Cancer as a Metabolic Disease

On the Origin, Management, and Prevention of Cancer

Thomas N. Seyfried

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A John Wiley & Sons, Inc., Publication

Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

Library of Congress Cataloging-in-Publication Data:

Seyfried, Thomas N., 1946–
Cancer as a metabolic disease : on the origin, management, and prevention of cancer / by Thomas N. Seyfried.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-470-58492-7 (cloth)
I. Title.
[DNLM: 1. Neoplasms–diet therapy. 2. Neoplasms–metabolism. 3. Energy Metabolism. 4. Ketogenic Diet. 5. Mitochondria–metabolism. QZ 200]
616.99′40654–dc23
2011049798

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

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

(PhD, 1999), Michaela Ranes (BS, 1998; MS, 2000), Dia Banerjee (MS, 2001), Michael Drage (MS, 2006), Christine Denny (BS, 2005; MS, 2006), Weihua Zhou (MS, 2006), Laura Abate (PhD, 2006), Michael Kiebish (PhD, 2008), Leanne Huysentruyt (PhD, 2008), John Mantis (PhD, 2010), and Laura Shelton (PhD, 2010). I would also like to acknowledge my current students Linh Ta and Zeynep Akgoc for their continued productivity. I would also like to thank the following undergraduate students for their input and help, including Katherine Holthause, Jeremy Marsh, Jeffery Ling, Will Markis, Tiernan Mulrooney, Todd Sanderson, Todd Theman, Lisa Mahoney, Michelle Levine, Emily Coggins, Erin Wolfe, Ivan Urits, Taryn LeRoy, and Emily Gaudiano. I would like to thank those students from my BI503 class on *Current Topics in Cancer Research* for their input.

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.

Chapter 1

Images of Cancer

Cancer is a devastating disease both physically and emotionally and is projected to overtake heart disease as the leading killer of people in industrialized societies. Cancer is complex. The disease involves multiple time- and space-dependent changes in the health status of cells, which ultimately lead to malignant tumors. Abnormal cell growth (neoplasia) is the biological endpoint of the disease. Tumor cell invasion of surrounding tissues and spread to distant organs is the primary cause of morbidity and mortality in most cancer patients. This phenomenon is referred to as *metastasis*. The biological process by which normal cells are transformed into malignant cancer cells has been the subject of an enormous research effort in the biomedical sciences for more than a century. Despite this effort, cures or long-term management strategies for metastatic cancers are as challenging today as they were 40 years ago when President Richard M. Nixon declared a war on cancer with the National Cancer Act (1–3). According to the American Cancer Society, 569,490 people died in the United States from cancer in 2010 (4). This comes to about 1500 people each day! Remarkably, the number of deaths in 2002 was 555,500 providing quantitative evidence of no real progress in management over a 8-year period (5). All one needs to do is read the obituary pages from any local newspaper to know that the "cancer war" is not going well.

How is it possible that we are not winning the cancer war when this disease is under constant investigation in many major pharmaceutical companies and in most leading medical centers throughout the world? One would think that effective nontoxic therapies would be readily available from all this attention. We constantly hear in the media of new breakthroughs in the fight against cancer, yet high profile celebrities and politicians continue to die from the disease. If the breakthroughs are real or meaningful, shouldnt the wealthy and powerful have access to any potential life-saving therapy? That these folks are just as vulnerable as the rest of us to the ravages of the disease clearly indicates that the war is not won. The road to the cancer front is littered with major breakthroughs that never materialized into effective solutions. A plateau in overall death rates for some cancers has been due more to better awareness and avoidance of risk factors, for example, smoking for

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

lung cancer, than to any real advances in the management of systemic metastasis, the most deadly feature of the disease (6, 7). Clearly, we are not wining the war on cancer, as Guy Faguet has emphasized (8).

HOW CANCER IS VIEWED

The image of cancer depends on your perspective. It depends on whether you are a cancer patient, a friend or family member of a patient, an oncologist, a pathologist, a statistician, or a person who does basic research on the disease. The image of cancer can be framed from these various perspectives.

