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Cover Figure

Precursor T-cell acute lymphoblastic leukemia. Bone marrow smear showing small and medium sized blasts with basophilic cytoplasm and cytoplasmic vacuoles. A mitotic figure is also noted. Courtesy of Rosangela Invernizzi, Pavia, Italy. See articles on T-cell acute lymphoblastic leukemia on pages 493, 524 and 533.

Editorials and Perspectives

481 Adhesion molecules and hydroxyurea in the pathophysiology of sickle cell disease
Clarissa Johnson and Marilyn J. Telen

The vaso-occlusive process in sickle cell disease is responsible for much of the morbidity and mortality observed in this condition, and adhesion molecules play a crucial role in it. Hydroxyurea treatment has proven clinical benefit in sickle cell disease, and Drs. Johnson and Telen discuss how this drug may affect the adhesive interactions between blood cells and the endothelium leading to vaso-occlusion. See related article on page 502.

486 Fanconi anemia is a highly penetrant cancer susceptibility syndrome
Inderjeet Dokal

Over the last 20 years, major advances have been made in our understanding of the biology of Fanconi anemia, which now represents one of the best-defined inherited bone marrow failure syndromes. In this perspective article, Dr. Dokal analyzes the factors predisposing to malignancy in Fanconi anemia. See related article on page 511.

489 The epidemiology of acquired aplastic anemia
Neal S. Young and David W. Kaufman

Our understanding of the epidemiology of aplastic anemia has improved considerably based on several decades of laboratory and clinical research. Drs. Young and Kaufman summarize our current knowledge and discuss clinical implications of epidemiological studies. See related article on page 518.

493 Signaling pathways involved in the development of T-cell acute lymphoblastic leukemia
Frank J.T. Staal and Anton W. Langerak

T-cell acute lymphoblastic leukemia results from the malignant transformation of normal developing T cells in the thymus, the so-called thymocytes. Drs. Staal and Langerak analyze the signaling pathways involved in the pathophysiology of this disorder. See related articles on page 524 and 533.

498 Protein S deficiency
Armando D'Angelo and Silvana Viganò D'Angelo

An association of familial protein S deficiency with increased venous thromboembolic risk was first reported in 1984. In this perspective article, Drs. D'Angelo and Viganò D'Angelo summarize our current understanding of the pathophysiology of protein S deficiency. See related article on page 574.

Original Articles

502 Sickle Cell Disease
Modulation of erythroid adhesion receptor expression by hydroxyurea in children with sickle cell disease

Marie-Hélène Odièvre, Viviane Bony, Malika Benkerrou, Claudine Lapoumèroulie, Corinne Alberti, Rolande Ducrocq, Evelyne Jacqz-Aigrain, Jacques Elion, and Jean-Pierre Cartron

Hydroxyurea is currently employed for prevention of vaso-occlusive events in patients with sickle cell disease, but its mechanism of action is largely unknown. Findings of this study suggest that hydroxyurea acts during erythroid development by modulating adhesion receptor expression. See related perspective article on page 481.

511 Fanconi Anemia
Cancer risks in Fanconi anemia: findings from the German Fanconi Anemia Registry
Philip S. Rosenberg, Blanche P. Alter, and Wolfram Ebell

Fanconi anemia is an inherited genomic instability syndrome associated with progressive bone marrow failure and a high risk of acute myeloid leukemia and solid tumors. This study confirms this high risk, the estimated ratio of observed to expected malignancies being 868 for acute myeloid leukemia and 26 for all solid tumors. See related perspective article on page 486.

518 Aplastic Anemia
Epidemiology of aplastic anemia: a prospective multicenter study
Eva Montané, Luisa Ibáñez, Xavier Vidal, Elena Ballarín, Ramon Puig, Nuria García, Joan-Ramon Laporte, and the Catalan Group for the Study of Agranulocytosis and Aplastic Anemia

Aplastic anemia is a rare disease whose incidence varies considerably worldwide. In this study conducted in the metropolitan area of Barcelona, the overall incidence was 2.34 per million inhabitants per year. The survival rate at 2 years was 57%, confirming the severity of this condition. See related perspective article on page 489.

