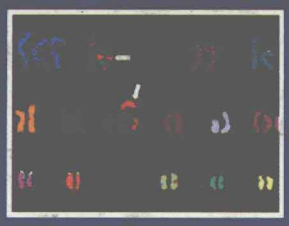
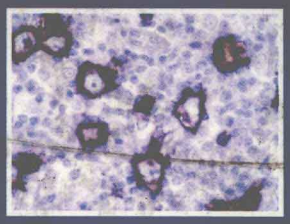
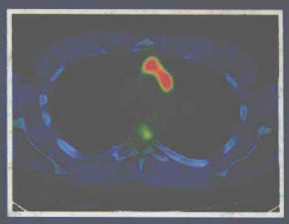




THE Lymphomas

SECOND EDITION

GEORGE P. CANELLOS

T. ANDREW LISTER

BRYAN YOUNG

SAUNDERS

ELSEVIER

THE LYMPHOMAS

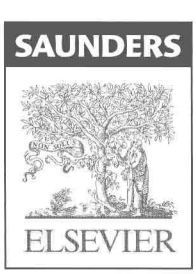
Second Edition

Editors

George P. Canellos, M.D., F.R.C.P., Dr.S (Hon.)
William Rosenberg Professor of Medicine
Harvard Medical School
Department of Medical Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

T. Andrew Lister, M.D., F.R.C.P., F.R.C.Path.
Professor of Medical Oncology
Cancer Research UK Medical Oncology Unit
St. Bartholomew's Hospital
London, United Kingdom

Bryan D. Young, Ph.D.
Professor of Molecular Oncology
Cancer Research UK Medical Oncology Unit
St. Bartholomew's Hospital Medical School
London, United Kingdom



SAUNDERS
ELSEVIER

1600 John F. Kennedy Blvd.
Suite 1800
Philadelphia, PA 19103-2899

THE LYMPHOMAS, SECOND EDITION

ISBN-13: 978-0-7216-0081-9
ISBN-10: 0-7216-0081-6

Notice

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our knowledge, changes in practice, treatment and drug therapy may become necessary or appropriate. Readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of the practitioner, relying on their own experience and knowledge of the patient, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions. To the fullest extent of the law, neither the Publisher nor the Editors assumes any liability for any injury and/or damage to persons or property arising out or related to any use of the material contained in this book. It is the responsibility of the treating practitioner, relying on independent expertise and knowledge of the patient, to determine the best treatment and method of application for the patient

The Publisher

Library of Congress Cataloging-in-Publication Data
The lymphomas / [edited by] George Canellos, T. Andrew Lister, Bryan Young.—2nd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 0-7216-0081-6
1. Lymphomas. I. Canellos, Geogre P. (George Peter), 1934 II. Lister, T. A. (Thomas Andrew) III. Young, G. Bryan (Gordon Bryan)
[DNLM: 1. Lymphoma WH 525 L9852 2006]
RC280.L9L953 2006
616.99′446—dc22

2005056129

Acquisitions Editor: Dolores Meloni
Developmental Editor: Kristina Oberle
Project Manager: David Saltzberg

Printed in China

Last digit is the print number: 9 8 7 6 5 4 3 2 1

To the memory of our
colleague, Dr. Stanley Korsmeyer.

Preface

Research in the field of malignant lymphoma has moved faster than any other component of medical oncology. The second edition of *The Lymphomas* is an attempt to bring the changing basic science and clinical information up-to-date and to conform with the new understanding of the biological features and natural history of the various malignant lymphomas. Since the last edition, there has been a comprehensive review by the World Health Organization resulting in a classification scheme that embodied some of the principles of the REAL [revised European American lymphoma] classification as well as a consensus among pathologists and clinicians regarding the appropriateness of the various subdivisions of Hodgkin lymphoma and non-Hodgkin's lymphoma. New contributors who are active in their various fields of specialization have been brought into the second edition, bringing a new vitality to this edition. A molecular biologic basis of the cytogenetic translocations that characterize the various forms of lymphoma has been completely updated. The immunophenotypic as well as molecular genetic abnormalities are described, which may lend themselves to the targeted therapy. To that end, the section on biological therapy has been completely rewritten with a comprehensive consideration of all of the new information available on the biological therapy of lymphoma. The major subdivisions within the WHO classification have been separated and discussed individually. As in the previous edition, the therapeutic modalities—such as chemotherapy, radiation therapy, and bone marrow transplantation—are updated in separate chapters.

The pace of biological discovery is very quick leading to a host of new agents targeted to cell surface markers as well as unique molecular abnormalities. Microarray technology has begun to define the various lymphomas according to molecular genetic signatures which correlate with natural history. In addition, this technique may define specific abnormalities against which targeted therapies could be developed. The basic scientific sections have a new editor in Dr. Bryan Young, who has been an active investigator in the field. This second edition is an attempt to offer the reader a comprehensive view of the basic and clinical science in the field with recommendations as to therapeutic approaches. It is assumed that this field will continue to change as new therapeutic tactics emerge.

The editors wish to thank all of the contributors, their administrative assistants and secretaries for their dedicated efforts with this Second Edition. The editors gratefully acknowledge the inspiration of their mentors in the field of lymphoma therapy, some of whom have passed on, including Professor G. Hamilton Fairley, Professor Timothy McElwain, Drs. Paul Carbone and John Ultmann.

George P. Canellos
T. Andrew Lister
Bryan D. Young

Contributors

Ranjana Advani, M.D.
Assistant Professor of Medicine, Department of Medicine and Oncology, Stanford University, Stanford, California, USA

James O. Armitage, M.D.
Joe Shapiro Professor of Medicine, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA

Francesco Bertoni, M.D.
Honorary Senior Lecturer, Barts and The London, London, United Kingdom; Head of the Functional Genomics Unit, Laboratory of Experimental Oncology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland

Magnus Björkholm, M.D., Ph.D.
Department of Medicine, Division of Hematology, Karolinska Hospital, Stockholm, Sweden

Kristie A. Blum, M.D.
Assistant Professor of Medicine, Division of Hematology and Oncology, The Ohio State University, The Arthur G. James Comprehensive Cancer Center, Columbus, Ohio, USA

Jennifer R. Brown, M.D., Ph.D.
Instructor in Medicine, Harvard Medical School, Department of Medical Oncology, Dana-Farber Cancer Institute, Department of Medicine, Brigham & Women's Hospital, Boston, Massachusetts, USA

John C. Byrd, M.D.
Division of Medicinal Chemistry, Department of Pharmacy, The Ohio State University Columbus, Ohio, USA

Elias Campo, M.D. Ph.D.
Professor of Pathology, Chief, Department of Pathology and Hematopathology Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain

George P. Canellos, M.D., F.R.C.P., DR.S (Hon.)
William Rosenberg Professor of Medicine, Harvard Medical School, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA

Franco Cavalli, M.D., F.R.C.P.
Professor of Medicine, University of Bern, Switzerland, Director of the Oncology Institute of Southern Switzerland, Ospedale San Giovanni, Bellinzona, Switzerland

Bruce D. Cheson, M.D.
Head of Hematology, Georgetown University Hospital, Washington, DC, USA

Bertrand Coiffier, M.D.
Hospices Civils de Lyon & Université Claude Bernard, Lyon, France; Hematology Department, Pierre Benite, France

Joseph M. Connors, M.D., F.R.C.P.C.
British Columbia Cancer Agency, Vancouver, BC, Canada

Andrew Davies, B.Sc., B.M., M.R.C.P.
Clinical Research Fellow and Honorary Lecturer, Department of Medical Oncology, Institute of Cancer and the CR-UK Clinical Centre, Barts and the London, Queen Mary's School of Medicine and Dentistry, London, United Kingdom

Martin Dreyling, M.D., Ph.D.
University Hospital Grosshadern, Department of Internal Medicine III, Ludwig-Maximilians-University, Munich, Germany

