# FRONTIERS IN GASTROINTESTINAL CANCER

Edited by BERNARD LEVIN, M.D.

ROBERT H. RIDDELL, M.D.

# FRONTIERS IN GASTROINTESTINAL CANCER

# Edited by

#### BERNARD LEVIN, M.D.

Formerly: Associate Professor, Department of Medicine
Director, Gastrointestinal Oncology Service
University of Chicago Hospitals and Clinics
Present address: Professor, University of Texas
Section of Digestive Diseases and Gastrointestinal Oncology
Division of Medicine, M.D. Anderson Hospital, Houston

#### ROBERT H. RIDDELL, M.D.

Formerly: Associate Professor of Pathology University of Chicago Hospitals and Clinics-Present address: Professor, Department of Pathology McMaster University, Hamilton, Ontario

ELSEVIER
New York • Amsterdam • Oxford

Elsevier Science Publishing Co., Inc. 52 Vanderbilt Avenue, New York, New York 10017

Distributors outside the United States and Canada

Elsevier Science Publishers B.V. P.O. Box 211, 1000 AE Amsterdam, The Netherlands

© 1984 Elsevier Science Publishing Co., Inc.

The chapter by John Y. Killen, Jr., and Susan S. Ellenberg, as a U.S. government work, cannot be copyrighted and lies in the public domain.

This book has been registered with the Copyright Clearance Center, Inc. For further information, please contact the Copyright Clearance Center, Salem, Massachusetts.

ISBN 0-444-00852-7 ISSN 0743-930X

Manufactured in the United States of America

## PREFACE

Gastrointestinal cancer continues to be a significant factor in much human suffering. Unknown causes, changing epidemiological patterns, the difficulty of early diagnosis, and the apparent resistance of some malignancies to chemotherapeutic agents all serve to heighten the immense clinical and scientific challenges faced by the investigator and practicing physician.

The critical reader may well consider the term "frontiers" to be rather presumptuous. However, we feel that this volume does present a selection of important topics that convey some of the exciting scientific and clinical advances in this field. Distinguished investigators responded enthusiastically to our invitation to contribute manuscripts. We specifically requested them to discuss their own work in the context of the overall area. These "minireviews" cover topics ranging from etiology, pathogenesis, histopathology, and experimental carcinogenesis to therapy. We believe that our authors have succeeded admirably but will leave to the reader the ultimate judgment of our failure or success. At the very least, we hope we have been able to stimulate interest and controversy in this important area.

## **CONTRIBUTORS**

#### Editors

#### BERNARD LEVIN, M.D.

Formerly: Associate Professor, Department of Medicine and Director of the Gastrointestinal Oncology Service, University of Chicago Hospitals and Clinics Present address: Professor, University of Texas, Section of Digestive Diseases and Gastrointestinal Oncology, Division of Medicine, M.D. Anderson Hospital, Houston

#### ROBERT H. RIDDELL, M.D.

Formerly: Associate Professor of Pathology, University of Chicago Hospitals and Clinics

Present address: Professor, Department of Pathology, McMaster University, Hamilton, Ontario

#### Chapter Authors

VINCENT G. ALLFREY, Ph.D.

Laboratory of Cell Biology, Rockefell University, New York, New York

#### JEANNIE CHAMBERS, ? ...

Department of Radiation Oncology, The Johns Hopkins Hospital, Baltimore, Maryland

#### GARY M. CLARK, Ph.D.

Department of Medicine, Division of Oncology, University of Texas Health Science Center at San Antonio

#### WILLIAM D. DEWYS, M.D.

From the Prevention Program, Division of Cancer Prevention and Control, National Cancer Institute, Bethesda, Maryland

#### DANIEL E. DOSORETZ, M.L.

Assistant Professor, Department of Radiation Therapy, Massachusetts General Hospital and Harvard Medical School Boston, Massachusetts

此为试读,需要完整PDF请访问: www.ertongbook.com

#### KAMBIZ DOWLATSHAHI, M.D., F.R.C.S.

Assistant Professor, Department of Surgery, University of Chicago

#### DAVID M. EDDY, M.D., Ph.D.

Director, Center for Health Policy Reseach and Education, Duke University, Durham, North Carolina

#### SUSAN S. ELLENBERG, Ph.D.

Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland

#### WILLIAM D. ENSMINGER, M.D., PH.D.

Professor, Departments of Internal Medicine and Pharmacology, University of Michigan, Ann Arbor

#### DAVID S. ETTINGER, M.D.

Department of Medical Oncology, The Johns Hopkins Hospital, Baltimore, Maryland

#### I. GEBOERS

Licensee in Mathematics, Assistant, Division of Epidemiology, University of Louvain, Belgium

