

NUTRITION, GROWTH, AND CANCER

EDITORS: George P. Tryfiates
Kedar N. Prasad



1990年7月24日

NUTRITION, GROWTH, AND CANCER

Proceedings of the First International Symposium on Nutrition, Growth, and
Cancer held in Athens, Greece, April 26-30, 1987

Editors

George P. Tryfiates

Department of Biochemistry

West Virginia University

Medical Center

Morgantown, West Virginia

Kedar N. Prasad

Center for Vitamins and Cancer Research

University of Colorado

Health Sciences Center

Denver, Colorado

ALAN R. LISS, INC. • NEW YORK

Address all inquiries to the Publisher
Alan R. Liss, Inc., 41 East 11th Street, New York, NY 10003

Copyright © 1988 Alan R. Liss, Inc.

Printed in the United States of America.

Under the conditions stated below the owner of copyright for this book hereby grants permission to users to make photocopy reproductions of any part or all of its contents for personal or internal organizational use, or for personal or internal use of specific clients. This consent is given on the condition that the copier pay the stated per-copy fee through the Copyright Clearance Center, Incorporated, 27 Congress Street, Salem, MA 01970, as listed in the most current issue of "Permissions to Photocopy" (Publisher's Fee List, distributed by CCC, Inc.), for copying beyond that permitted by sections 107 or 108 of the US Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale.

Library of Congress Cataloging-in-Publication Data

**International Symposium on Nutrition, Growth, and
Cancer (1st : 1987 : Athens, Greece)
Nutrition, growth, and cancer.**

(Progress in clinical and biological research ;
v. 259)

"Sponsored by the International Association for
Vitamin and Nutritional Oncology and the National
Hellenic Research Foundation"—P. facing t.p.
Includes index.

1. Cancer—Nutritional aspects—Congresses.
2. Cancer—Prevention—Congresses. 3. Carcinogenesis—
Congresses. 4. Human growth—Congresses.

I. Tryfiates, George P. II. Prasad, Kedar N.

III. International Association for Vitamin and Nutritional
Oncology. IV. Ethnikon Hidryma Ereunōn (Greece)

V. Title. VI. Series. [DNLN: 1. Neoplasms—etiology—
congresses. 2. Neoplasms—prevention & control—
congresses. 3. Nutrition—congresses. 4. Vitamins—
congresses. W1 PR668E v.259 / QZ 200 I61237 1987n]

RC268.45.I58 1987 616.99'4 87-29753
ISBN 0-8451-5109-6

PROGRESS IN CLINICAL AND BIOLOGICAL RESEARCH

Series Editors

Nathan Back
George J. Brewer

Vincent P. Eijssvoegel
Robert Grover

Kurt Hirschhorn
Seymour S. Kety

Sidney Udenfriend
Jonathan W. Uhr

RECENT TITLES

Vol 210: Ionic Currents in Development,
Richard Nuccitelli, *Editor*

**Vol 211: Transfusion Medicine: Recent
Technological Advances,** Kris Murawski, Frans
Peetoom, *Editors*

**Vol 212: Cancer Metastasis: Experimental and
Clinical Strategies,** D.R. Welch, B.K. Bhuyan,
L.A. Liotta, *Editors*

**Vol 213: Plant Flavonoids in Biology and
Medicine: Biochemical, Pharmacological, and
Structure-Activity Relationships,** Vivian
Cody, Elliott Middleton, Jr., Jeffrey B.
Harborne, *Editors*

**Vol 214: Ethnic Differences in Reactions to
Drugs and Xenobiotics,** Werner Kalow, H.
Werner Goedde, Dharam P. Agarwal, *Editors*

**Vol 215: Megakaryocyte Development and
Function,** Richard F. Levine, Neil Williams,
Jack Levin, Bruce L. Evatt, *Editors*

**Vol 216: Advances in Cancer Control: Health
Care Financing and Research,** Lee E.
Mortenson, Paul F. Engstrom, Paul N.
Anderson, *Editors*

Vol 217: Progress in Developmental Biology,
Harold C. Slavkin, *Editor*. Published in two
volumes.