Andrew L. Feldman, M.D.
Clinical Fellow, Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

Howard A. Fine, M.D.
Chief of the Neuro-Oncology Branch, National Cancer Institute, National Institutes of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA

Richard I. Fisher, M.D.
Samuel E. Durand Professor of Medicine, Director, James P. Wilmot Cancer Center, Director, Hematology-Oncology Division, Director of Cancer Services, Strong Health, University of Rochester School of Medicine, Rochester, New York, USA

Jonathan W. Friedberg, M.D.
Assistant Professor of Medicine and Oncology, University of Rochester School of Medicine, James P. Wilmot Cancer Center, Rochester, New York, USA

John G. Gribben, M.D.
Cancer Research UK Medical Oncology Unit, St. Bartholomew's Hospital, Barts and the London School of Medicine and Dentistry, London, United Kingdom

Wolfgang Hiddemann, M.D., Ph.D.
University Hospital Grosshadern, Department of Internal Medicine III, Ludwig-Maximilians-University, Munich, Germany

Richard T. Hoppe, M.D.
Henry S. Kaplan-Harry Lebeson Professor of Cancer Biology, Department of Radiation Oncology, Stanford University School of Medicine, Stanford, California, USA

Doug Horsman, M.D.
Director, Cancer Genetics Laboratory, British Columbia Cancer Agency, Vancouver, British Columbia, Canada

Roland Hustinx, M.D., Ph.D.
Centre Hospitalier Universitaire Sart Tilman, University of Liège, Belgium

Naoko Ishibe, Sc.D.
Nuclear Medicine, Centre Hospitalier Universitaire Sart Tilman, Belgium

Elaine S. Jaffe, M.D.
Chief, Hematopathology Section, Acting Chief, Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

Guy Jerusalem, M.D., Ph.D.
Medical Oncology, Centre Hospitalier Universitaire Sart Tilman, University of Liège, Belgium

Youn H. Kim, M.D.
Professor of Dermatology, Director, Multidisciplinary Cutaneous Lymphoma Clinic, Department of Dermatology, Stanford University School of Medicine, Stanford, California, USA

Anton W. Langerak, Ph.D.
Department of Immunology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

Rifca Le Dieu, M.B.B.S.
Clinical Research Fellow, Cancer Research UK Medical Oncology Unit, St. Bartholomew's Hospital, Barts and the London School of Medicine and Dentistry, London, United Kingdom

Georg Lenz, M.D.
Fellow, Metabolism Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

Alexandra M. Levine, M.D.
Keck School of Medicine, University of Southern California, Los Angeles, California, USA

Raymond Liang, M.D., F.R.C.P., F.R.A.C.P.
S.H. Ho Chair Professor in Haematology and Oncology, Department of Medicine, University of Hong Kong, Hong Kong

T. Andrew Lister, M.D., F.R.C.P., F.R.C.Path.
Professor of Medical Oncology, Centre for Medical Oncology, Institute of Cancer and the CR-UK Clinical Centre, Barts and the London, Queen Mary's School of Medicine and Dentistry, London, United Kingdom

Jay S. Loeffler, M.D.
Herman and Joan Suit Professor of Radiation Oncology, Harvard Medical School, Chair, Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts, USA

Gerard Lozanski, M.D.
Department of Pathology, Ohio State University, Columbus, Ohio, USA

Masao Matsuoka, M.D., Ph.D.
Institute for Virus Research, Kyoto University, Kyoto, Japan

Silvia Montoto, M.D.
Senior Lecturer, Centre for Medical Oncology, Institute of Cancer and the CR-UK Clinical Centre, Barts and the London, Queen Mary's School of Medicine and Dentistry, London, United Kingdom

Emili Montserrat, M.D., Ph.D.
Professor of Medicine, Director, Institute of Hematology and Oncology Hospital Clínic, University of Barcelona, Barcelona, Spain

Andrea K. Ng, M.D., M.P.H.
Assistant Professor of Radiation Oncology, Harvard Medical School, Brigham and Women's Hospital, Boston, Massuchusetts, USA

Vassaliki I. Pappa, M.D.
Second Department of Internal Medicine, Propaedeutic, University of Athens, Attikon University General Hospital, Athens, Greece

Stefania Pittaluga, M.D., Ph.D.
Staff Clinician, Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

Rodney H. Reznek, M.B., Ch.B., F.R.C.P., F.R.C.R.
Professor of Diagnostic Imaging and Consultant Radiologist, Cancer Imaging, St. Bartholomew's Hospital, London, United Kingdom

Ama Z. Rohatiner, M.D., F.R.C.P.
Professor of Hemato-Oncology, Centre for Medical Oncology, Institute of Cancer and the CR-UK Clinical Centre, Barts and the London, Queen Mary's School of Medicine and Dentistry, London, United Kingdom

Vaskar Saha, M.D.
Cancer Research UK Children's Cancer Group, Department of Paediatric Haematology and Oncology, Institute of Cancer, Barts and The London School of

Medicine and Dentistry, Queen Mary University of London, London, United Kingdom

A. Shankar, M.D.
Cancer Research UK Children's Cancer Group, Department of Paediatric Haematology and Oncology, Institute of Cancer, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom

Tamara N. Shenkier, M.D., F.R.C.P.C.
Medical Onoclogist, British Columbia Cancer Agency, Clinical Assistant Professor of Medicine, University of British Columbia, Vancouver, BC, Canada

Arthur T. Skarin, M.D., F.A.C.P., F.C.C.P.
Associate Professor of Medicine, Harvard Medical School, Department of Medical Oncology, Dana-Farber Cancer Institute, Department of Medicine, Brigham & Women's Hospital, Boston, Maryland, USA

Louis M. Staudt, M.D., Ph.D.
Chief, Lymphoid Malignancies Section, Metabolism Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

John W. Sweetenham, M.D.
Professor of Medicine, Hematology and Oncology, Cleveland Clinic Foundation, Cleveland, Ohio, USA

Lode J. Swinnen, M.D.
Division of Hematological Malignancy, Department of Oncology, Johns Hopkins Cancer Center, Baltimore, Maryland, USA

Tomasz Szczepański, M.D., Ph.D.
Silesian School of Medicine, Department of Pediatric Hematology and Oncology, Zabrze, Poland

Catherine Traullé, M.D.
Hospices Civils de Lyon, Hematology Department, Centre Hospitalier Lyon-Sud, Pierre Benite, France

Margaret Tucker, M.D.
Director, Human Genetics Program, Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, Maryland, USA

Vincent H.J. van der Velden, Ph.D.
Department of Immunology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

Jacques J.M. van Dongen, M.D., Ph.D.
Department of Immunology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

Sarah J. Vinnicombe, B.Sc.(Hons.), M.R.C.P., F.R.C.R.
Department of Diagnostic Imaging, St Bartholomew's Hospital, London, United Kingdom

Rein Willemze, M.D.
Leiden University Medical Center, Department of Dermatology, Leiden, The Netherlands

Wyndham H. Wilson, M.D., Ph.D.
Senior Investigator and Chief, Lymphoma Therapeutics Section, Metabolism Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

Joachim Yahalom, M.D.
Co-chair, Lymphoma Disease Management Team, Attending, Department of Radiation Oncology, Member, Memorial Sloan-Kettering Cancer Center, Professor of Radiation Oncology in Medicine, Weill Medical College of Cornell University, New York, New York, USA