- 524 **Acute Lymphoblastic Leukemia**
Bone marrow stromal cells and the upregulation of interleukin-8 production in human T-cell acute lymphoblastic leukemia through the CXCL12/CXCR4 axis and the NF- κ B and JNK/AP-1 pathways

Maria T. Scupoli, Massimo Donadelli, Federica Cioffi, Maria Rossi, Omar Perbellini, Giorgio Malpeli, Silvia Corbioli, Fabrizio Vinante, Mauro Krampera, Marta Palmieri, Aldo Scarpa, Cristina Ariola, Robin Foà, and Giovanni Pizzolo

Cytokines released in the bone marrow likely play an important role in the growth of T-cell acute lymphoblastic leukemia. Findings of this study suggest that CXCL12 (also known as SDF-1) can regulate interleukin-8 production in leukemic T cells. See related perspective article on page 493.

- 533 **Acute Lymphoblastic Leukemia**
In vitro validation of γ -secretase inhibitors alone or in combination with other anti-cancer drugs for treatment of T-cell acute lymphoblastic leukemia

Kim De Keersmaecker, Idoia Lahortiga, Nicole Mentens, Cedric Folens, Leander Van Neste, Sofie Bekaert, Peter Vandenberghe, Maria D. Otero, Peter Marynen, and Jan Cools

Activating NOTCH-1 mutations are common in T-cell acute lymphoblastic leukemia. Inhibition of NOTCH-1 signaling by γ -secretase inhibitors causes cell cycle block. Findings of this study suggest that prolonged treatment with γ -secretase inhibitors and combinations with other drugs are required to obtain visible effects on T-cell acute lymphoblastic leukemia cells lines. See related perspective article on page 493.

- 543 **Malignant Lymphomas**
Detection of somatic quantitative genetic alterations by multiplex polymerase chain reaction for the prediction of outcome in diffuse large B-cell lymphomas

Fabrice Jardin, Philippe Ruminy, Jean-Pierre Kerckaert, Françoise Parmentier, Jean-Michel Picquenot, Sabine Quief, Céline Villenet, Gérard Buchonnet, Mario Tosi, Thierry Frebourg, Christian Bastard, and Hervé Tilly

Genomic gains and losses play a crucial role in the development of diffuse large B-cell lymphoma. This study shows that multiplex polymerase chain reaction of short fluorescent fragments is a reliable method for detecting somatic quantitative genetic alterations in diffuse large B-cell lymphoma.

- 551 **Malignant Lymphomas**
Minimal residual disease detection in mantle cell lymphoma: methods and significance of four-color flow cytometry compared to consensus IGH-polymerase chain reaction at initial staging and for follow-up examinations

Sebastian Bötcher, Matthias Ritgen, Sebastian Buske, Stefan Gesk, Wolfram Klapper, Eva Hoster, Wolfgang Hiddemann, Michael Unterhalt, Martin Dreyling, Reiner Siebert, Michael Kneba and Christiane Pott on behalf of the EU MCL MRD Group

Multicolor flow cytometry is increasingly employed in the diagnosis and follow-up of mantle cell lymphoma. Findings of this study indicate that multicolor flow cytometry is a very valuable method for accurate initial staging of mantle cell lymphoma.

- 560 **Multiple Myeloma**
Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: updated time-to-events results and prognostic factors for time to progression

Maria Victoria Mateos, José M. Hernández, Miguel T. Hernández, Norma C. Gutiérrez, Luis Palomera, Marta Fuertes, Pedro García-Sánchez, Juan J. Lahuerta, Javier de la Rubia, María-José Terol, Ana Sureda, Joan Bargay, Paz Ribas, Adrian Alegre, Felipe de Arriba, Albert Oriol, Dolores Carrera, José García-Laraña, Ramón García-Sanz, Joan Bladé, Felipe Prósper, Gemma Mateo, Dixie-Lee Esseltine, Helgi van de Velde, and Jesús F. San Miguel

Novel therapeutic agents have become available for patients with multiple myeloma in the last few years. This study conducted by the Spanish PETHEMA and GEM groups investigated the effect of bortezomib plus melphalan and prednisone in elderly patients with newly diagnosed multiple myeloma. Treatment was highly active and well tolerated, with 85% of patients alive at 3 years.