**Vol 218: Evolutionary Perspective and the
New Genetics,** Henry Gershowitz, Donald L.
Rucknagel, Richard E. Tashian, *Editors*

**Vol 219: Recent Advances in Arterial Diseases:
Atherosclerosis, Hypertension, and
Vasospasm,** Thomas N. Tulenko, Robert H.
Cox, *Editors*

**Vol 220: Safety and Health Aspects of Organic
Pollutants,** Vesa Riihimäki, Ulf Ulfvarson,
Editors

Vol 221: Developments in Bladder Cancer,
Louis Denis, Tadao Nijijima, George Prout, Jr.,
Fritz H. Schröder, *Editors*

Vol 222: Dietary Fat and Cancer, Clement Ip
Diane F. Birt, Adrienne E. Rogers, Curtis
Metlin, *Editors*

Vol 223: Cancer Drug Resistance, Thomas C.
Hall, *Editor*

**Vol 224: Transplantation: Approaches to
Graft Rejection,** Harold T. Meryman, *Editor*

**Vol 225: Gonadotropin Down-Regulation in
Gynecological Practice,** Rune Rolland, Dev R.
Chadha, Wim N.P. Willemsen, *Editors*

**Vol 226: Cellular Endocrinology: Hormonal
Control of Embryonic and Cellular
Differentiation,** Ginette Serrero, Jun Hayashi,
Editors

Vol 227: Advances in Chronobiology, John E.
Pauly, Lawrence E. Scheving, *Editors*.
Published in two volumes.

**Vol 228: Environmental Toxicity and the
Aging Processes,** Scott R. Baker, Marvin
Rogul, *Editors*

**Vol 229: Animal Models: Assessing the Scope
of Their Use in Biomedical Research,** Junichi
Kawamata, Edward C. Melby, Jr., *Editors*

**Vol 230: Cardiac Electrophysiology and
Pharmacology of Adenosine and ATP: Basic
and Clinical Aspects,** Amir Pelleg, Eric L.
Michelson, Leonard S. Dreifus, *Editors*

**Vol 231: Detection of Bacterial Endotoxins
With the Limulus Amebocyte Lysate Test,**
Stanley W. Watson, Jack Levin, Thomas J.
Novitsky, *Editors*

**Vol 232: Enzymology and Molecular Biology
of Carbonyl Metabolism: Aldehyde
Dehydrogenase, Aldo-Keto Reductase, and
Alcohol Dehydrogenase,** Henry Weiner, T.
Geoffrey Flynn, *Editors*

**Vol 233: Developmental and Comparative
Immunology,** Edwin L. Cooper, Claude
Langlet, Jacques Bierne, *Editors*



Vol 234: The Hepatitis Delta Virus and Its Infection, Mario Rizzetto, John L. Gerin, Robert H. Purcell, *Editors*

Vol 235: Preclinical Safety of Biotechnology Products Intended for Human Use, Charles E. Graham, *Editor*

Vol 236: First Vienna Shock Forum, Günther Schlag, Heinz Redl, *Editors*. Published in two volumes: Part A: *Pathophysiological Role of Mediators and Mediator Inhibitors in Shock*. Part B: *Monitoring and Treatment of Shock*.

Vol 237: The Use of Transrectal Ultrasound in the Diagnosis and Management of Prostate Cancer, Fred Lee, Richard McLeary, *Editors*

Vol 238: Avian Immunology, W.T. Weber, D.L. Ewert, *Editors*

Vol 239: Current Concepts and Approaches to the Study of Prostate Cancer, Donald S. Coffey, Nicholas Bruchovsky, William A. Gardner, Jr., Martin I. Resnick, James P. Karr, *Editors*

Vol 240: Pathophysiological Aspects of Sickle Cell Vaso-Occlusion, Ronald L. Nagel, *Editor*

