patients with essential thrombocytosis
Valerio De Stefano, Tommaso Za, Elena Rossi, Alessia Fiorini, Angela Ciminello, Claudia Luzzi, Patrizia Chiussolo, Simona Sica, and Giuseppe Leone

The role of JAK2 mutations in the thrombotic risk associated with essential thrombocytosis has been unclear. In this study, the authors show an effect of the mutation that is most clearly seen in young patients and when acting in combination with another thrombotic risk factor, factor V Leiden.
Multiple Myeloma
A phase II study of bortezomib in patients with MALT lymphoma
Marlene Troch, Constanze Jonak, Leonhard Müllauer, Andreas Püspök, Michael Formanek, Wolfgang Hauff, Christoph C. Zielinski, Andreas Chott, and Markus Raderer

The activity of bortezomib in patients with MALT lymphoma is unclear. This study shows that bortezomib is active in patients with MALT lymphoma. However, an unexpectedly high rate of toxicities was seen, warranting assessment of combination schedules with bortezomib at a lower dose than given in this study.

Letters to the Editor

Chronic Myeloid Leukemia
Sustained durability of responses and improved progression-free and overall survival with imatinib treatment for accelerated phase and blast crisis chronic myeloid leukemia: long-term follow-up of the STI571 0102 and 0109 trials
Richard T. Silver, Jorge Cortes, Roger Waltzman, Manisha Mone, and Hagop Kantarjian

Malignant Lymphomas
R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: influence of prior autologous stem-cell transplantation on outcome
Alejandro Martin, Maria-Dolores Caballero

Continuing Medical Education

Hematopoietic growth factors for the treatment of aplastic anemia
Codanin-1 gene mutation in congenital dyserythropoietic anemia type I
The risk of chronic lymphocytic leukemia and indolent non-Hodgkin's lymphomas among relatives of patients with chronic lymphocytic leukemia
Platelet receptors and signaling in the dynamics of thrombus formation