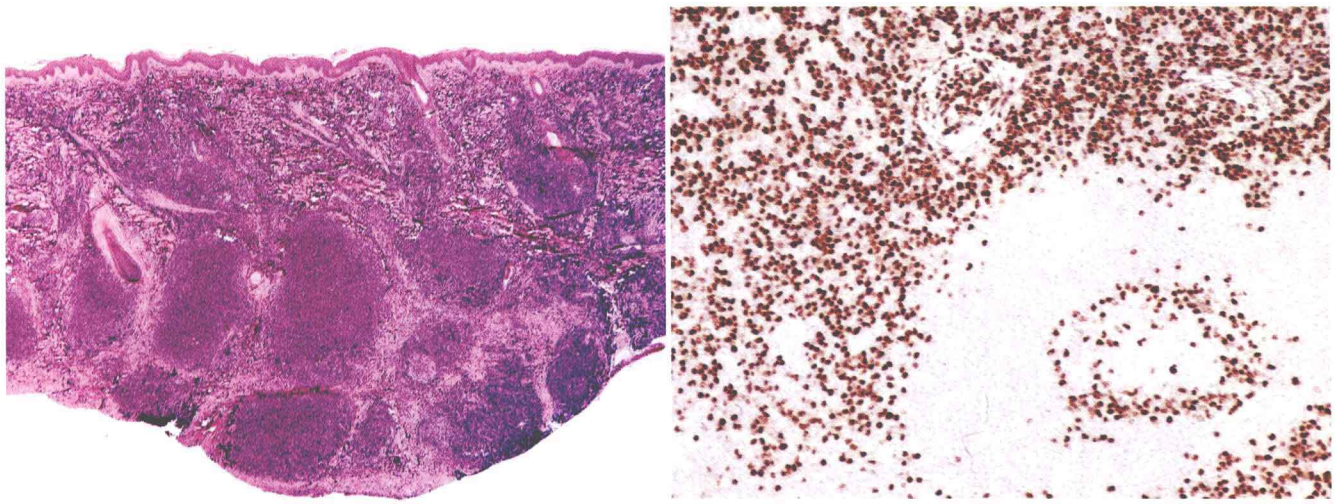
Bryan D. Young, Ph.D.
Professor of Molecular Oncology, Cancer Research UK Medical Oncology Unit, St. Bartholomew's Hospital Medical School, London, United Kingdom

Andrew Zelenetz, M.D., Ph.D.
Chief, Lymphoma Service, Head, Laboratory of Hemato-Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

Pier Luigi Zinzani, M.D., Ph.D.
Institute of Hematology and Medical Oncology "Seràgnoli", University of Bologna, Bologna, Italy

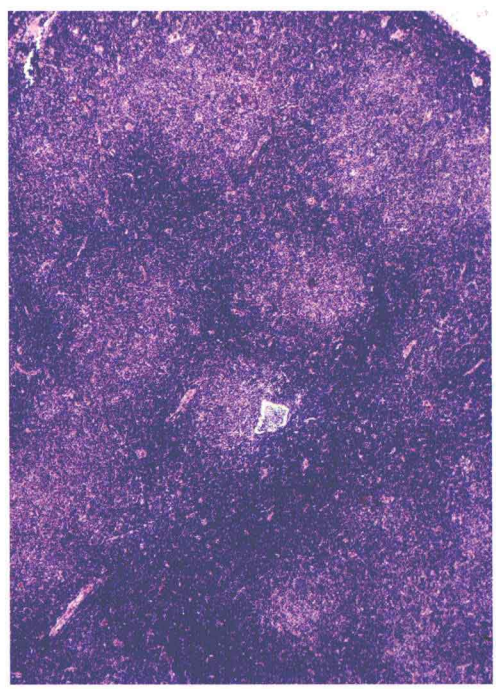
Emanuele Zucca, M.D.
Privatdozent of Oncology/Haematology, University of Bern, Switzerland, Head of the Lymphoma Unit, Oncology Institute of Southern Switzerland, Ospedale San Giovanni Bellinzona, Switzerland

Color Plate Section



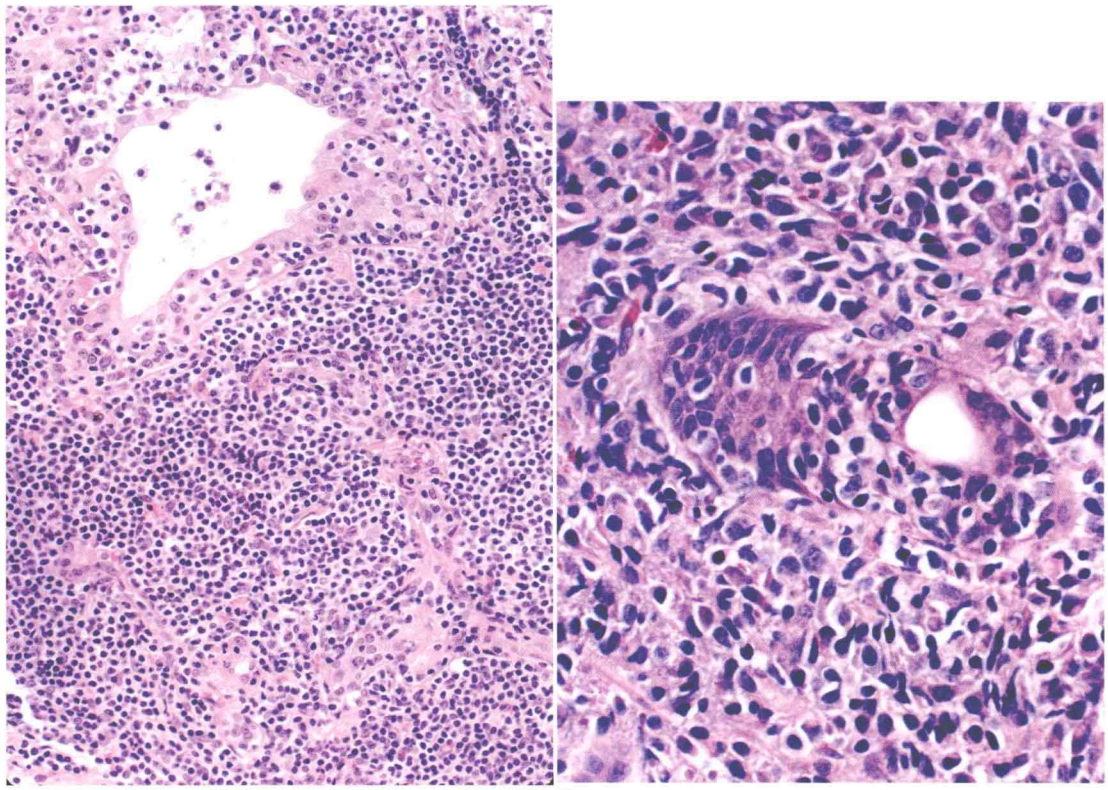
A B

Figure 1–1. Precursor B-lymphoblastic leukemia/lymphoma. **A:** This scalp lesion was the initial presenting site of disease in this 10-year-old female. The tumor infiltrates the reticular dermis, but leaves a Grenz zone beneath the epidermis. **B:** Lymphoblasts demonstrate nuclear staining for terminal deoxynucleotidyl transferase (TdT). This example of lymph node involvement shows diffuse paracortical involvement with relative sparing of germinal centers **(lower right).**