Vol 241: Genetics and Alcoholism, H. Werner Goedde, Dharam P. Agarwal, *Editors*

Vol 242: Prostaglandins in Clinical Research, Helmut Sinzinger, Karsten Schrör, *Editors*

Vol 243: Prostate Cancer, Gerald P. Murphy, Saad Khoury, René Küss, Christian Chatelain, Louis Denis, *Editors*. Published in two volumes: Part A: *Research, Endocrine Treatment, and Histopathology*. Part B: *Imaging Techniques, Radiotherapy, Chemotherapy, and Management Issues*

Vol 244: Cellular Immunotherapy of Cancer, Robert L. Truitt, Robert P. Gale, Mortimer M. Bortin, *Editors*

Vol 245: Regulation and Contraction of Smooth Muscle, Marion J. Siegelman, Andrew P. Somlyo, Newman L. Stephens, *Editors*

Vol 246: Oncology and Immunology of Down Syndrome, Ernest E. McCoy, Charles J. Epstein, *Editors*

Vol 247: Degenerative Retinal Disorders: Clinical and Laboratory Investigations, Joe G. Hollyfield, Robert E. Anderson, Matthew M. LaVail, *Editors*

Vol 248: Advances in Cancer Control: The War on Cancer—15 Years of Progress, Paul F. Engstrom, Lee E. Mortenson, Paul N. Anderson, *Editors*

Vol 249: Mechanisms of Signal Transduction by Hormones and Growth Factors, Myles C. Cabot, Wallace L. McKeehan, *Editors*

Vol 250: Kawasaki Disease, Stanford T. Shulman, *Editor*

Vol 251: Developmental Control of Globin Gene Expression, George Stamatoyanopoulos, Arthur W. Nienhuis, *Editors*

Vol 252: Cellular Calcium and Phosphate Transport in Health and Disease, Felix Bronner, Meinrad Peterlik, *Editors*

Vol 253: Model Systems in Neurotoxicology: Alternative Approaches to Animal Testing, Abraham Shahar, Alan M. Goldberg, *Editors*

Vol 254: Genetics and Epithelial Cell Dysfunction in Cystic Fibrosis, John R. Riordan, Manuel Buchwald, *Editors*

Vol 255: Recent Aspects of Diagnosis and Treatment of Lipoprotein Disorders: Impact on Prevention of Atherosclerotic Diseases, Kurt Widhalm, Herbert K. Naito, *Editors*

Vol 256: Advances in Pigment Cell Research, Joseph T. Bagnara, *Editor*

Vol 257: Electromagnetic Fields and Neurobehavioral Function, Mary Ellen O'Connor, Richard H. Lovely, *Editors*

Vol 258: Membrane Biophysics III: Biological Transport, Mumtaz A. Dinno, William McD. Armstrong, *Editors*

Vol 259: Nutrition, Growth, and Cancer, George P. Tryfiates, Kedar N. Prasad, *Editors*

Vol 260: Management of Advanced Cancer of the Prostate and Bladder, Philip H. Smith, Michele Pavone-Macaluso, *Editors*

Vol 261: Nicotine Replacement: A Critical Evaluation, Ovide F. Pomerleau, Cynthia S. Pomerleau, *Editors*

Please contact the publisher for information about previous titles in this series.

此为试读, 需要完整PDF请访问: www.ertongbook.com

NUTRITION, GROWTH, AND CANCER

The First International Symposium on
Growth and Cancer was sponsored by the

International Association for
Vitamin and Nutritional Oncology
and the National Institute
Research Foundation

International Organizing Committee
George B. Tytler, Chairman (USA)
Kajal K. Puri (USA)
T. Bass (Canada)
Gunnar Björk (USA)
J.E. Evanson (Sweden)
Leonida Santambrogio (Italy)

**The First International Symposium on Nutrition,
Growth, and Cancer was sponsored by the:**

International Association for
Vitamin and Nutritional Oncology
and the National Hellenic
Research Foundation

