TABLE OF CONTENTS

Forword xiii

Preface xv

1. Images of Cancer 1

How Cancer is Viewed 2

References 13

2. Confusion Surrounds the Origin of Cancer 15

The Oncogenic Paradox 18

Hallmarks of Cancer 18

Reassessment 26

References 27

3. Cancer Models 31

Problems with Some Cancer Models 31

Animal Charges as a Major Impediment to Cancer Research 38

Problems with Tumor Histological Classification 39

Personal Perspective on Cancer 44

References 45

4. Energetics of Normal Cells and Cancer Cells 47

Metabolic Homeostasis 47

The Constancy of the G ATP 54

ATP Production in Normal Cells and Tumor Cells 55

Energy Production Through Glucose Fermentation 57

Glutaminolysis with or without Lactate Production 61

Transamination Reactions 64

TCA Cycle, Substrate-Level Phosphorylation 66

Cholesterol Synthesis and Hypoxia 67

Summary 67

References 68

5. Respiratory Dysfunction in Cancer Cells 73

Normal Mitochondria 74

Morphological Defects in Tumor Cell Mitochondria 77

Proteomic Abnormalities in Tumor Cell Mitochondria 79

Lipidomic Abnormalities in Tumor Cell Mitochondria 81

Cardiolipin: A Mitochondrial-Specific Lipid 83

Cardiolipin and Abnormal Energy Metabolism in Tumor Cells 85

Complicating Influence of the In Vitro Growth Environment on Cardiolipin Composition and Energy Metabolism 92

Mitochondrial Uncoupling and Cancer 97

Cancer Cell Heat Production and Uncoupled Mitochondria 98

Personal Perspective 99

Summary 100

References 101

6. The Warburg Dispute 107

Sidney Weinhouse's Criticisms of the Warburg Theory 108

Alan Aisenberg's Criticisms of the Warburg Theory 110

Sidney Colowick's Assessment of the Aisenberg Monograph 113

Apples and Oranges 114

References 116

7. Is Respiration Normal in Cancer Cells? 119

Pseudo-Respiration 119

How Strong is the Scientific Evidence Showing that Tumor Cells can Produce Energy Through OxPhos? 124

OxPhos Origin of ATP in Cancer Cells Reevaluated 124

What About OxPhos Expression in Other Tumors? 127

The Pedersen Review on Tumor Mitochondria and the Bioenergetics of Cancer Cells 128

References 129

8. Is Mitochondrial Glutamine Fermentation a Missing Link in the Metabolic Theory of Cancer? 133

Amino Acid Fermentation can Maintain Cellular Energy Homeostasis During Anoxia 133

Evidence Suggesting that Metastatic Mouse Cells Derive Energy from Glutamine Fermentation 134

Fermentation Energy Pathways can Drive Cancer Cell Viability Under Hypoxia 138

Competing Explanations for the Metabolic Origin of Cancer 141

Chapter Summary 143

References 143

9. Genes, Respiration, Viruses, and Cancer 145

Does Cancer have a Genetic Origin? 145

Respiratory Insufficiency as the Origin of Cancer 150

Germline Mutations, Damaged Respiration, and Cancer 154

Somatic Mutations and Cancer 158

Revisiting the Oncogene Theory 160

Mitochondrial Mutations and the Absence or Presence of Cancer 163

Viral Infection, Damaged Respiration, and the Origin of Cancer 165

Summary 168

References 168

10. Respiratory Insufficiency, the Retrograde Response, and the Origin of Cancer 177

The Retrograde (RTG) Response: An Epigenetic System Responsible for Nuclear Genomic Stability 177

Inflammation Injures Cellular Respiration 181

Hypoxia-Inducible Factor (HIF) Stability is Required for the Origin of Cancer 182

Mitochondria and the Mutator Phenotype 183

Calcium Homeostasis, Aneuploidy, and Mitochondrial Dysfunction 186

Mitochondrial Dysfunction and Loss of Heterozygosity (LOH) 187 Tissue Inflammation, Damaged Respiration, and Cancer 188 References 189

11. Mitochondria: The Ultimate Tumor Suppressor 195

Mitochondrial Suppression of Tumorigenicity 195 Normal Mitochondria Suppress Tumorigenesis in Cybrids 196 Evidence from rho0 Cells 198 Normal Mitochondria Suppress Tumorigenesis In Vivo 199 Normal Mouse Cytoplasm Suppresses Tumorigenic Phenotypes 200 Enhanced Differentiation and Suppressed Tumorigenicity in the Liver Microenvironment 202 Summary of Nuclear-Cytoplasmic Transfer Experiments 203 References 204

12. Abnormalities in Growth Control, Telomerase Activity, Apoptosis, and Angiogenesis Linked to Mitochondrial Dysfunction 207