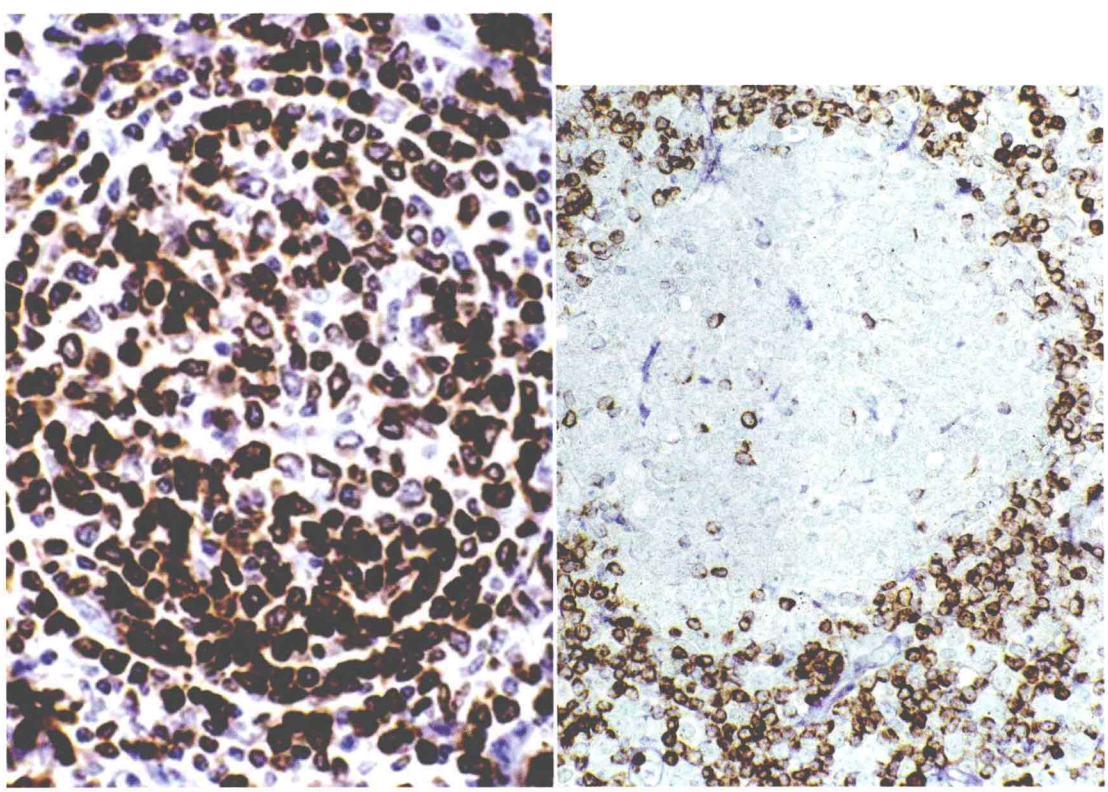
A

Figure 1–2. CLL/SLL, lymph node. **A:** The lymph node shows diffuse architectural effacement with a pseudofollicular pattern, seen as pale areas representing proliferation or growth centers.



A B

Figure 1–4. MALT lymphoma. **A:** In this lung lesion, monocytoid-appearing cells with pale cytoplasm infiltrate and surround the bronchial epithelium. **B:** Lymphoepithelial lesion in a case of gastric MALT lymphoma, showing lymphoma cells invading an epithelial gland.



B C

Figure 1–5. Follicular lymphoma, lymph node. **B:** The t(14;18) translocation leads to overexpression of Bcl-2 protein in the neoplastic follicles of follicular lymphoma (dark cytoplasmic staining). **C:** Bcl-2 protein is not expressed in reactive, non-neoplastic germinal center B cells. The positive cells seen represent reactive T cells.

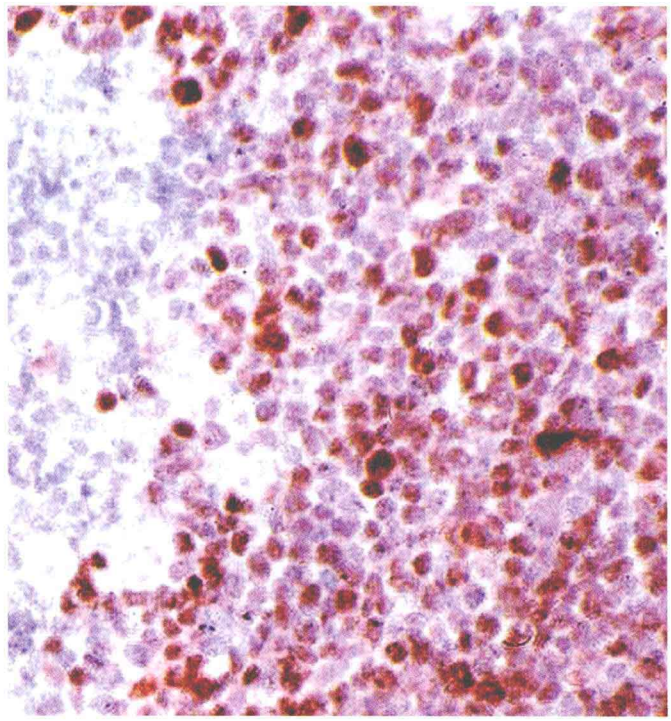
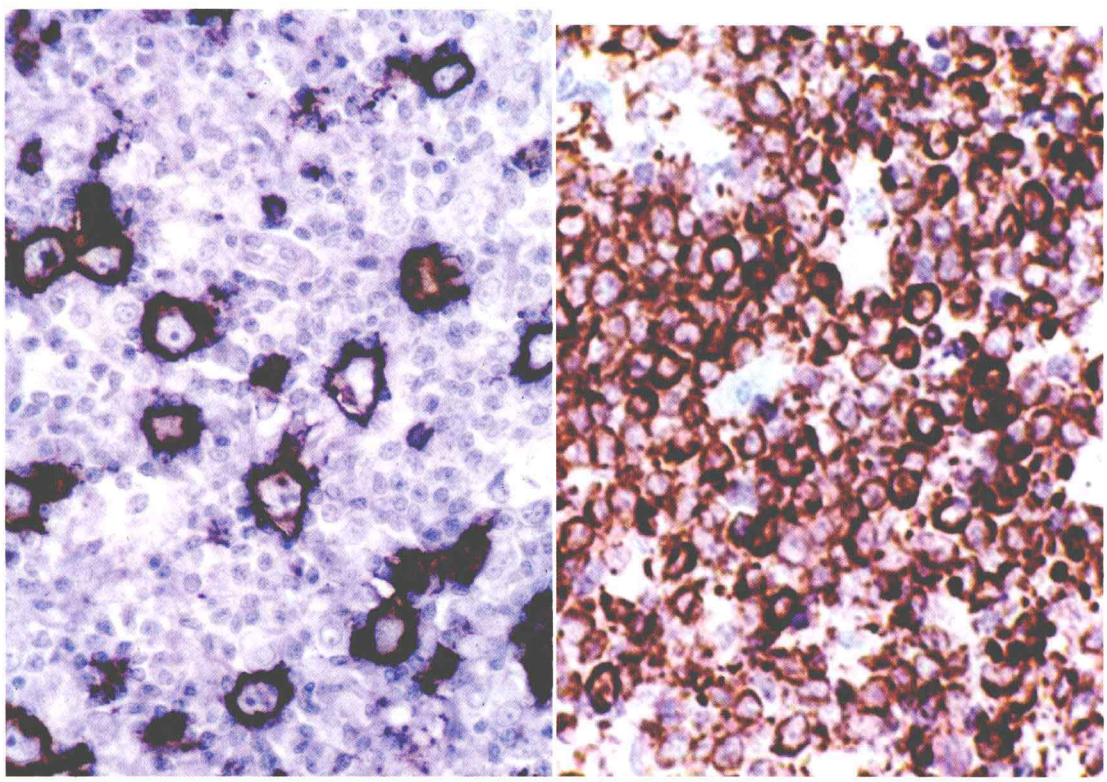
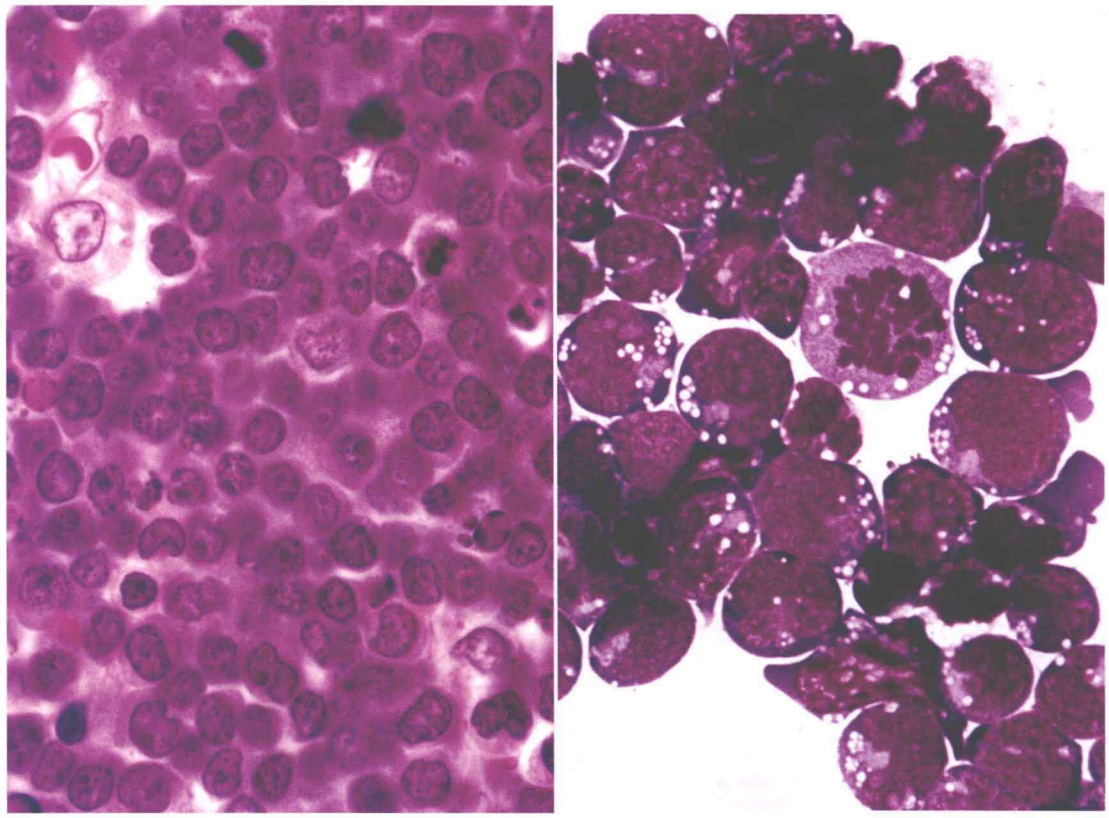