International Organizing Committee
George P. Tryfiates, Chairperson (USA)
Kedar N. Prasad (USA)
T. Basu (Canada)
Carmia Borek (USA)
A.E. Evangelopoulos (Greece)
Leonida Santamaria (Italy)

Contributors

Tapán K. Basu, Department of Foods and Nutrition, University of Alberta, Edmonton, Alberta, Canada T6G 2M8 [217]

Giovanni Bernardo, Tumour Center, Institute of General Pathology, Rome, Italy [177]

Amalia Bianchi, Institute of Pharmacology, Rome, Italy [177]

Ronald E. Bishop, Department of Biochemistry, West Virginia University School of Medicine, Morgantown, WV 26506 [295]

R.K. Boutwell, Department of Oncology, McArdle Laboratory for Cancer Research, University of Wisconsin-Madison, Madison, WI 53706 [81]

Konstantin Charalambopoulos, Department of Experimental Physiology, University of Ioannina, GR- 45332 Ioannina, Greece [377]

Sylva C. Charalambous, Institute of Biology, National Research Center of Natural Sciences, Demokritos, Athens 153 10, Greece [13]

Michael W. Conner, Department of Pathology, Boston University School of Medicine, Boston, MA 02118 [105]

Nelly Courtis, Department of Biochemistry, G. Papanikolaou Research Center, Hellenic Anticancer Institute, Athens 115 22, Greece [27]

Hector F. DeLuca, Department of Biochemistry, University of Wisconsin-Madison, Madison, WI 53706 [41]

M. Ebadi, Department of Pharmacology, University of Nebraska College of Medicine, Omaha, NE 68105 [161]

Athanasios E. Evangelopoulos, Biological Research Center, The National Hellenic Research Foundation, Athens 116 35, Greece [391,413]

Erhard E. Fasske, Department of Pathology, Research Institute for Experimental Biology and Medicine, D-2061 Borstel, Federal Republic of Germany [377]

Hans P. Fortmeyer, Tierversuchsanlage des Klinikum, J.W. Goethe - Universität, D-6000 Frankfurt, Federal Republic of Germany [283]

Stavros Garyfallides, Department of Biochemistry, G. Papanikolaou Research Center, Hellenic Anticancer Institute, Athens 115 22, Greece [27]

The numbers in brackets are the opening page numbers of the contributors' articles.

Antonia Gounaris, Department of Biochemistry, G. Papanikolaou Research Center, Hellenic Anticancer Institute, Athens 115 22, Greece [27]

Alfred B. Hanck, Unit of Social and Preventive Medicine, CH-4052 Basel, Switzerland [307]

Maria Havredaki, Institute of Biology, National Research Center of Natural Sciences, Demokritos, Athens 153 10, Greece [27]

Moriaki Hayashi, Department of Chemotherapy, Saitama Cancer Center Research Institute, Saitama 362, Japan [131]

Anne M. Hodgson, Department of Foods and Nutrition, University of Alberta, Edmonton, Alberta, Canada T6G 2M8 [217]

Yoshio Honma, Department of Chemotherapy, Saitama Cancer Center Research Institute, Saitama 362, Japan [131]

Motoo Hozumi, Department of Chemotherapy, Saitama Cancer Center Research Institute, Saitama 362, Japan [131]

Robert T. Johnson, Cancer Research Campaign, Mammalian Cell DNA Repair Group, Department of Zoology, University of Cambridge, Cambridge CB2 3EJ, England [1]

George I. Kallistratos, Department of Experimental Physiology, University of Ioannina, GR- 45332 Ioannina, Greece [377]

Spyridon Karkabounas, Department of Experimental Physiology, University of Ioannina, GR- 45332 Ioannina, Greece [377]

Takashi Kasukabe, Department of Chemotherapy, Saitama Cancer Center Research Institute, Saitama 362, Japan [131]

Nicolaos Katsaros, Institute of Chemistry, National Research Center of Natural Sciences, Demokritos, Athens 153 10, Greece [13]