Figure 1.1a shows the number of genetic alterations detected through sequencing and copy number analyses in each of the 24 different pancreatic cancers. According to the figure, point mutations are more common in pancreatic cancer than are larger deletions or amplifications. The authors of this study, and of many similar studies, believe that the cataloguing of mutations found in various tumors will be important for disease identification and management. While cataloguing cancer genetic defects is interesting, it is important to recognize that the defects often vary from one neoplastic cell to another within the same tumor (12).

Figure 1.1b shows the percentage of genetic alterations found in brain tumors (glioblastoma multiforme). Similar kinds of alterations are found in pancreatic and ovarian cancers. Primary sequence alterations and significant copy number changes for components of the RTK/RAS/PI(3)K (A), p53 (B), and RB (C) signaling pathways are shown. The different shades of gray are indicative of different degrees of genetic alteration (13). For each altered component of a particular pathway, the nature of the alteration and the percentage of tumors affected are indicated. Boxes contain the final percentages of glioblastomas containing alterations in at least one known component gene of the designated pathway. It is also interesting to note that no alterations in any of the pathways occur in about 15% of glioblastomas despite similarity in histological presentation. It remains unclear how these genomic alterations relate to the origin or progression of the disease.

Akt (v-Akt murine thymoma viral oncogene) or PKB (protein kinase-B) is a serine/threonine kinase that is involved in mediating various biological responses, such as inhibition of programmed cell death (apoptosis), stimulation of cell proliferation, and enhancement of tumor energy metabolism (Fig. 1.2). Akt expression is generally greater in cancer cells than in normal cells. Although targeting of Akt-related pathways is part of cancer drug development, the simple restriction of calorie intake will reduce Akt expression in tumors (14). This image is synthesized from information on the molecular biology of cancer. I refer to these types of cancer images as *balloons on strings*. They convey an ordered arrangement of pathways for a disease that is biologically chaotic. SABiosciences is a QIAGEN company specializing in molecular array technologies that can help analyze gene expression changes, epigenomic patterns, microRNA expressions, and so on.