Figure 1–6. Mantle cell lymphoma, lymph node. A monotonous lymphoid infiltrate highlighted by nuclear staining for cyclin D1 maintains its mantle zone pattern, surrounding a non-neoplastic germinal center (negative staining, **left**).



B C

Figure 1–7. Diffuse large B-cell lymphoma. **B:** In the T-cell/histiocyte-rich variant of DLBCL, a background of small non-neoplastic T cells surrounds the large neoplastic B lymphocytes, which are highlighted by immunostaining for CD20. **C:** A case of DLBCL demonstrating Bcl-2 protein expression (dark cytoplasmic staining), a finding generally associated with adverse outcome.



A B

Figure 1–8. Burkitt's lymphoma. **A:** The cells are uniform, round to oval, with multiple small basophilic nucleoli. The nuclear size is similar to that of the "starry sky" histiocyte in the **upper left.** Mitotic activity is present. **B:** A touch preparation demonstrates lipid vacuoles in the deeply basophilic cytoplasm.

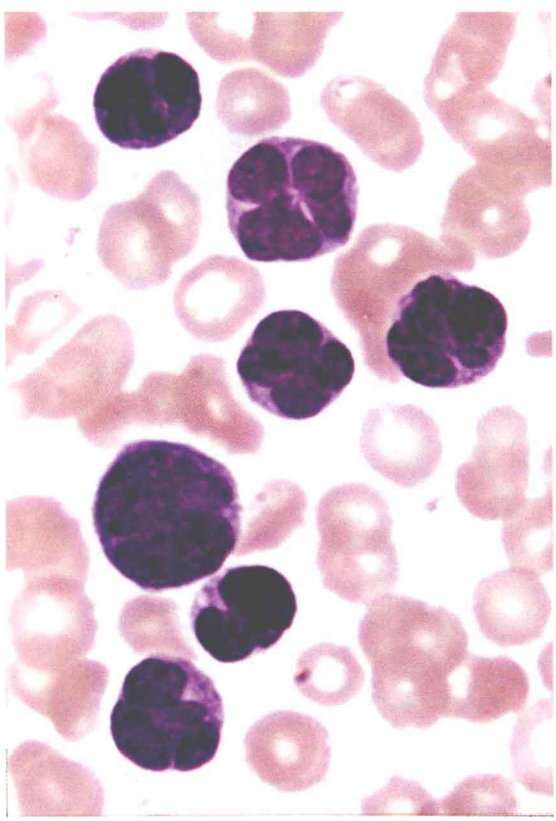


Figure 1–10. Adult T-cell leukemia/lymphoma. Markedly polylobated ("flower") cells circulate in the peripheral blood.

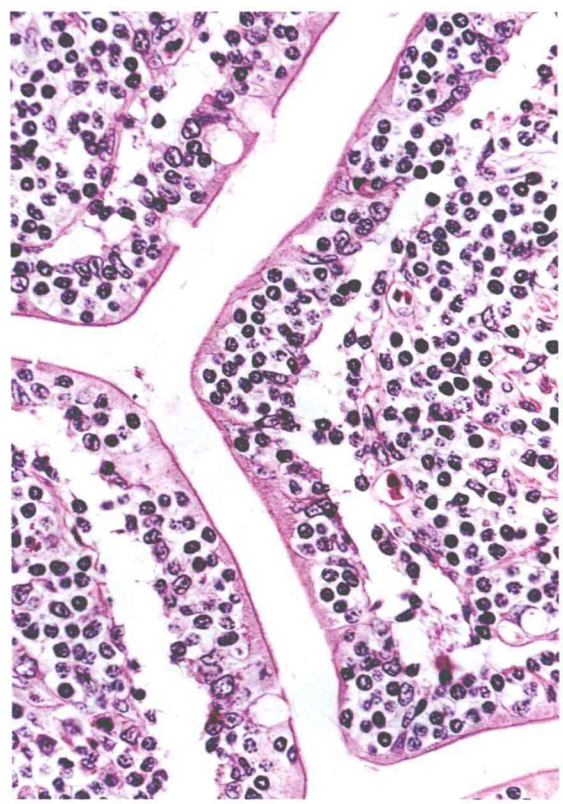


Figure 1–12. Enteropathy-type T-cell lymphoma. Atypical lymphocytes with pale cytoplasm infiltrate the epithelial mucosa and lamina propria of small intestinal villi.

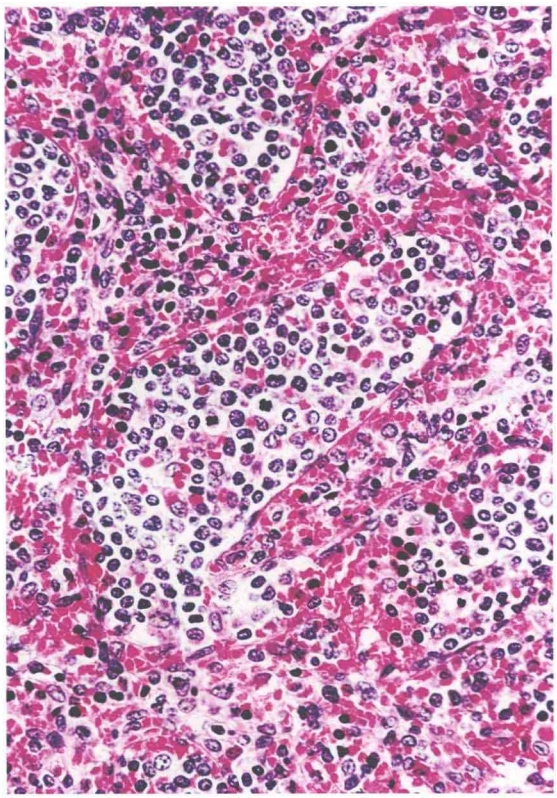


Figure 1–13. Hepatosplenic T-cell lymphoma. This liver biopsy shows a monotonous population of medium-sized cells with pale cytoplasm distending the hepatic sinusoids.

