# Cancer as a Metabolic Disease

## On the Origin, Management, and Prevention of Cancer

Thomas N. Seyfried

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*This book is dedicated to the millions of people who have suffered and died from toxic cancer therapies*

# Contents

# Foreword

Cancer persists as a major disease of mortality and is afflicting more people today than ever before. Few families remain untouched by this insidious and vicious disease. In fact, cancer is predicted to overtake heart disease as the prime cause of death in industrialized societies during this century. I have worked in the cancer metabolism field since the late 1960s and have extensively published works on the metabolic basis and properties of cancer. While I do not know Dr. Seyfried personally, I am very impressed with the excellent job he has done in highlighting abnormal energy metabolism as the central issue of the cancer problem. I recognized long ago the pivotal role of mitochondria and of aerobic glycolysis in sustaining and promoting cancer growth. The Nobel laureate, Otto Warburg, was the first to provide evidence during the early part of the last century for the involvement of disturbed respiration with compensatory fermentation (glycolysis) as a common property of cancer, thus perceived to be related to its uncontrolled growth and progression. Few subjects have been as controversial in the cancer field as Otto Warburg and his theory of cancer. It is nice to see how Seyfried shows that Warburg was largely correct in defining the nature of the disease as involving insufficient respiration with compensatory fermentation. I knew personally many of the key figures and their research mentioned in Seyfried's book, including Dean Burk, Peter Mitchell, Sidney Weinhouse, and my former Department Chair, Albert Lehninger, among others. Nevertheless, there were times in my early career when I felt almost alone in considering energy metabolism as important to the cancer problem. I even remember one of my colleagues, an expert in DNA technology, dumping Lehninger's "Warburg Flasks" in the trash as relics of a bygone era in cancer research. Fortunately for him, Lehninger was no longer the Department Chair, and fortunately for me, I salvaged many of these flasks and am now glad I did. After reading Seyfried's book, I think these flasks will become valuable as collector items.

The cancer field went seriously off course during the mid-1970s when many investigators began considering cancer as primarily a genetic disease rather than as a metabolic disease. The metabolic defects in cancer cells were thought to arise as secondary consequences of genomic instability. Seyfried provides substantial evidence documenting the inconsistencies of the gene "only" theory. He critically reevaluates the evidence linking cancer progression to a Darwinian process and raises the intriguing possibility that cancer progression is an example of Lamarckian evolution. When viewed collectively, the documented inconsistencies of the gene

"only" theory make it clear why little progress has been made in the cancer war and in the development of effective nontoxic therapies. A key point made by Seyfried is that most of the genomic instability seen in cancer likely arises as a consequence rather than as the cause of the disease. When viewed more as a metabolic disease, many cost effective therapeutic strategies become recognized for cancer management. I know this first hand from our studies of 3-bromopyruvate (3BP), discovered in my laboratory by Dr. Young Ko, as a potent anticancer agent. This is a low cost drug with powerful and quick antitumor effects against multiple cancers in animal models and in cancer patients. 3BP works primarily by targeting tumor cell energy metabolism, thus depleting the energy-rich compound "ATP" essential for growth. At the effective doses used, it does this without toxicity to normal cells. Seyfried's book provides substantial evidence showing how cancer can be managed using various other drugs and diets that target energy metabolism. In addition, the restriction of glucose and glutamine, which drive cancer energy metabolism, cripples the ability of cancer cells to replicate and disseminate. The gene theory has deceived us into thinking that cancer is more than a single disease. Certainly, tumors do not all grow at the same rate. Nevertheless, cancer is a singular disease involving aberrant energy metabolism as Warburg originally showed and as I, and more recently many others, have documented in biochemical studies. Seyfried drives home this message throughout his book.

Seyfried's treatise refocuses attention on the central issue of cancer as a metabolic disease according to Warburg's original theory. The book is unique in linking nearly all aspects of the disease to respiratory insufficiency with compensatory fermentation. Cancer has remained incurable for many due largely to a general misunderstanding of its origin, biology, and metabolism. Hopefully, Seyfried's thoughtful analysis of the "cancer problem" will change our understanding of the disease and move the field in the right direction toward solutions and therapies, such as 3BP, that act much faster and more effectively than those currently available.