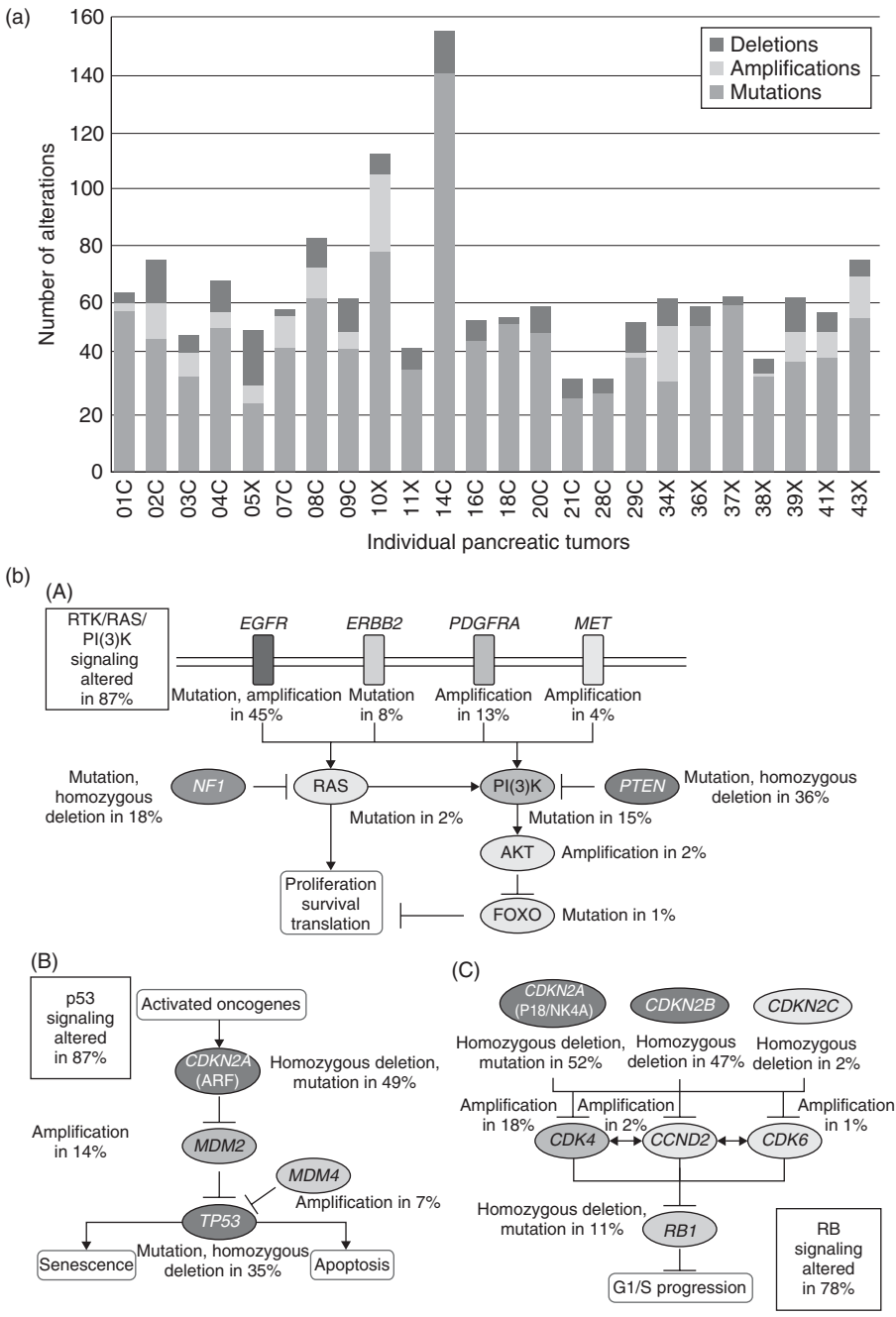


Figure 1.1 Cancer images from cancer genome projects. *Source:* (a) Modified from Jones et al. (13); (b) Reprinted from Jones et al (13). To see this figure in color please go to ftp://ftp.wiley.com/public/sci_tech_med/cancer_metabolic_disease.