Theodossia Kazazoglou, Department of Biochemistry, G. Papanikolaou Research Center, Hellenic Anticancer Institute, Athens 115 22, Greece [27]

Fragiskos N. Kolisis, Biological Research Center, The National Hellenic Research Foundation, Athens 116 35, Greece [413]

Hans A. Ladner, Department of Radiology, University Gynecology Clinic, D-7800 Freiburg, Federal Republic of Germany [273]

Scott M. Lippman, Section of Hematology/Oncology, Arizona Cancer Center, Tucson, AZ 85724 [229]

Reuben Lotan, Department of Tumor Biology, The University of Texas, M.D. Anderson Hospital and Tumor Institute, Houston, TX 77030 [261]

Dimitra A. Mangoura, Departments of Psychiatry and Pharmacology, University of Colorado School of Medicine, Denver, CO 80262 [57]

Curtis Mettlin, Department of Cancer Control and Epidemiology, Roswell Park Memorial Institute, Buffalo, NY 14263 [149]

Frank L. Meyskens, Jr., Section of Hematology/Oncology, Arizona Cancer Center, Tucson, AZ 85724 [229]

Gaetano Mobilio, Urological Clinic, University of Verona, Verona, Italy [177]

Paul M. Newberne, Department of Pathology, Boston University School of Medicine, Boston, MA 02118 [105]

S. Nikolaropoulos, Institute of Biological Research, The National Hellenic Research Foundation, Athens 116 35, Greece [391]

Junko Okabe-Kado, Department of Chemotherapy, Saitama Cancer Center Research Institute, Saitama 362, Japan [131]

Voula K. Ostrem, Department of Biochemistry, University of Wisconsin-Madison, Madison, WI 53706 [41]

A.C. Papageorgiou, Institute of Biological Research, The National Hellenic Research Foundation, Athens 116 35, Greece [391]

Chan H. Park, Department of Medicine, University of Kansas Medical Center, Kansas City, KS 66103 [321]

Kedar N. Prasad, Department of Radiology, Center for Vitamins and Cancer Research, University of Colorado Health Sciences Center, Denver, CO 80262 [xv,xvii,363]

Carlo Ravetto, Tumour Center, Institute of General Pathology, Rome, Italy [177]

Richard M. Salkeld, Department of Clinical Nutrition, F. Hoffmann-LaRoche and Co. Ltd., CH-4002 Basel, Switzerland [273]

Giuseppe Santagati, Medical Clinic, University of Pavia, Pavia, Italy [177]

Leonida Santamaria, Tumour Center, Institute of General Pathology, Rome, Italy [177]

Eleftherios G. Sideris, Institute of Biology, National Research Center of Natural Sciences, Demokritos, Athens 153 10, Greece [13]

T.G. Sotiroidis, Institute of Biological Research, The National Hellenic Research Foundation, Athens 116 35, Greece [391]

Shoshana Squires, Cancer Research Campaign, Mammalian Cell DNA Repair Group, Department of Zoology, University of Cambridge, Cambridge CB2 3EJ, England [1]

S. Swanson, Department of Pharmacology, University of Nebraska College of Medicine, Omaha, NE 68105 [161]

Christy C. Tangney, Department of Foods and Nutrition, University of North Carolina at Greensboro, Greensboro, NC 27412-5001 [331]

Norman J. Temple, Department of Foods and Nutrition, University of Alberta, Alberta, Edmonton, Canada T6G 2M8 [217]

Theoni Trangas, Department of Biochemistry, G. Papanikolaou Research Center, Hellenic Anticancer Institute, Athens 115 22, Greece [27]

George P. Tryfiates, Department of Biochemistry, West Virginia University School of Medicine, Morgantown, WV 26506 [xv,xvii,295]

Chris M. Tsiapalis, Department of Biochemistry, G. Papanikolaou Research Center, Hellenic Anticancer Institute, Athens 115 22, Greece [27]

