

Cover Figure

Congo red staining and analysis under polarized light showing the diagnostic green birefringence of amyloid deposits. This illustration is taken from the perspective article by Drs. Palladini and Merlini on page 1044.

Editorials and Perspectives

1039 The hereditary stomatocytoses Joanna F. Flatt and Lesley J. Bruce

Hereditary stomatocytosis describes a wide spectrum of autosomal dominantly inherited hemolytic disorders in which the basal red cell membrane cation permeability is increased. In this perspective article, Drs. Flatt and Bruce summarize our current knowledge in the field. See related article on page 1049.

1041 Flow cytometry immunophenotyping for diagnosis of myelodysplastic syndrome Mario Cazzola

In this perspective article, Dr. Cazzola examines standard and novel tools for the diagnosis of myelodysplastic syndrome. Flow cytometry immunophenotyping may provide complementary information in the diagnostic approach to a patient with this condition. See related articles on pages 1066, 1124 and 1160.

1044 Current treatment of AL amyloidosis Giovanni Palladini and Giampaolo Merlini

Several effective chemotherapy regimens have been developed during the last decade significantly improving the outlook of patients with AL amyloidosis. Drs. Palladini and Merlini describe our current knowledge in the field and examine future perspectives. See related article on page 1094.

Original Articles

1049 Red Cell Disorders A novel erythroid anion exchange variant (Gly796Arg) of hereditary stomatocytosis associated with dyserythropoiesis Achille Iolascon, Luigia De Falco, Franck Borgese, Maria Rosaria Esposito, Rosa Anna Avisati, Pietro Izzo, Carmelo Piscopo, Helene Guizouarn, Andrea Biondani, Antonella Pantaleo, and Lucia De Franceschi

Stomatocytoses are a group of inherited autosomal dominant hemolytic anemias and include overhydrated hereditary stomatocytosis, dehydrated hereditary stomatocytosis, hereditary cryohydrocytosis and familial pseudohyper-

kalemia. This article describes a novel variant of hereditary stomatocytosis due to a de novo band 3 mutation associated with signs of dyserythropoiesis. See related perspective article on page 1039.

1060 Red Cell Disorders Red blood cell aggregation, aggregate strength and oxygen transport potential of blood are abnormal in both homozygous sickle cell anemia and sickle-hemoglobin C disease Julien Tripette, Tamas Alexy, Marie-Dominique Hardy-Dessources, Daniele Mougenel, Eric Beltan, Tawfik Chalabi, Roger Chout, Maryse Etienne-Julan, Olivier Hue, Herbert J. Meiselman, and Philippe Connes

Recent evidence suggests that red cell aggregation and the ratio of hematocrit to blood viscosity, an index of the oxygen transport potential of blood, might considerably modulate blood flow dynamics in the microcirculation. The findings of this study indicate that patients with sickle cell disease and those with sickle cell hemoglobin C disease have low ratios of hematocrit to blood viscosity as compared to normal controls. This may play a role in tissue hypoxia and clinical status of these patients.

1066 Myelodysplastic Syndromes Diagnostic utility of flow cytometry in low-grade myelodysplastic syndromes: a prospective validation study Kiyoyuki Ogata, Matteo G. Della Porta, Luca Malcovati, Cristina Picone, Norio Yokose, Akira Matsuda, Taishi Yamashita, Hideto Tamura, Junichi Tsukada, and Kazuo Dan

The diagnosis of myelodysplastic syndromes is not always straightforward when patients lack specific diagnostic markers, such as blast excess, karyotype abnormality, and ringed sideroblasts. This article proposes a flow cytometry protocol that can be used in the diagnostic work-up of low-grade myelodysplastic syndrome patients who lack specific diagnostic markers. See related perspective article on page 1041.

1075 Myelodysplastic Syndromes Ectopic expression of C/EBP α and ID1 is sufficient to restore defective neutrophil development in low-risk myelodysplasia Christian R. Geest, Miranda Buitenhuis, Edo Vellenga, and Paul J. Coffey

Although a number of genetic defects in myelodysplastic progenitor cells have been described, the intracellular signaling pathways underlying aberrant regulation of hematopoiesis remain relatively undefined. The findings of this study suggest that targeting the ID1 and C/EBP α transcriptional regulators may be of benefit in the design of novel therapies for low-risk myelodysplastic syndromes.

- 1085 **Myeloproliferative Neoplasms**
The fusion proteins TEL-PDGFR β and FIP1L1-PDGFR α escape ubiquitination and degradation
Federica Toffalini, Anders Kallin, Peter Vandenberghe, Pascal Pierre, Lucienne Michaux, Jan Cools, and Jean-Baptiste Demoulin

Upon growth factor-induced activation, receptor tyrosine kinases such as the PDGF and FGF receptors are targeted for lysosomal degradation via a mechanism that involves ubiquitination of receptor lysines. In this study, it is shown that constitutively active oncogenic fusion proteins that contain PDGF or FGF receptor moieties, caused by specific chromosomal translocations in chronic myeloid neoplasms, escape this negative regulatory mechanism.