#### LEONARD L. GUNDERSON, M.D., M.S.

Associate Professor in Oncology, Mayo Clinic, Rochester, Minnesota

#### JOHN W. GYVES, M.D.

Instructor, Department of Internal Medicine, University of Michigan, Ann Arbor

#### FREDDIE ANN HOFFMAN, M.D.

Clinical Investigations Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland

#### R. BRUCE HOSKINS, M.D.

Clinical Assistant Professor in Radiology, Southern Illinois University Medical School; Radiotherapist, St. Johns Hospital, Springfield, Illinois

#### IANET A. HOUGHTON, Ph.D.

Department of Biochemical and Clinical Pharmacology, St. Jude Children's Research Hospital, Memphis, Tennessee

#### PETER I. HOUGHTON, Ph.D.

Department of Biochemical and Clinical Pharmacology, St. Jude Children's Research Hospital, Memphis, Tennessee

#### J. V. JOOSSENS, M.D.

Professor of Medicine, Head, Division of Epidemiology, University of Louvein, Belgium

#### LEONARD B. KAHN, M.B., B.CH., M.MED.PATH., M.R.C.PATH.

Chaairman, Department of Laboratories, Long Island Jewish—Hillside Medical Center; Professor of Pathology, State University of New York at Stony Brook

#### IOHN Y. KILLEN, Ir., M.D.

Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland

#### JERRY L. KLEIN, Ph.D.

Department of Radiation Oncology, The Johns Hopkins Hospital, Baltimore, Maryland

#### GENE KOPELSON, M.D.

Assistant Professor in Therapeutic Radiology, Tufts New England Medical Center, Boston, Massachusetts

#### KEN KOPHER, B.S.

Department of Radiation Oncology, The Johns Hopkins Hospital, Baltimore, Maryland

#### STEVEN LANGE, M.D.

Division of Medical Oncology, Vincent T. Lombardi Cancer Research Center, Georgetown University, Washington, D.C.

#### TERENCE A. LAWSON, Ph.D.

The Eppley Institute for Research in Cancer and the Department of Pathology and Laboratory Medicine, University of Nebraska Medical Center, Omaha

#### PETER K. LEIGHNER, Ph.D.

Department of Radiation Oncology, The Johns Hopkins Hospital, Baltimore, Maryland

#### BERNARD LEVIN, M.D.

Formerly: Associate Professor, Department of Medicine, and Director of the Gastrointestinal Oncology Service, University of Chicago Hospitals and Clinics Present address: Professor, University of Texas, Section of Digestive Diseases and Gastrointestinal Oncology, Division of Medicine, M.D. Anderson Hospital, Houston

#### DAVID M. LOESCH, M.D.

Department of Medicine, Division of Oncology, University of Texas Health Science Center at San Antonio. Present address: Wright-Patterson Air Force Base, Dayton, Ohio

#### ALAIN P. MASKENS, M.D.

Groupe de Recherche Alimentation et Cancer, Brussels, Belgium

#### RABIA MIR. M.D.

Attending Pathologist, Long Island Jewish-Hillside Medical Center; Assistant Professor in Pathology, State University of New York at Stony Brook

#### SOHRAB MOBARHAN, M.D.

Associate Professor, Department of Medicine, Section of Gastroenterology, University of Illinois, Chicago

#### RICHARD C. NAIRN, M.D.

Professor and Chairman, Department of Pathology and Immunology, Monash University, and Alfred Hospital, Melbourne, Australia

#### STANLEY E. ORDER, M.D., Sc.D.

Director of Radiation Oncology, The Johns Hopkins Hospital, Baltimore, Maryland

xvi CONTRIBUTORS

#### ERIC PIHL, M.D.

Associate Professor, Department of Pathology and Immunology, Monash University, and Alfred Hospital, Melbourne, Australia

#### MORRIS POLLARD, D.V.M., Ph.D.

Lobund Laboratory, University of Notre Dame, Notre Dame, Indiana

#### PARVIZ M. POUR. M.D.

The Eppley Institute for Research in Cancer and the Department of Pathology and Laboratory Medicine, University of Nebraska Medical Center, Omaha

#### AMELIA REICHMANN, M.D.

Melamid Cytogenetics Laboratory, Section of Gastroenterology, Department of Medicine, University of Chicago

#### ROBERT H. RIDDELL, M.D.

Formerly: Associate Professor of Pathology, University of Chicago Hospitals and Clinics

Present address: Professor, Department of Pathology, McMaster University, Hamilton, Ontario

#### TYVIN A. RICH, M.D.

Assistant Professor, Joint Center for Radiation Therapy, Harvard Medical School, Boston, Massachusetts

#### PHILIP S. SCHEIN, M.D., F.A.C.P.

Division of Medical Oncology, Vincent T. Lombardi Cancer Research Center, Georgetown University, Washington, D.C.