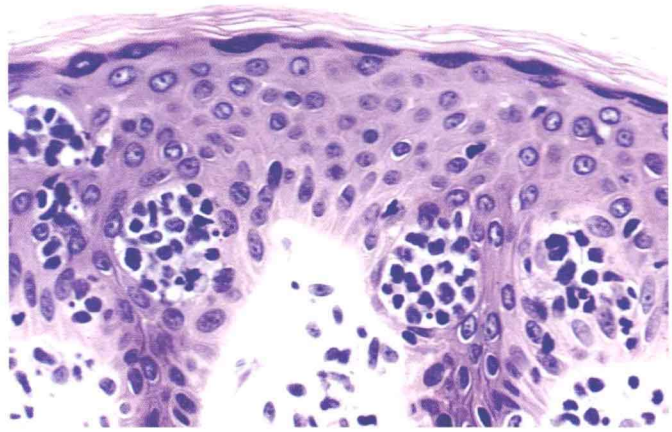


Figure 1–15. Mycosis fungoides. This skin biopsy shows neoplastic lymphocytes with convoluted nuclei forming Pautrier microabscesses within the epidermis.

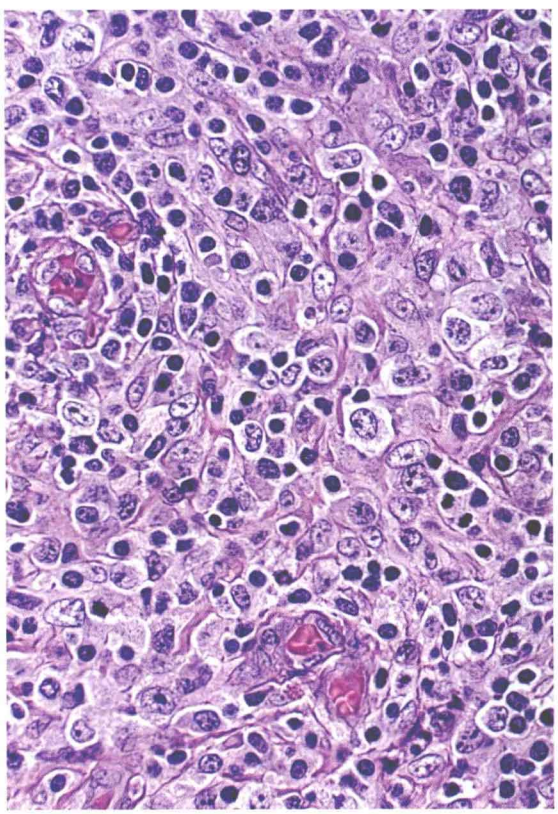
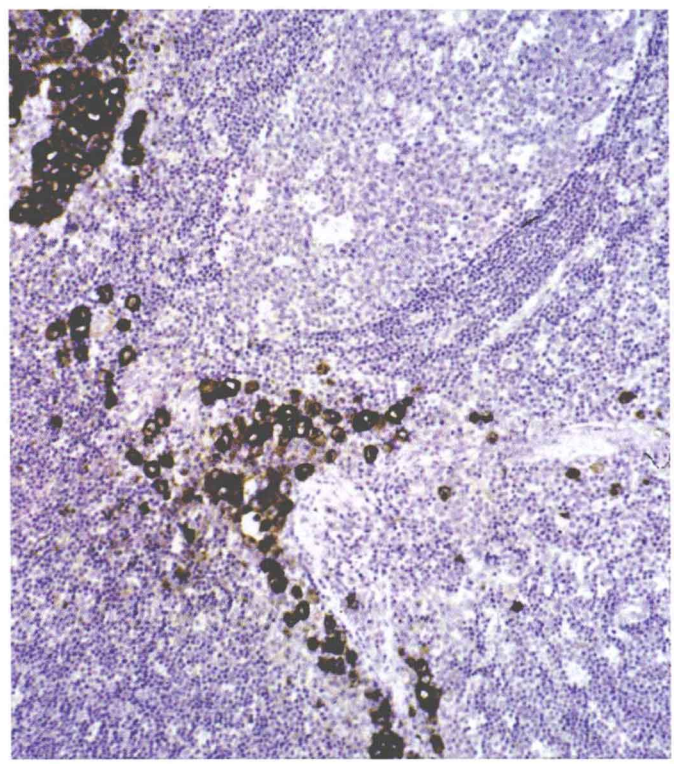
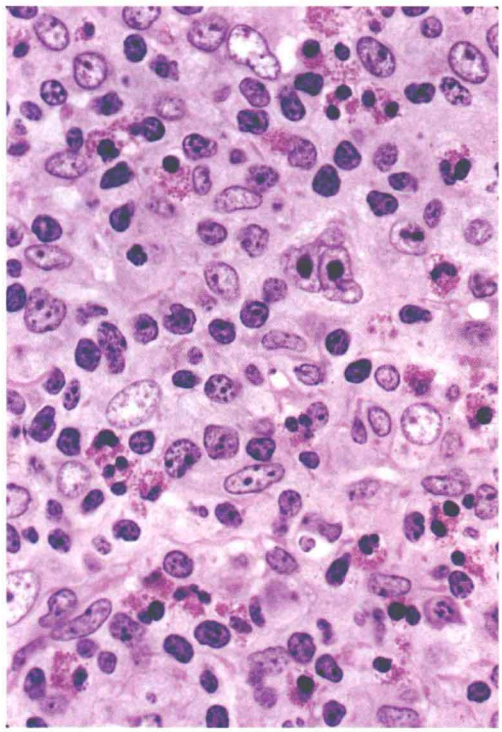


Figure 1–16. Angioimmunoblastic T-cell lymphoma. There is an infiltrate of atypical lymphoid cells with pale cytoplasm in a mixed inflammatory background, and prominent post-capillary venules with plump endothelial cells.



B

Figure 1–18. Systemic anaplastic large cell lymphoma (ALCL). **B:** The malignant cells are strongly positive for CD30 by immunohistochemistry.



B

Figure 1–19. Hodgkin's lymphoma. **B:** Mixed-cellularity Hodgkin's lymphoma, showing classic Reed–Sternberg cells admixed with lymphocytes, plasma cells, and eosinophils.