- 566 **Platelet Disorders**
The effect of platelet activation on the hypercoagulability induced by murine monoclonal antiphospholipid antibodies

Aurelie Membre, Denis Wahl, Veronique Latger-Cannard, Jean-Pierre Max, Patrick Lacolley, Thomas Lecompte, and Veronique Regnault

Antiphospholipid antibodies are associated with an increased risk of thrombosis. Findings of this study suggest that platelet activation reinforces the hypercoagulability induced by interference of antiphospholipid antibodies/target complexes with coagulation reactions on membrane surfaces.

- 574 **Disorders of Hemostasis**
Functional characterization of twelve natural PROS1 mutations associated with anticoagulant protein S deficiency

Begoña Hurtado, Xavier Muñoz, Maria Carme Mulero, Gemma Navarro, Pere Domènech, Pablo García de Frutos, Mercè Pérez-Riba, and Núria Sala

The molecular mechanisms by which PROS1 mutations result in protein S deficiency are still unknown for many mutations. Findings of this study indicate that the main mechanism for the deficiency associated with mutations that generate a premature termination codon is not the synthesis of a truncated protein, but the exclusion of the mutated allele.

- 581 **Infectious Disorders**
A prospective analysis of the genotypic diversity and dynamics of the *Candida albicans* colonizing flora in neutropenic patients with de novo acute leukemia

Frédéric Dalle, Ingrid Lafon, Coralie L'Ollivier,

Emmanuelle Ferrant, Pierre Sicard,
Catherine Labruère, Ahmed Jebrane, Aline Laubriet,
Odile Vagner, Denis Caillot, and Alain Bonnin

This study was aimed at investigating the dynamics and heterogeneity of C. albicans flora in patients with de novo acute leukemia. Its findings suggest that genetic evolution of the colonizing C. albicans flora is uncommon in patients with acute leukemia.

Decision Making and Problem Solving

- 588** **Sickle Cell Disease**
Quality of life of female caregivers of children with sickle cell disease: a survey
Xandra W. van den Tweel, Janneke Hatzmann, Elske Ensink, Johanna H. van der Lee, Marjolein Peters, Karin Fijnvandraat, and Martha Grootenhuis

This Dutch survey demonstrates a lower quality of life in female caregivers of children with sickle cell disease than in the healthy female population and caregivers of healthy children with the same socio-economic status. Therefore, better support is needed to improve the quality of life of both children with sickle cell disease and their caregivers.

- 594** **Acute Myeloid Leukemia**
Improvements in survival of adults diagnosed with acute myeloblastic leukemia in the early 21st century
Dianne Pulte, Adam Gondos, and Hermann Brenner

This study shows that 5- and 10-year relative survival has improved substantially for younger patients with acute myeloid leukemia over the last 25 years. By contrast, survival remains poor in the oldest age group, which include a large proportion of patients with acute myeloid leukemia.

Brief Reports

- 601** **Hematopoiesis**
Differential role of CD97 in interleukin-8-induced and granulocyte colony-stimulating factor-induced hematopoietic stem and progenitor cell mobilization
Melissa van Pel, Henny Hagoort, Mark J. Kwakkenbos, Jörg Hamann, and Willem E. Fibbe

CD97 is a transmembrane receptor involved in neutrophil migration. This study shows that CD97 plays a role in interleukin-8-induced hematopoietic stem cell and progenitor mobilization.