#### HELMUT SCHMIDT, M.D.

Department of Medicine, University of Erlangen, Erlangen, West Germany

#### STANLEY S. SIEGELMAN, M.D.

Department of Diagnostic Radiation, The Johns Hopkins Hospital, Baltimore, Maryland

#### ROBERT SILGALS, M.D.

Division of Medical Oncology, Vincent T. Lombardi Cancer Research Center, Georgetown University, Washington, D.C.

#### FREDERICK P. SMITH, M.D., F.A.C.P.

Division of Medical Oncology, Vincent T. Lombardi Cancer Research Center, Georgetown University, Washington, D.C.

#### I. C. TALBOT, M.D., F.R.C.PATH.

Department of Pathology, University of Leicester, United Kingdom

#### JOEL E. TEPPER, M.D.

Assistant Professor in Radiation Therapy, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts

#### DANIEL D. VON HOFF, M.D.

Department of Medicine, Division of Oncology, University of Texas Health Science Center at San Antonio CONTRIBUTORS xvii

MOODY D. WHARAM, M.D.

Department of Radiation Oncology, The Johns Hopkins Hospital, Baltimore, Maryland

ARIE J. ZUCKERMAN, M.D., D.Sc., F.R.C.P., F.R.C.PATH

Department of Medical Microbiology, and WHO Collaborating Centre for Reference and Research on Viral Hepatitis, London School of Hygiene and Tropical Medicine (University of London)

CURRENT ONCOLOGY Nathaniel I. Berlin, Series Editor-in-Chief

TITLES IN CURRENT ONCOLOGY

FRONTIERS IN GASTROINTESTINAL CANCER
Bernard Levin and Robert H. Riddell, Editors-in-Chief

# CONTENTS

Preface	xi
Contributors	xiii
· · · · · · · · · · · · · · · · · · ·	
DIET AND ENVIRONMENT IN THE ETIOLOGY	
OF ESOPHAGEAL CARCINOMA	1
Kambîz Dowlatshahi and Sohrab Mobarhan	
Geographic Incidence	1
Nutritional Factors	8
Discussion	12
Summary	13
LYMPHOID PROLIFERATIONS OF THE	
GASTROINTESTINAL TRACT	19
Leonard B. Kahn and Rabia Mir	
Lymphoid Hyperplasia	19
Lymphoma	24
CHEMOTHERAPY OF ADVANCED	
GASTROINTESTINAL MALIGNANCIES	41
Frederick P. Smith, Steven Lange, Robert Silgals,	
and Philip S. Schein	
Esophageal Cancer	41
Gastric Cancer Pancreatic Cancer	43
Colorectal Cancer	48
Conclusion	51 53
	33

此为试读,需要完整PDF请访问: www.ertongbook.com

PANCREATIC CANCER IN THE HAMSTER MODEL	61
Parviz M. Pour and Terence A. Lawson	
Characterization of the Model	61
Pancreatic Carcinogens and Their Metabolism	62
Histogenesis of Pancreatic Cancer	63
Mechanisms of Pancreatic Carcinogenesis	70
Modification of Pancreatic Carcinogenesis	74
Biologic Marker of Experimental Pancreatic Cancer	75
Comparative Studies	75
Suggested Direction of Future Work	76
PATHOPHYSIOLOGY OF ANOREXIA AND DISTURBANCES OF TASTE IN CANCER PATIENTS	81
William D. DeWys and Freddie Ann Hoffman	
Pathophysiology of Cancer Cachexia	81
Control of Food Intake	83
Taste Abnormalities in Cancer Patients	84
Learned Food Aversions and Eating	87
Therapeutic Considerations	87
ANTITUMOR EFFECT OF INDOMETHACIN IN RATS WITH	
AUTOCHTHONOUS INTESTINAL TUMORS	91
Morris Pollard	0.2
Model Tumor Systems	91
Stages of Carcinogenesis	92
The Lobund Experimental Protocol for Intestinal Cancer	92
Applications of the Model Tumor System	95
Discussion	99
Addendum	101
LARGE BOWEL CARCINOMA: SIGNIFICANCE OF LYMPH	
NODE REACTIONS	105
Richard C. Nairn and Eric Pihl	
Lymph Node Immunomorphology	106
Prognostic Significance of Lymph Node Patterns	108
Humoral Antibody Production by Regional Lymph Nodes	113
Cell-Mediated Immunity (CMI)	113
Antibody-Dependent Cellular Cytotoxicity (ADCC)	114
Natural Killer (NK) Cell Cytotoxicity, Histiocytes, and Macrophages	114
Conclusions and Outlook on the Future	115
EXPERIMENTAL CHEMOTHERAPY IN COLON CANCER	119
Janet A. Houghton and Peter J. Houghton	
The Model	120
Sensitivity of Tumors to 5-fluorouracil (FUra)	120
Metabolism of 5-fluorouracil	121
Mechanism of Cytotoxicity of 5-fluorouracil in Human Colorectal	
Xenografts	123