Areti Tsolomyty, Institute of Biology, National Research Center of Natural Sciences, Demokritos, Athens 153 10, Greece [13]

Ajit K. Verma, Department of Human Oncology, University of Wisconsin Clinical Cancer Center, Madison, WI 53792 [245]

Antonia Vernadakis, Departments of Psychiatry and Pharmacology, University of Colorado School of Medicine, Denver, CO 80262 [57]

Carlo Vetere, Ministry of Health, Rome, Italy [177]

George Wolf, Department of Applied Biological Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139 [201]

Gerold Zerlauth, Department of Applied Biological Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139; present address: Immuno AG, A-2304 Orth, Austria [201]

V.G. Zevgolis, Institute of Biological Research, The National Hellenic Research Foundation, Athens 116 35, Greece [391]

Preface

In recent years the possible role of specific nutrients in modifying the incidence of cancer has been the subject of intense scientific and clinical research efforts. At present the major research focus is on mechanisms of carcinogenesis and their modifications by nutrients, as well as on human epidemiology and intervention studies. The involvement of specific nutrients in the regulation of oncogene expression has just begun. An International Symposium on Nutrition, Growth, and Cancer, was organized in Athens, Greece, to discuss recent advances in nutrition and cancer research, with special emphasis on mechanistic studies. A large number of international scientists from various disciplines, including cell biology, biochemistry, nutrition, oncology, epidemiology, and public health, reviewed and discussed their most recent results. The positive interaction among these individual scientists provided new stimuli for further investigations into the relationship between nutrition and cancer.

The following topics were discussed in detail: a) effect of retinoids, beta-carotene, vitamin E, vitamin C, and vitamin D on cellular and molecular levels; b) mechanisms of carcinogenesis; c) prevention of cancer by retinoids, beta-carotene, vitamin E, and vitamin C; d) effect of fatty acids on proliferation of normal and transformed cells; e) epidemiological study; f) dietary modification of cancer incidence; g) clinical studies with retinoids and beta-carotene.

This volume provides up-to-date information on nutrition and cancer research and will be a useful reference source for nutritionists, cell biologists, pharmacologists, epidemiologists and oncologists.

The first International Symposium on Nutrition, Growth, and Cancer, was sponsored by International Association for Vitamins and Nutritional Oncology and the National Hellenic Foundation of Greece. This conference was supported by American International Hospital, Samuel Freeman Charitable Trust, Henkel Corporation, Livingston Clinic, Eastman Chemicals (Kodak), Hoffman-La Roche & Co., Twin Lab., J.J. Carlson Lab., International Life Sciences Institute, and BASF.

George P. Tryfiates
Kedar N. Prasad
August 1987

Present and Future Perspectives

It has been estimated that 75–80 percent of human cancers are caused by environmental agents, and 30–35 percent of these are thought to result from diet alone. Therefore, human cancer is a preventable disease.

During the last five years, rapid progress has been made in determining the role of specific dietary factors in the regulation of growth, differentiation, and transformation of mammalian cells. Through in vitro and animal experiments, dietary factors that increase the risk of cancer have been identified. Some of those factors are an integral part of the diet, some are additives, and others are formed after ingestion. Among the dietary factors that increase the risk of cancer are fat, high caloric intake, and food containing high levels of nitrites. Dietary factors that may reduce the risk of cancer include vitamins A, C, D, and E, beta-carotene, folic acid, and the mineral selenium. Most of the human epidemiological studies on nutrition and cancer have confirmed animal experiments conducted in vitro and in vivo, which suggest that the levels of vitamins A, C, and E are inversely related to the risk of cancer. These results have led to intervention studies in humans in which the effects of nutrients on cancer risk among high risk populations are being evaluated. Over 30 such intervention studies are in progress.