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# Preface

Cancer persists as a plague in modern society. The lack of progress in either managing or preventing cancer motivated me to write this treatise. I am a biochemical geneticist and have worked on the lipid biochemistry of cancer since the early 1980s. I have developed numerous mouse models for brain tumors and for systemic metastatic cancer. Several major findings planted the seed for this treatise. First, it became clear to me that the therapeutic action of some anticancer drugs operated largely through reduced caloric intake. Second, that reduced caloric intake could target the majority of cancer hallmarks. Third, that ketone bodies can serve as an alternative fuel to glucose in most cells with normal respiratory function. Fourth, that metastatic cancer arises from cells along macrophage lineage. Fifth, that all cancer cells regardless of tissue origin express a general defect in mitochondrial energy metabolism. Finally, that cancer can be effectively managed and prevented once it becomes recognized as a metabolic disease.

In recognizing cancer as a metabolic disease, it gradually became clear to me why so many people die from the disease. Many of the current cancer treatments exacerbate tumor cell energy metabolism, thus allowing the disease to progress and eventually become unmanageable. Most cancer patients do not battle their disease but are offered toxic concoctions that can eventually undermine their physiological strength and their will to resist. Cancer treatments are often feared as much as the disease itself. The view of cancer as a genetic disease has confounded the problem and is largely responsible for the failure to develop effective therapies. The view of cancer as a genetic disease is based on the flawed notion that somatic mutations cause cancer. Substantial evidence indicates that genomic instability is linked to protracted respiratory insufficiency. Once cancer becomes recognized as a metabolic disease with metabolic solutions, more humane and effective treatment strategies will emerge. My treatise highlights cancer as a metabolic disease and identifies the inconsistencies of the gene theory of cancer. Moreover, my treatise addresses most of the so-called provocative questions raised by the National Cancer Institute regarding outstanding issues in cancer research. This treatise lays the foundation for the eventual resolution of the disease.

I would like to thank my many students and colleagues for helping me in producing the data and in developing the concepts for this treatise. I thank my former graduate students Mary Louise Roy (MS, 1987), Michelle Cottericho (MS, 1992), Mohga El-Abbadi (PhD, 1995), Hong Wei Bai (PhD, 1996), John Brigande (BS, 1989; MS, 1992; PhD, 1997), Jeffrey Ecsedy (PhD, 1998), Mark Manfredi

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I would like to thank faculty colleagues in the Boston College Biology Department, including Drs. Thomas Chiles, Fr. Richard McGowan SJ, and Jeffery Chuang. I would like to thank Dr. Robert K. Yu, Dr. James Fox and my son Dr. Nicholas T. Seyfried for technical assistance. I would like to thank Avtar Roopa for provocative discussion. I would like to thank the late Drs. Sanford Palay, Harry Zimmerman, and Allan Yates for their encouragement and assistance. I would also like to give special acknowledgement to Dr. Purna Mukherjee and Roberto Flores. Purna was the first to make me aware of the powerful therapeutic action of calorie restriction. She is superbly trained in the areas of angiogenesis and inflammation and her work provided seminal information on the mechanisms by which dietary energy reduction can both treat and prevent cancer. Roberto Flores is exceptional in his dedication to finding the truth underlying the metabolic origin of cancer and in questioning the metabolic origin of cancer. Finally, I would like to thank my institution, Boston College, for providing animal care support over the first 23 years of my employment there (1985–2008). The data collected supporting my treatise would not have been possible without this invaluable institutional support. This support was consistent with the Ignatian philosophy of service to others.