- 605** **Sickle Cell Disease**
Increased adhesive properties of neutrophils in sickle cell disease may be reversed by pharmacological nitric oxide donation
Andreia A. Canalli, Carla F. Franco-Penteado, Sara T.O. Saad, Nicola Conran, and Fernando F. Costa

Adhesive interactions between blood cells and endothelium lead to vaso-occlusion in sickle cell disease. This study suggests that pharmacological nitric oxide donation may reduce neutrophil adhesion to vascular endothelium.

- 610** **Thalassemia Syndrome**
Peptide-nucleic acid-mediated enriched polymerase chain reaction as a key point for non-invasive prenatal diagnosis of β -thalassemia
Silvia Galbiati, Barbara Foglieni, Maurizio Travi, Cristina Curcio, Gabriella Restagno, Luca Sbaiz, Maddalena Smid, Federica Pasi, Augusto Ferrari, Maurizio Ferrari, and Laura Cremonesi

This study describes a novel approach to non-invasive prenatal diagnosis of β -thalassemia based on microchip analysis of fetal DNA extracted from maternal plasma.

- 615** **Langerhans Cell Histiocytosis**
Neurodegenerative central nervous system disease as late sequelae of Langerhans cell histiocytosis.
Report from the Japan LCH Study Group
Shinsaku Imashuku, Yoko Shiota, Ryoji Kobayashi, Gaku Hosoi, Hisanori Fujino, Shiro Seto, Hisashi Wakita, Akira Oka, Nagisa Okazaki, Naoto Fujita, Toshinori Minato, Kenichi Koike, Yukiko Tsunematsu, and Akira Morimoto for the Japan LCH Study Group (JLSG)

Langerhans' cell histiocytosis can affect the central nervous system, where it frequently manifests as diabetes insipidus. Cerebellar ataxia and other neurological defects can represent late sequelae of this disorder.

- 619** **Multiple Myeloma**
Hepatocyte growth factor promotes migration of human myeloma cells
Randi Utne Holt, Unn-Merete Fagerli, Vadim Baykov, Torstein Baade Rø, Håkon Hov, Anders Waage, Anders Sundan, and Magne Børset

This study demonstrates that myeloma cells can be attracted to hepatocyte growth factor in concentrations known to be present in the bone marrow of patients with multiple myeloma.

- 623** **Multiple Myeloma**
Primary extramedullary plasmacytoma: similarities with and differences from multiple myeloma revealed by interphase cytogenetics
Karin Bink, Eugenia Haralambieva, Marcus Kremer, German Ott, Christine Beham-Schmid, Laurence de Leval, Suat Cheng Peh, Hubert R. Laeng, Uta Jütting, Peter Hutzler, Leticia Quintanilla-Martinez, and Falko Fend

Primary extramedullary plasmacytoma and multiple myeloma show similar chromosomal alterations, as detected by fluorescence in situ hybridization.

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- 627 **Transfusion Medicine**
Accurate Rh phenotype determination by reticulocyte mRNA typing shortly after multiple transfusions
Ingrid Randen, Kirsten Sørensen, Reidun Hauge, Anine B. Dahlberg, Mohammad R. Mirlashari, Keith M. Thompson, and Jens Kjeldsen-Kragh
- This study describes a method for correctly typing patients' own Rh-antigens after multiple transfusions.*

Letters to the Editor

- 631 **Acute Myeloid Leukemia**
Single nucleotide polymorphism microarray analysis of karyotypically normal acute myeloid leukemia reveals frequent copy number neutral loss of heterozygosity
Anne Tyybäkiöja, Erkki Elonen, Hanna Vauhkonen, Janna Saarela, and Sakari Knuutila
- 633 **Acute Myeloid Leukemia**
Relapse and death during first remission in acute myeloid leukemia
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- 635 **Platelet Disorders**
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- 637 **Thrombosis**
Role of polymorphisms of CC-chemokine receptor-5 gene in acute myocardial infarction and biological implications for longevity
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Continuing Medical Education

Minimal residual disease detection in mantle cell lymphoma

Survival of adults with acute myeloblastic leukemia

Analysis of *Candida albicans* colonization in neutropenic *de novo* acute leukemia patients

Epidemiology of aplastic anemia