Human cancer is the result of extracellular, cellular, and host-mediated events. Extracellular events include formation of nitrosamine from nitrite and tertiary amines at acid pH in the stomach, formation of nitramine from inhaled nitrous oxides, production of tertiary amines at neutral pH in the lung and possibly other organs, and the formation of fecal mutagens from a variety of food substances, especially meat. These extracellular events may be more important for some tumors than others. Alpha tocopherol and vitamin C prevent the formation of nitrosamine and nitramines and reduce the level of fecal mutagens.

The cellular events of carcinogenesis involve multiple steps including tumor initiation and promotion phases. The molecular events of carcinogenesis are associated with activation of multiple oncogenes, some of which confer

immortalization (eg, activation of *c-myc* in NIH 3T3 fibroblasts) while others induce transformation (eg, *H-ras* in NIH 3T3 fibroblasts). In addition, the activation of some oncogenes is associated with the progression of certain tumors (eg, *N-myc* in human neuroblastoma). Recent studies suggest that vitamins A, C, D, and E affect the process of carcinogenesis on both the cellular and the molecular levels. For example, vitamins A, C, and E block the action of tumor promoters and initiators. These vitamins as well as vitamin D, induce cell differentiation in newly transformed and established tumor cells in culture. Vitamins A, D, and E also reduce the expression of certain oncogenes (*c-myc*, *H-ras*, and *N-myc*) in some tumor cells in culture. However, the mechanisms of action of vitamins A, C, D, and E in cancer prevention remain poorly defined.

In addition to the extracellular and cellular events of carcinogenesis, cancer risk is also influenced by host-mediated events. These include competency of the immune system, detoxification of toxic chemicals, and metabolic activation of chemical carcinogenesis. Vitamins A, C, and E seem to stimulate cellular immunity, accelerate the detoxification rate of some toxic chemicals, and block the metabolic activation of some chemical carcinogens. Thus, in any strategy for cancer prevention in humans, the extracellular, cellular, molecular, and host-mediated events should be taken into consideration. It is our firm belief that we must know more about the molecular mechanisms of action of vitamins and the interaction of vitamins with other nutrients before we can utilize them in a most effective manner for our health.

Animal studies have convincingly established that the intake of certain supplemental nutrients reduces the risk of cancer induced by a wide range of tumor initiators and promoters, but that an excess of other nutrients enhances cancer risk. Most of the human epidemiological studies have confirmed the animal studies, but others have failed to substantiate the results obtained from animal models. The main reason for this inconsistency is that we have not performed human experiments analogous to those with animals. Such experiments can only be performed during actual intervention studies among populations at high risk of developing cancer. Some such studies are in progress and others are being planned. It could take one, two, or more decades before conclusive results from such studies become available for practical application. It should be pointed out that human intervention investigations are not as simple as they might appear because of great variations in dietary habits, life styles, and attitudes toward the proposed studies. During the last five years remarkable progress has been made in redefining the methodological issues, which may reduce the impact of the confounding factors on data interpretation. Laboratory experiments have given us an adequate biological rationale for using nutrients in human cancer-prevention investigations. In the design of any human intervention study, the issue of methodologies is as important as

the issue of biological considerations for use in chemoprevention. Attempts to refine one at the expense of the other may produce inconsistent results.

In any proposed human clinical investigations, the vitamin type, form, and frequency of intake must be given. Furthermore, it is important to estimate a) nutrient levels on the basis of dietary intake; b) actual levels of vitamins in feces, plasma, and tissues (normal, preneoplastic, and neoplastic tissues when available); and c) monitor the immune competency of the host at least twice a year. In the absence of such a comprehensive effort, results of human intervention studies will be difficult to interpret.

We are very much encouraged by the new mechanistic data on the effects of nutrients in animal and human carcinogenesis from various laboratories around the world. The new tools of cellular and molecular biology are being used more and more to study the mechanisms of action of specific nutrients. The near future promises development of new concepts and the modification of old ones. Laboratory studies indicate that, for the first time, we have some naturally occurring molecules that, if used properly, may markedly reduce the incidence of human cancer. Without doubt there is a long way to go before our goals of reducing cancer incidence and achieving more effective cancer treatments are reached. However, we have made an excellent beginning.