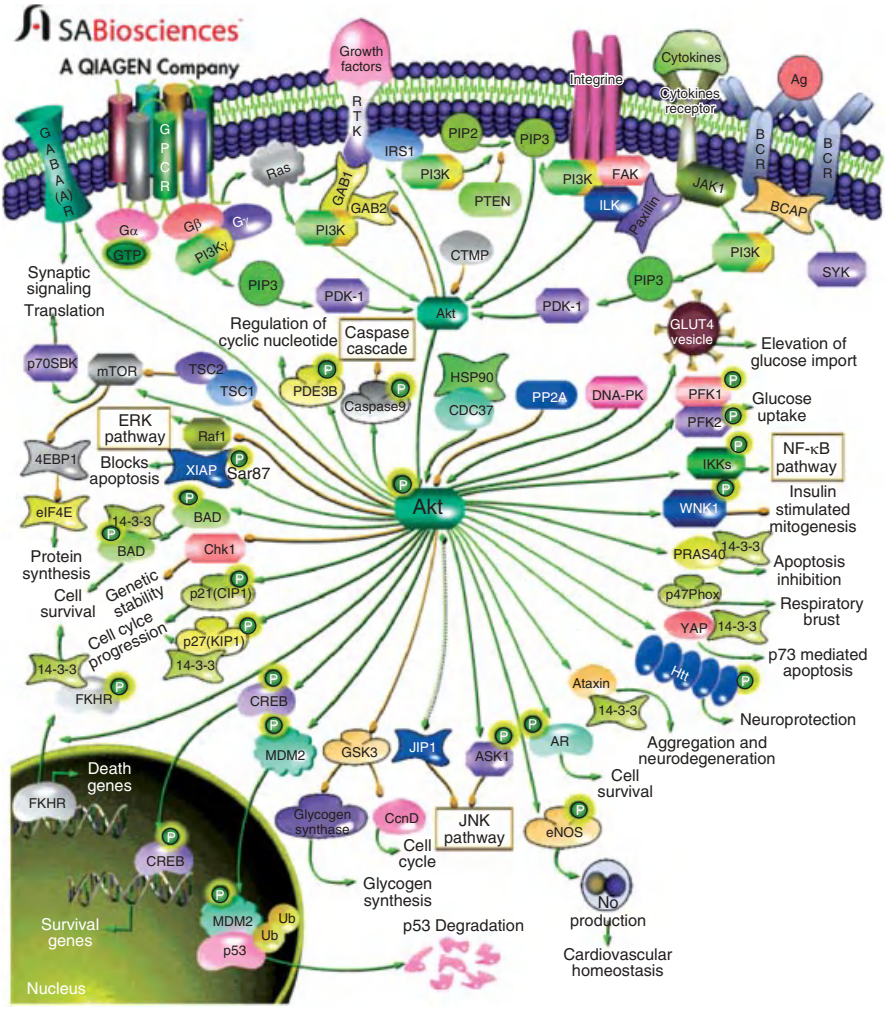



**Figure 1.2** See full caption on page 4.

*Cancer as a Metabolic Disease: On the Origin, Management and Prevention of Cancer*, First Edition. Thomas Seyfried.

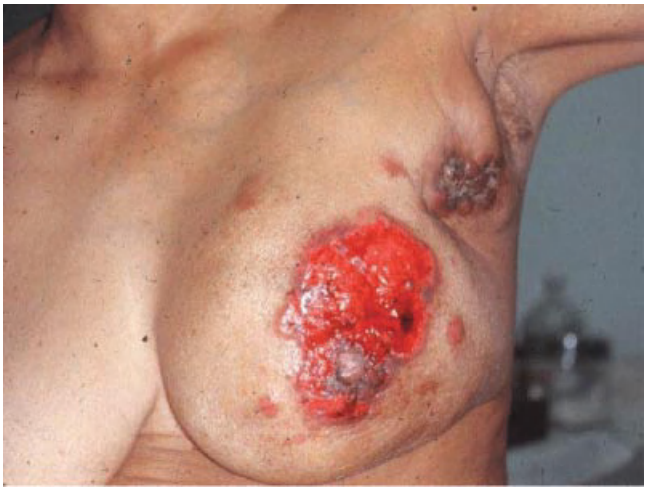
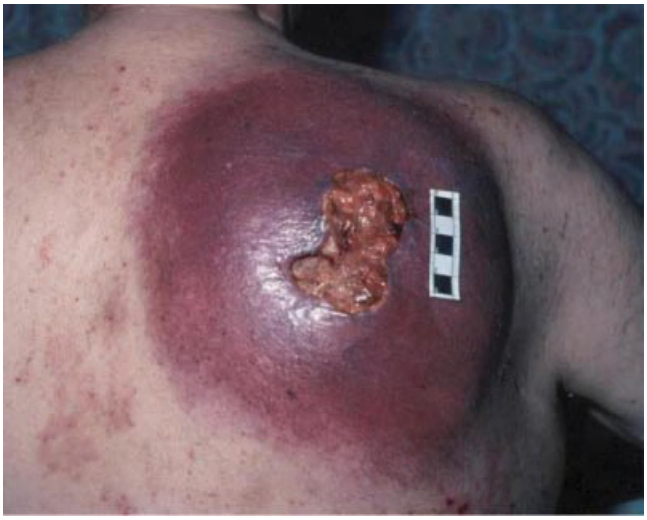