Natural Resistance of Human Colorectal Xenografts to 5-fluorouracil Increased Formation of the Covalent Ternary Complex Selective Protection of the Host During Therapy with 5-fluorouracil Selective Increase in 5-fluorouracil Activation in Tumors Conclusions and Future Directions	124 126 127 129 132
CONTROL OF EXPERIMENTAL COLON CANCER BY SODIUM CYANATE	139
Vincent G. Allfrey	200
Cyanate Inhibition of Protein and DNA Synthesis in Tumor Cells In Vivo Cyanate Activation for Suppression of Protein Synthesis in Cultured	139
Tumor Cells	141
Mechanism of Cyanate Inhibition of Protein Synthesis Induction of Cyanate Sensitivity in Cells Transformed by an Oncogenic	145
Virus Butyrate Effects on Cyanate Sensitivity of Cultured Tumor Cells	147 147
Cyanate Inhibition of Growth of Murine Colonic Tumors	148
HEPATIC ARTERIAL THERAPIES FOR PRIMARY AND	450
SECONDARY HEPATIC CARCINOMAS	153
William D. Ensminger and John W. Gyves	
Perspectives on Regional Therapy for Hepatic Cancers	153
Rationale for Hepatic Arterial Chemotherapy Problems Unique to Hepatic Arterial Chemotherapy	154
Hepatic Arterial Versus Systemic Chemotherapy for Hepatic Tumor	154 156
Tumor Microcirculation	157
Effects of Vasoconstrictors on Liver and Tumor Microcirculation Microspheres to Improve Selectivity Based in Microcirculation	158
Differences	159
Amplification of the Selective Effect of Yttrium-90 Microspheres	160
Prospects for Success with an Aggressive Integrated Approach	160
Concluding Remarks	161
DIET AND ENVIRONMENT IN THE ETIOLOGY OF	
GASTRIC CANCER	167
. V. Joossens and J. Geboers	
Nonenvironmental Factors	167
Dietary and Environmental Factors	168
The Gastric Cancer–Stroke Relationship	178
Summary	179
THE SIGNIFICANCE OF CHROMOSOMAL CHANGES IN	-
HUMAN LARGE BOWEL TUMORS	185
Amelia Reichmann and Bernard Levin	
Chromosomal Abnormalities in Human Large Bowel Tumors Karotypic Patterns and the Correlation with Anatomic Distribution in	185
Large Bowel Tumors	188

The Relationship Between Chromosomal Abnormalities and Embryologic and Physiologic Characteristics Benign Colonic Adenomas and Their Premalignant Potential Significance of Chromosomal Changes in Human Large Bowel Tumors Glossary of Cytogenetic Terms	188 139 190
CELL CLONING TECHNIQUES IN THE SELECTION OF CHEMOTHERAPEUTIC AGENTS FOR GASTROINTESTINAL TUMORS	193
David M. Loesch, Gary M. Clark, and Daniel D. Von Hoff	
Materials and Methods Results Discussion	193 195 200
COST-EFFECTIVENESS OF COLORECTAL CANCER SCREENING	263
David M. Eddy	
Methods	203
Results	206
Variations Summary and Conclusions	212 217
RADIOLABELED ANTIBODIES IN THE TREATMENT OF PRIMARY LIVER MALIGNANCIES Stanley E. Order, Jerry L. Klein, Peter K. Leichner, Moody D. Wharam, Jeannie Chambers, Ken Kopher,	221
David S. Ettinger, and Stanley S. Seigelman	200
Antigens Initial Pilot Studies of Primary Liver Tumors	222 223
Toxicity	223
Response	224
Intrahepatic Biliary Carcinoma	225
Present Conclusions New Approaches	226 231
THE ROLE OF HEPATITIS B VIRUS IN PRIMARY HEPATOCELLULAR CARCINOMA	235
Arie J. Zuckerman	
Properties of Hepatitis B Virus and Serologic Markers of Infection The Carrier State of Hepatitis B Virus Epidemiologic and Geographic Correlations Between Hepatitis B Infection and Primary Hepatocellular Carcinoma	236 238
Production of Hepatitis B Surface Antigen by Cell Lines Derived from Human Hepatocellular Carcinoma	239
Integration of Hepatitis B Viral DNA in the PLC/PRF/5 Cell Line	241
Heterotransplantability of the PLC/PRF/5 Cells	242