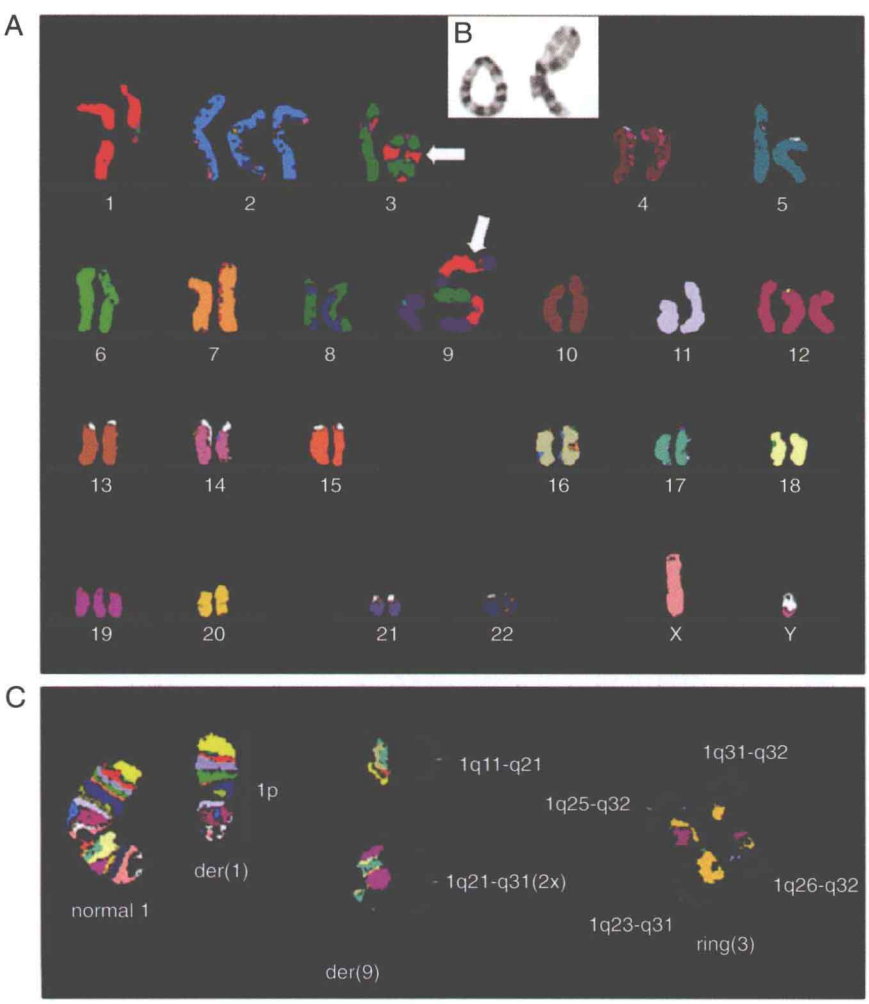


Figure 2–3. Multicolor karyotype (MFISH) of a representative case of diffuse, large B-cell lymphoma. **A:** The karyotype reveals a deletion of the q arm of chromosome 1, trisomy for chromosomes 2, 12, and 19, and two complex rearrangements *(white arrows)* representing a large-ring chromosome 3 composed of alternating segments of material from chromosome 1 and chromosome 3, and a large derivative chromosome 9 composed of alternating segments of material from chromosomes 1, 3, and 9. **B:** G-banded image of ring (3) and der (9). **C:** Multicolor banding pattern of the chromosome 1 segments of der (1), der (9), and ring (3). Normal chromosome 1 is shown on the left.

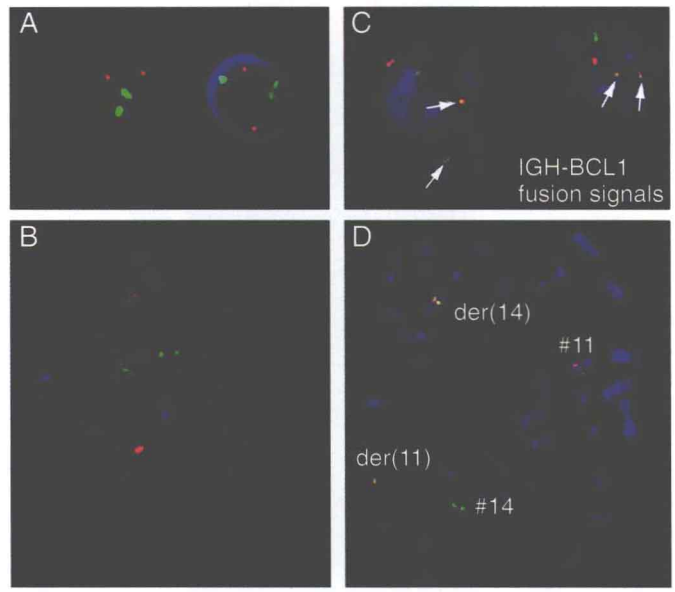


Figure 2–4. Locus-specific FISH images of a representative case of mantle cell lymphoma obtained with a commercial Vysis LSI IGH/BCL1 dual-color, dual-fusion translocation probe. The normal pattern of two BCL1 (red) and two IGH (green) signals are evident in **(A),** an interphase nucleus, and **(B),** a metaphase. An abnormal pattern of one BCL1 signal (red), one IGH signal (green), and two IGH-BCL1 fusion signals are evident in **(C),** an interphase nucleus (fusion signals indicated by *white arrows*), and **(D),** in a metaphase containing the t(11;14) of MCL (normal and derivative chromosomes indicated with *white lettering*).

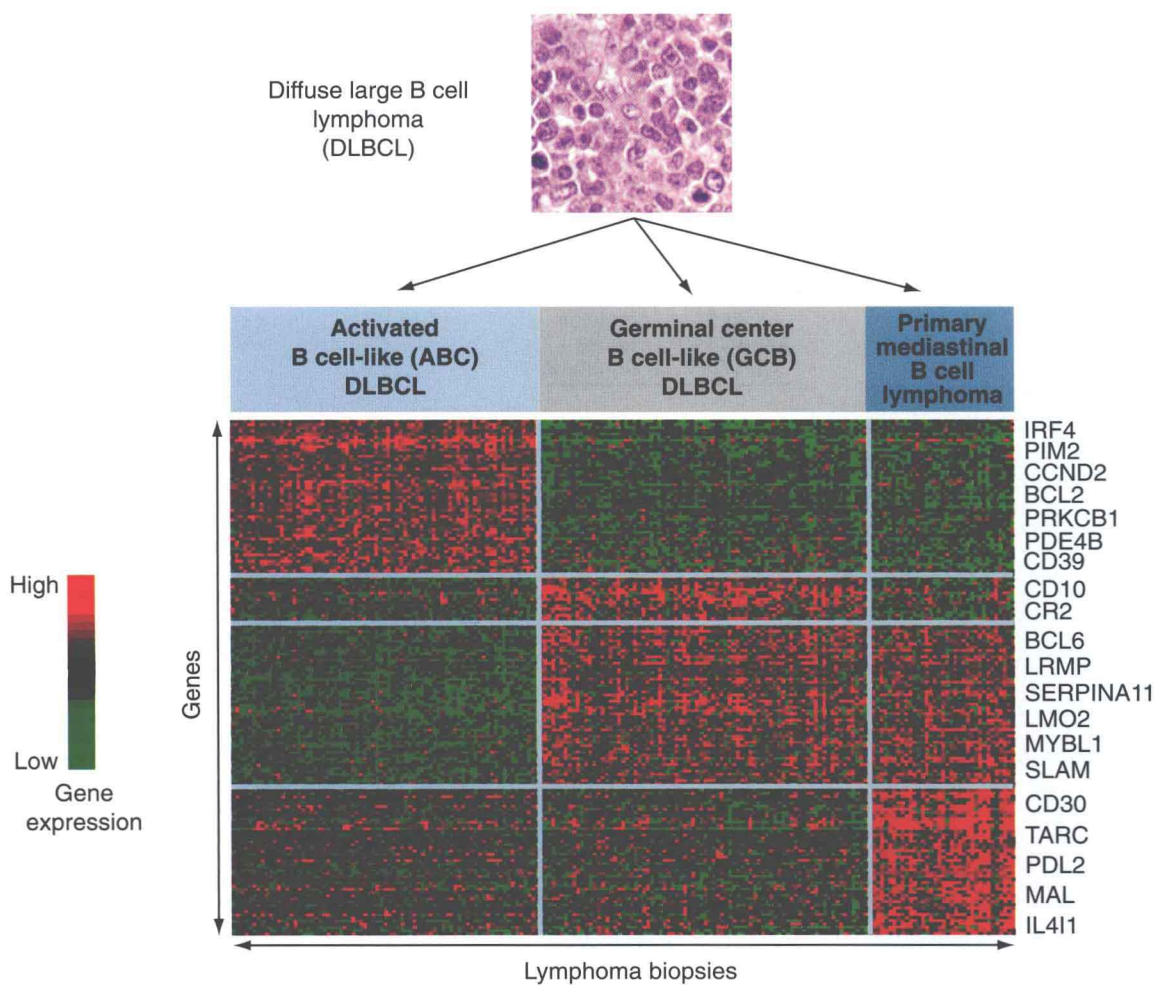
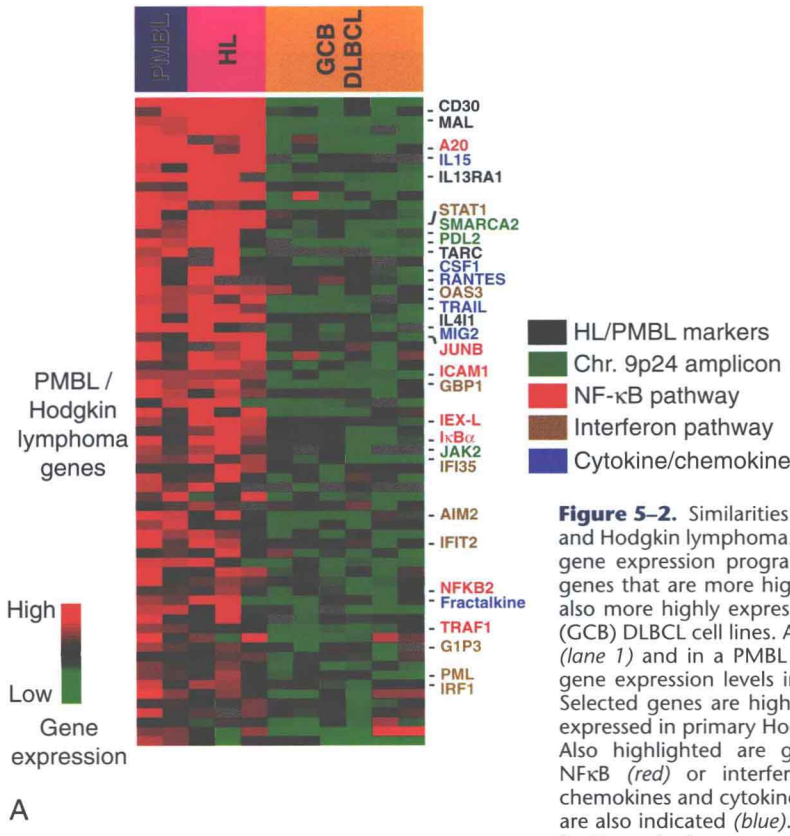
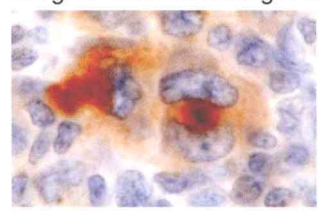