- 1094 **Amyloidosis**
Histological regression of amyloid in AL amyloidosis is exclusively seen after normalization of serum free light chain
Ingrid I. van Gameraen, Martin H. van Rijswijk, Johan Bijzet, Edo Vellenga, and Bouke P. Hazenberg

Amyloidosis is thought to be a dynamic process of deposition and resolution. This implies that after elimination of the precursor protein, amyloid deposits in organs might resolve in the course of time resulting in improvement of both organ function and clinical performance. The findings of this study indicate that achievement of complete response of amyloidogenic free light chain following chemotherapy is associated with a significant reduction in amyloid deposition in fat tissue. See related perspective article on page 1044.

- 1101 **Stem Cell Transplantation**
Timing and severity of community acquired respiratory virus infections after myeloablative versus non-myeloablative hematopoietic stem cell transplantation
Joshua T. Schiffer, Kate Kirby, Brenda Sandmaier, Rainer Storb, Lawrence Corey, and Michael Boeckh

Respiratory virus infections are important causes of morbidity and mortality after hematopoietic cell transplantation. Their clinical course can be severe with progression to lower respiratory tract infection, co-infection with serious pulmonary co-pathogens, and high mortality. The findings of this retrospective cohort study indicate that viral lower respiratory tract infection during the first 100 days after hematopoietic cell transplantation was less common among patients undergoing non-myeloablative conditioning regimens than in those receiving myeloablative conditioning, despite a similar overall rate of acquisition.

Review Article

- 1109 **Acute Leukemia**
Chronic inflammatory disease, lymphoid tissue neogenesis and extranodal marginal zone B cell lymphomas
Richard J. Bende, Febe van Maldegem, and Carel J.M. van Noesel

Chronic autoimmune or pathogen-induced immune reactions resulting in lymphoid neogenesis are associated with development of malignant lymphomas, mostly extranodal marginal zone B-cell lymphomas. This review article examines the role of chronic inflammatory responses and the molecular mechanisms involved in the development and progression of extranodal marginal zone B-cell lymphomas.

Decision Making and Problem Solving

- 1124 **Myelodysplastic Syndromes**
Standardization of flow cytometry in myelodysplastic syndromes: report from the first European LeukemiaNet working conference on flow cytometry in myelodysplastic syndromes
Arjan A. van de Loosdrecht, Canan Alhan, Marie Christine Béné, Matteo G. Della Porta, Angelika M. Dräger, Jean Feuillard, Patricia Font, Ulrich Germing, Detlef Haase, Christa H. Homburg, Robin Ireland, Joop H. Jansen, Wolfgang Kern, Luca Malcovati, Jeroen G. te Marvelde, Gulham J. Mufti, Kiyoyuki Ogata, Alberto Orfao, Gert J. Ossenkoppele, Anna Porwit, Frank W. Preijers, Stephen J Richards, Gerrit Jan Schuurhuis, Dolores Subirá, Peter Valent, Vincent H.J. van der Velden, Paresh Vyas, August H. Westra, Theo M. de Witte, Denise A. Wells, Michael R. Loken, and Theresia M. Westers

This article describes the results of the first European LeukemiaNet working conference on flow cytometry immunophenotyping in myelodysplastic syndrome. This report is a very comprehensive analysis of the topic, and provides detailed information on what is currently known in the field. See related perspective article on page 1041.

- 1135 **Acute Leukemia**
How and why minimal residual disease studies are necessary in leukemia: a review from WP10 and WP12 of the European LeukaemiaNet
Marie C. Béné and Jaspal S. Kaeda

Disease reappears in the majority of leukemia patients who enter remission. For many years investigators have focused on detecting the "minimal residual disease" ultimately responsible for these relapses. Two primary methods, one based on polymerase chain reaction technology, the other on flow cytometry are in increasing use. This paper describes the application of such methodologies not only to chronic myeloid leukemia, childhood acute lymphoblastic leukemia, and acute promyelocytic leukemia but to other types of leukemia.