Growth Signaling Abnormalities and Limitless Replicative Potential 208

Linking Telomerase Activity to Cellular Energy and Cancer 209

Evasion of Programmed Cell Death (Apoptosis) 209

Sustained Vascularity (Angiogenesis) 210

References 211

13. Metastasis 215

Metastasis Overview 215

Cellular Origin of Metastasis 217

Macrophages and Metastasis 221

Carcinoma of Unknown Primary Origin 232

Many Metastatic Cancers Express Multiple Macrophage Properties 233

Linking Metastasis to Mitochondrial Dysfunction 233

Revisiting the "Seed and Soil" Hypothesis of Metastasis 235

Revisiting the Mesenchymal Epithelial Transition (MET) 236

Genetic Heterogeneity in Cancer Metastases 237

Transmissible Metastatic Cancers 240

The Absence of Metastases in Crown-Gall Plant Tumors 240

Chapter Summary 241

References 241

14. Mitochondrial Respiratory Dysfunction and the Extrachromosomal Origin of Cancer 253

Connecting the Links 254

Addressing the Oncogenic Paradox 255

Is Cancer Many Diseases or a Singular Disease of Energy Metabolism? 258

References 258

15. Nothing in Cancer Biology Makes Sense Except in the Light of Evolution 261

Revisiting Growth Advantage of Tumor Cells, Mutations, and Evolution 262

Tumor Cell Fitness in Light of the Evolutionary Theory of Rick Potts 269 Cancer Development and Lamarckian Inheritance 271 Can Teleology Explain Cancer? 272 References 272 16. Cancer Treatment Strategies 277 Current Status of Cancer Treatment 277 The "Standard of Care" for Glioblastoma Management 280 References 285 17. Metabolic Management of Cancer 291 Is it Dietary Content or Dietary Composition that Primarily Reduces Tumor Growth? 292 Dietary Energy Reduction and Therapeutic Fasting in Rodents and Humans 294 Ketogenic Diets 295 Glucagon and Insulin 297 **Basal Metabolic Rate 298** Ketones and Glucose 298 Metabolic Management of Brain Cancer Using the KD 299 Glucose Accelerates Tumor Growth! 301 Glucose Regulates Blood Levels of Insulin and Insulin-Like Growth Factor 1 302 Dietary Energy Reduction is Antiangiogenic 302 Dietary Energy Reduction Targets Abnormal Tumor Vessels 307 **Dietary Energy Reduction is Proapoptotic 309** Dietary Energy Reduction is Anti-Inflammatory 310 Targeting Energy Metabolism in Advanced Cancer 314 Differential Response of Normal Cells and Tumor Cells to Energy Stress 316 Dietary Energy Reduction is Anti-Invasive in Experimental Glioblastoma 318 Influence of Growth Site and Host on Tumor Progression 322 Implications of Dietary Energy Reduction for Anticancer Therapeutics 324 **Targeting Glucose 325** Metformin 326 Synergistic Interaction of the Restricted Ketogenic Diet (KD-R) and 2-Deoxyglucose (2-DG) 327 Can Synergy Occur with the KD-R and Hyperbaric Oxygen Therapy? 331 **Targeting Glutamine 333** Glutamine Targeting Inhibits Systemic Metastasis 334 **Targeting Phagocytosis 339** Targeting the Microenvironment 340 Dietary Energy Reduction as a Mitochondrial Enhancement Therapy (MET) 341 Summary 341 References 341 18. Patient Implementation of Metabolic Therapies for Cancer Management 355 Introduction 355

Guidelines for Implementing the Restricted Ketogenic Diet as a Treatment Strategy for Cancer 356

Complicating Issues for Implementing the KD-R as a Treatment Strategy for Cancer 366

Radiation and Chemotherapy is a Standard Treatment for Many Malignant Cancers 366

Compliance 367

Cancer as a Genetic Disease 367

Mechanism of Action? 368

Cachexia 368

Summary 369

References 370

19. Cancer Prevention 375

Cell Phones and Cancer 376

Alzheimer's Disease and Cancer Risk 377

Ketone Metabolism Reduces Cancer Risk 378

Mitochondrial Enhancement Therapy 379

Therapeutic Fasting and Cancer Prevention 379

Autophagy and Autolytic Cannibalism: A Thermodynamic Approach to Cancer Prevention 381

Cancer Prevention by Following Restricted Ketogenic Diet 382

References 384

20. Case Studies and Personal Experiences in Using the Ketogenic Diet for Cancer Management 387

Effects of a Ketogenic Diet on Tumor Metabolism and Nutritional Status in Pediatric Oncology Patients: Comments from Dr. Linda Nebeling 387

Raffi's Story: Comments from Miriam Kalamian 389

Biological Plausibility that Cancer is a Metabolic Disease Dependent for Growth on Glucose and Glutamine: Comments from Dr. Bomar Herrin 395

Using the Restricted Ketogenic Diet for Brain Cancer Management: Comments from Neuro-Oncologist, Dr. Kraig Moore 397

The Ketogenic Diet for Brain Cancer Management: Comments from Beth Zupec-Kania 400

Summary 402

References 403

21. Conclusions 405

Major Conclusions 407

References 408

Index 409