Figure 5–1. Definition of molecularly and clinically distinct subgroups of diffuse large B-cell lymphoma (DLBCL) by gene expression profiling. Gene expression differences between germinal center B-cell–like (GCB) DLBCL, activated B-cell–like DLBCL, and primary mediastinal B-cell lymphoma (PMBL). Each row represents gene expression data from an individual biopsy sample, and each column represents a single gene on the DNA microarray. Relative gene expression is indicated according to the color bar shown at the left. Representative genes that distinguish the DLBCL subgroups are indicated. Not shown are ~18% of DLBCLs that do not fit any of the three gene expression subgroups well.



A

Mal expression in a Hodgkin Reed-Sternberg cell



B

Figure 5–2. Similarities between primary mediastinal B-cell lymphoma (PMBL) and Hodgkin lymphoma. **A:** PMBL and Hodgkin's lymphoma (HL) share a broad gene expression program. The 69 genes depicted are all PMBL "signature" genes that are more highly expressed in PMBL than in other DLBCLs, and are also more highly expressed in HL cell lines than in germinal center B-cell–like (GCB) DLBCL cell lines. Average gene expression levels in primary PMBL tumors *(lane 1)* and in a PMBL cell line, K1106 *(lane 2)*, are shown. Also shown are gene expression levels in three HL cell lines and in six GCB DLBCL cell lines. Selected genes are highlighted that have been shown to be characteristically expressed in primary Hodgkin's Reed–Sternberg cells and/or PMBL cells *(black)*. Also highlighted are genes that are activated by signaling through the NFκB *(red)* or interferon *(brown)* pathways. Numerous genes encoding chemokines and cytokines, many of which are activated by the NF-κB pathway, are also indicated *(blue)*. PMBL and HL tumors frequently harbor a gain/amplification of chromosome region 9p24, which contains several genes that are characteristically expressed in both lymphoma types *(green)*. **B:** Detection of Mal protein expression in a primary Hodgkin's Reed–Sternberg cell by immunohistochemistry.

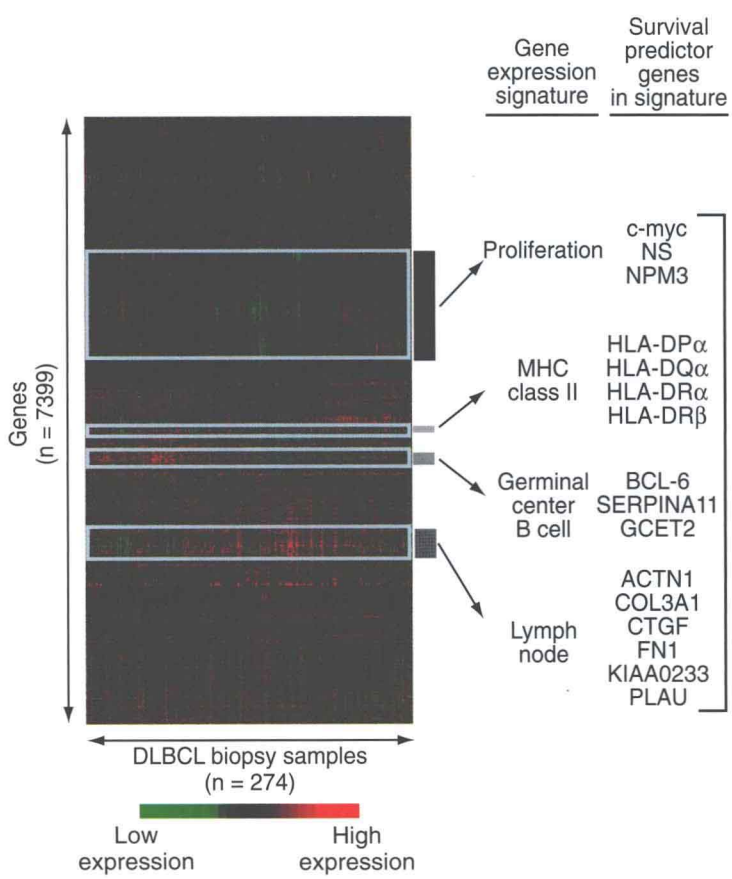


Figure 5–4. A gene expression–based predictor of survival following chemotherapy for DLBCL. Hierarchical clustering of the gene expression data reveals gene expression signatures containing survival predictor genes. A hierarchical clustering algorithm was used to organize genes based on their expression across 274 DLBCL biopsy samples. Four gene expression signatures are indicated, each of which is composed of coordinately expressed genes that reflect a specific biological aspect of the tumors (see text for details). A supervised method was used to discover genes whose expression patterns were correlated with the length of survival, and the majority of these "survival predictor genes" belonged to one of the four indicated gene expression signatures.[10] Shown are 16 representative survival predictor genes from these four signatures that were used to create a multivariate model of survival.