Brief Reports

- 1151 Hematopoietic Stem Cells**
Mesenchymal stem cells efficiently inhibit the proinflammatory properties of 6-sulfo LacNAc dendritic cells
Rebekka Wehner, Diana Wehrum, Martin Bornhäuser, Senming Zhao, Knut Schäkel, Michael P. Bachmann, Uwe Platzbecker, Gerhard Ehninger, E. Peter Rieber, and Marc Schmitz
Mesenchymal stem cells (MSC) exert modulatory effects on the immune system and may have a role in the treatment of steroid-refractory graft-versus-host disease. Here it is shown that MSC inhibit the maturation of a subpopulation of human dendritic cells called slanDC, thereby impairing their ability to produce proinflammatory cytokines and to stimulate the proliferation of CD4⁺ and CD8⁺ T lymphocytes.
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- 1157 Thalassemia Syndromes**
Severe intrauterine anaemia: a new form of $\epsilon\gamma\delta\beta$ thalassemia presenting in utero in a Norwegian family
Anne Brantberg, Sturla H. Eik-Nes, Nigel Roberts, Chris Fisher, and William G. Wood
This report describes a type of $\epsilon\gamma\delta\beta$ -thalassemia due to a rare private deletion, detected early and successfully treated with intrauterine blood transfusions.
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- 1160 Myelodysplastic Syndromes**
Reduced CD38 expression on CD34⁺ cells as a diagnostic test in myelodysplastic syndromes
Nicolas Goardon, Emmanouil Nikolousis, Alexander Sternberg, Wai-Kit Chu, Charles Craddock, Peter Richardson, Richard Benson, Mark Drayson, Graham Standen, Paresh Vyas, and Sylvie Freeman
This report indicates that a reduced mean fluorescence intensity of CD38 expression on CD34⁺ cells can be used as a surrogate marker for abnormalities in the CD34⁺ compartment of patients with myelodysplastic syndrome. See related perspective article on page 1041.
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- 1164 Acute Lymphoblastic Leukemia**
Heterogeneous breakpoints in patients with acute lymphoblastic leukemia and the dic(9;20)(p11-13;q11) show recurrent involvement of genes at 20q11.21
Qian An, Sarah L. Wright, Anthony V. Moorman, Helen Parker, Mike Griffiths, Fiona M. Ross, Teresa Davies, Christine J. Harrison, and Jon C. Strefford
Dicentric chromosomes are rare in acute lymphoblastic leukemia, dic(9;20) being a recurrent aberration. This study provides insight into the breakpoint complexity underlying dicentric chromosomal formation in acute lymphoblastic leukemia and highlights putative target gene loci.

- 1170 Malignant Lymphomas**
Mutational analysis of TP53, PTEN, PIK3CA and CTNNB1/ β -catenin genes in human herpesvirus 8-associated primary effusion lymphoma
Emmanuelle Boulanger, Agnès Marchio, Saw-See Hong, and Pascal Pineau
This report characterizes the molecular genetic alterations harbored by neoplastic B cells in primary effusion lymphoma. By studying both cell lines and primary tumor samples, the authors show that mutations in P53 and CDKN2A/ARF although uncommon in clinical material, are associated with an EBV-negative immunophenotype

Letters to the Editor

- 1175 Congenital Neutropenia**
Respiratory distress and sudden death of a patient with GSDIb chronic neutropenia: possible role of pegfilgrastim
Jean Donadieu, Blandine Beaupain, Frédérique Rety-Jacob, and Raphaëlle Nove-Josserand
- 1177 Chronic Myeloid Leukemia**
Longitudinal growth retardation in a prepubertal girl with chronic myeloid leukemia on long-term treatment with imatinib
Hansjoerg Schmid, Bernadette A.S. Jaeger, Judith Lohse, and Meinolf Suttrop
- 1179 Monoclonal Gammopathies**
Risk of solid tumors and myeloid hematological malignancies among first-degree relatives of patients with monoclonal gammopathy of undetermined significance
Sigurdur Y. Kristinsson, Lynn R. Goldin, Magnus Björkholm, Ingemar Turesson, and Ola Landgren
- 1181 Disorders of Hemostasis**
Cautions and caveats to the treatment of acquired hemophilia A
Angela Huth-Kühne

Errata Corrige

- 1182 High INDO (indoleamine 2,3-dioxygenase) mRNA level in blasts of acute myeloid leukemic patients predicts poor clinical outcome. Haematologica 2008; 93:1894-1898.**
Chamuleau MED, van de Loosdrecht AA, Hess CJ, Janssen JJWM, Zevenbergen A, Delwel R, Valk PJM, Löwenberg B, Ossenkoppele GJ
- 1182 Late relapse of acute myeloid leukemia with mutated NPM1 after eight years: evidence of NPM1 mutation stability. Haematologica 2009; 94:298-300.**
Meloni G, Mancini M, Gianfelici V, Martelli MP, Foa R, Falini B



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- 1182 Serum Dickkopf-1 is increased and correlates with reduced bone mineral density in patients with thalassemia-induced osteoporosis. **Reduction post-zoledronic acid administration.** Voskaridou E, Christoulas D, Xirakia C, Varvagiannis K, Boutsikas G, Bilalis A, Kastiris E, Papatheodorou A, Terpos E.
- 1183 Haematologica 2009; 94[supplement 2]
- 1183 Definition, diagnosis and treatment of immune thrombocytopenic purpura. Haematologica 2009; 94:759-762
George JN
- 1184 Regulation of serum hepcidin levels in sickle cell disease. Haematologica 2009;94:885-887
Kroot JJ, Laarakkers CM, Kemna EH, Biemond BJ, Swinkels DW.

Continuing Medical Education

Community-acquired respiratory virus infections after myeloablative versus non-myeloablative conditioning for transplantation

Histological regression of amyloid in AL amyloidosis

Pathogenesis of extranodal marginal zone B-cell lymphomas

Diagnostic utility of flow cytometry in myelodysplastic syndromes