Integration of Hepatitis B Virus DNA into the Genome of Liver Cells Animal Viruses That Are Phylogenetically Related to Human Hepatitis B	
Virus	245
MECHANISMS OF ADENOMA FORMATION IN THE COLON	249
Alain P. Maskens	7
The Tubular Adenoma	249
Successive Phases in the Emergence of a Tubular Adenoma	250
Mechanisms of Adenoma Formation	255
Summary and Conclusions	257
	*.
ADJUVANT CHEMOTHERAPY AND IMMUNOTHERAPY OF	
GASTROINTESTINAL CANCER	261
John Y. Killen, Jr. and Susan S. Ellenberg	
Principles of Adjuvant Therapy of Cancer	261
Gastric Cancer	262
Colon Cancer	264
Rectal Cancer	268 269
Esophageal Cancer Exocrine Pancreatic Cancer	270
Conclusions	270
RADIATION THERAPY IN THE MANAGEMENT OF	
GASTROINTESTINAL CANCER	273
Leonard L. Gunderson, Daniel E. Dosoretz, Gene Kopelson,	
Joel E. Tepper, Tyvin A. Rich, and R. Bruce Hoskins	
Esophageal Cancer	273
Gastric Cancer	274
Gallbladder and Extrahepatic Biliary Ducts	276
Pancreatic Carcinoma	277
Colorectal Cancer	280
Summary and Future Perspectives	286
LARGE BOWEL CARCINOMA: SIGNIFICANCE	
OF VENOUS INVASION	291
I. C. Talbot	
Identification of Venous Invasion	292
Incidence of Venous Invasion	293
Importance of Venous Invasion in Dissemination of Colorectal Cancer	294
Venous Invasion as an Indicator of Prognosis Biologic Phenomenon of Venous Invasion and Its Relationship to Tumor	294
Behavior	296
Suspected but Unproven Venous Invasion	301
Discussion Summary and Conclusions	303
	351125

CANCER IN BARRETT'S ESOPHAGUS AND INFLAMMATORY	
BOWEL DISEASE—WHAT'S NEW	307
Robert H. Riddell, Helmut Schmidt, and Bernard Levin	
Barrett's Esophagus	307
Heterotopic Gastric Mucosa	311
Inflammatory Bowel Disease and Neoplasia	313
Index	201
muex	321

# DIET AND ENVIRONMENT IN THE ETIOLOGY OF ESOPHAGEAL CARCINOMA

# KAMBIZ DOWLATSHAHI, M.D., F.R.C.S., AND SOHRAB MOBARHAN, M.D.

In most parts of the world, carcinoma of the esophagus is a rare disease. The incidence in the United States and Europe is 3 to 4 per 100,000 population per annum (Cutler and Young, 1975; Doll et al., 1970). In certain other areas, this rate increases more than twentyfold to almost 100 new cases per 100,000 population per annum, and esophageal cancer becomes the most frequently occuring neoplasm in the community (see Figures 1 and 2).

#### GEOGRAPHIC INCIDENCE

The sharp geographic demarcation between regions of high incidence of esophageal cancer and relatively close neighboring areas with a much lower incidence, such as in northeast Iran, has given rise to a great deal of scientific debate regarding the role of nutritional deficiencies and environmental carcinogens and their possible reciprocal interaction in the development of esophageal cancer. In recent years, a significant body of epidemiologic and biologic studies has accumulated suggesting that dietary factors, particularly micronutrients such as trace elements and vitamins, could influence carcinogenesis. These may act by modifying the activity of either carcinogens or host protective mechanisms against cancer. Esophageal cancer has a strong association with malnutrition secondary to poor economic conditions, special dietary habits, and/or alcoholism.

In our discussion, we will distinguish the predisposing factors, such as the nutritional status, from the promoting factors or carcinogens that act directly on the esophageal mucosa.

From the Department of Surgery, University of Chicago; and the Department of Medicine, Section of Gastroenterology, University of Illinois, Chicago.