Kedar N. Prasad
George P. Tryfiates
August 1987

Contents

Contributors	xi
Preface	
George P. Tryfiates and Kedar N. Prasad	xv
Present and Future Perspectives	
Kedar N. Prasad and George P. Tryfiates	xvii
 CARCINOGENESIS AND DIFFERENTIATION: MOLECULAR MECHANISMS	
Defects in Early and Late Stages of Nucleotide Excision Repair and the Origins of Cancer	
R.T. Johnson and Shoshana Squires	1
Mutagenesis, Carcinogenesis, and the Metal Elements—DNA Interaction	
Eleftherios G. Sideris, Sylva C. Charalambous, Areti Tsolomyty, and Nicolaos Katsaros	13
Molecular Aspects of Cell Differentiation at the Level of Messenger Polyadenylation-Deadenylation	
Chris M. Tsiapalis, Theoni Trangas, Nelly Courtis, Antonia Gounaris, Theodossia Kazazoglou, Stavros Garyfallides, and Maria Havredaki	27
Analogues of the Hormonal Form of Vitamin D and Their Possible Use in Leukemia	
Hector F. DeLuca and Voula K. Ostrem	41
Factors Influencing Glia Growth in Culture: Nutrients and Cell-Secreted Factors	
Antonia Vernadakis and Dimitra A. Mangoura	57
 DIET AND CANCER	
An Overview of the Role of Diet and Nutrition in Carcinogenesis	
R.K. Boutwell	81
Dietary Modifiers of Cancer	
Paul M. Newberne and Michael W. Conner	105

Modification by Vitamins and Nutrients of Induction of Terminal Differentiation of Myeloid Leukemia Cells	
Motoo Hozumi, Yoshio Honma, Takashi Kasukabe, Moriaki Hayashi, and Junko Okabe-Kado	131
Levels of Epidemiologic Proof in Studies of Diet and Cancer With Special Reference to Dietary Fat and Vitamin A	
Curtis Mettlin	149
The Status of Zinc, Copper, and Metallothionein in Cancer Patients	
M. Ebadi and S. Swanson	161
CANCER PREVENTION AND TREATMENT: RETINOIDS	
Cancer Chemoprevention by Carotenoids: Experimental Evidence and Human Interventions After Radical Surgery	
Leonida Santamaria, Amalia Bianchi, Gaetano Mobilio, Giuseppe Santagati, Carlo Ravetto, Giovanni Bernardo, and Carlo Vetere	177
Tumor Promotion, Vitamin A, and Fibronectin. A Review of Recent Work	
George Wolf and Gerold Zerlauth	201
Vitamin A, Beta-Carotene and Cancer	
Tapan K. Basu, Norman J. Temple, and Anne M. Hodgson	217
Retinoids as Anticancer Agents	
Scott M. Lippman and Frank L. Meyskens, Jr.	229
Inhibition of Phorbol Ester-Induced Ornithine Decarboxylase Gene Transcription by Retinoic Acid: A Possible Mechanism of Antitumor Promoting Activity of Retinoids	
Ajit K. Verma	245
Vitamin A Analogs (Retinoids) as Biological Response Modifiers	
Reuben Lotan	261
VITAMIN B₆ AND CANCER	
Vitamin B₆ Status in Cancer Patients: Effect of Tumour Site, Irradiation, Hormones, and Chemotherapy	
Hans A. Ladner and Richard M. Salkeld	273
New Experimental Possibilities in Nutritive Oncology by the Model of Human Tumors, Xenotransplanted and Passaged into Athymic Nude Mice	
Hans P. Fortmeyer	283
Tentative Structure of a Novel Vitamin B₆ Tumor Product	
George P. Tryfiates and Ronald E. Bishop	295
VITAMIN C, VITAMIN E, AND SELENIUM	
Vitamin C and Cancer	
Alfred B. Hanck	307
Vitamin C in Leukemia and Preleukemia Cell Growth	
Chan H. Park	321