**Figure 1.5a** See full caption on page 7.



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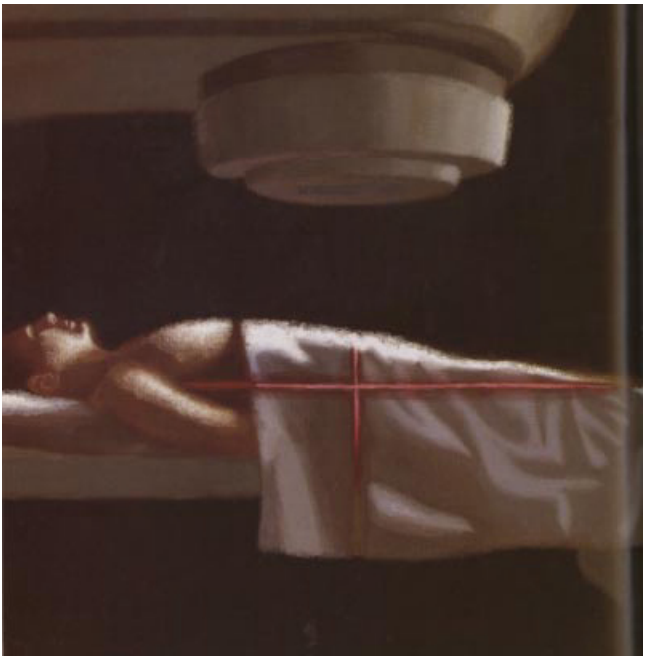

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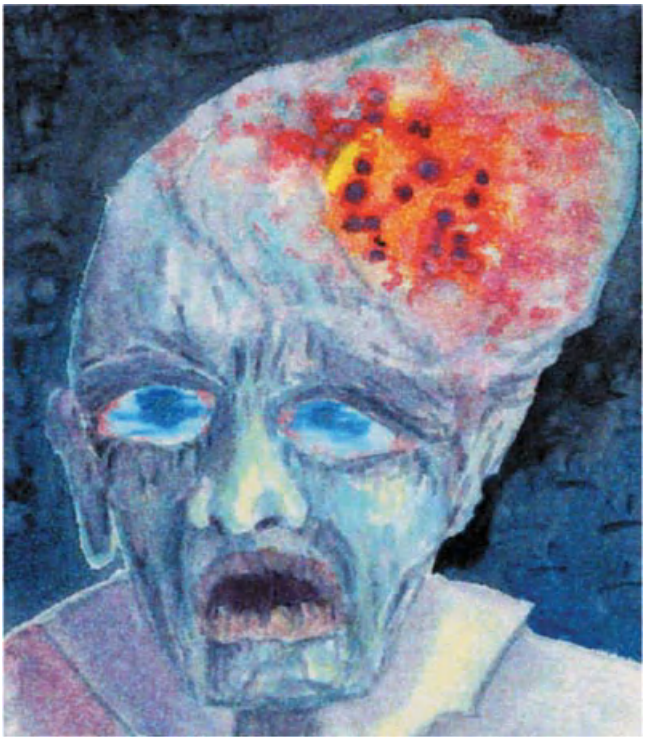
**Figure 1.8** See full caption on page 8.



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