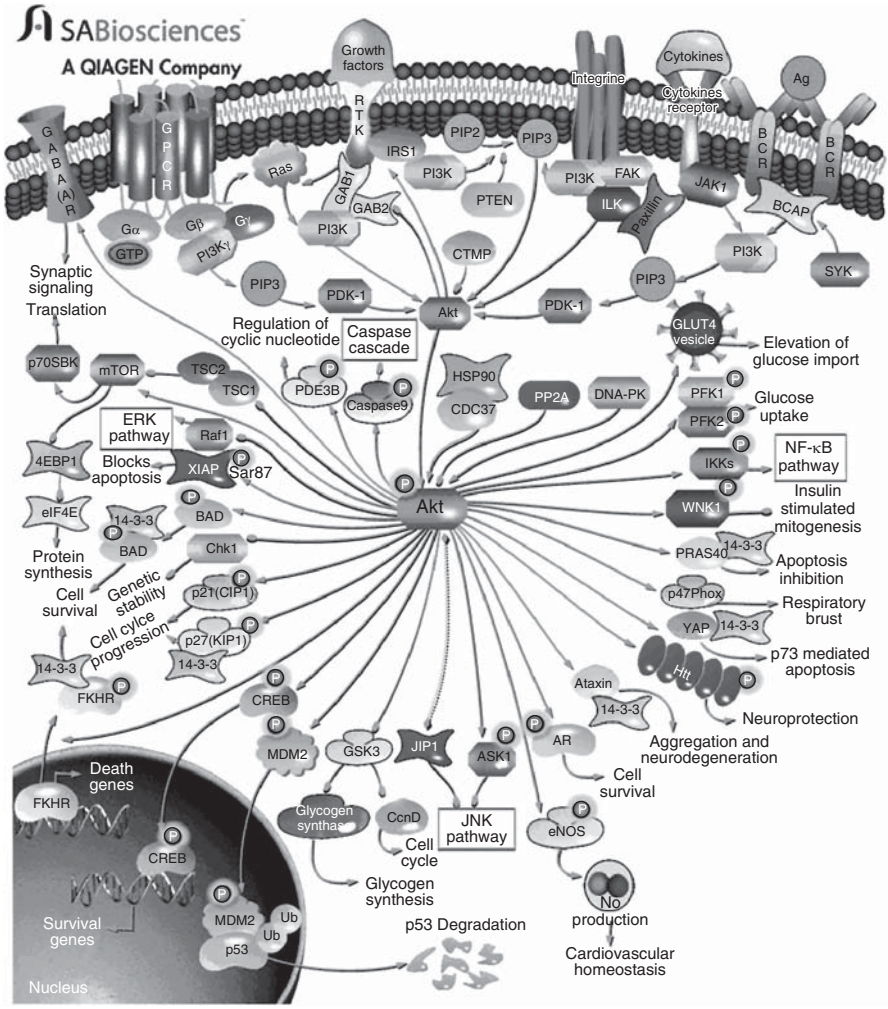


Figure 1.2 Akt signaling. *Source:* Reprinted with permission from SABiosciences. See color insert.

Angiogenesis involves the production of new blood vessels from existing blood vessels and involves interactions among numerous signaling molecules (Fig. 1.3). Cancer therapies that target angiogenesis are thought to help manage the disease. Besides expensive antiangiogenic cancer drugs such as bevacizumab (Avastin) (15), simple calorie restriction effectively targets angiogenesis in tumors (16, 17).

Figure 1.4 depicts the cancer images of cellular pathology.

The following is a list of the mortality rate of different cancers:

- Breast cancer killed about 40,170 women in 2010 (4).
- Lung and bronchus cancer killed about 159,390 persons in 2010 (4).

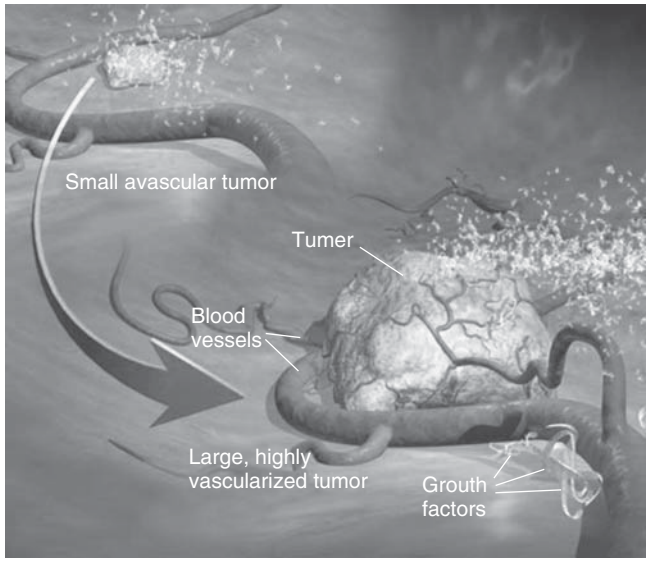


Figure 1.3 Tumor angiogenesis. *Source:* Reprinted with permission from BioOncology. To see this figure in color please go to ftp://ftp.wiley.com/public/sci_tech_med/cancer_metabolic_disease.

- Colon/rectum cancer killed about 49,920 persons in 2010 (4).
- Skin cancer killed about 11,590 persons in 2010 (4).
- Brain and nervous system cancer killed about 12,920 persons in 2010 (3).
- Liver and bile duct cancer killed about 18,910 people (4).

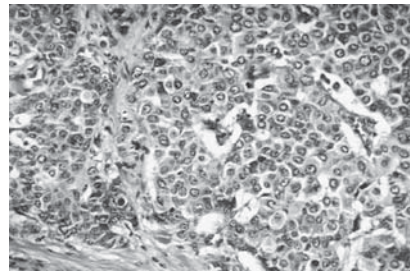
Cancer images of organ pathology are shown in Figure 1.5.

I think the artwork of Robert Pope, who died from the adverse effects of chemotherapy and radiation, is especially powerful in conveying the image of cancer from the perspective of the patient, the family, and the physician (19, 20). I also think the Commentary by Donald Cohodes on the experience of chemotherapy should be read as a supplement to Pope's book (21). I have included below a few of Pope's many paintings and drawings.

In the painting in Figure 1.6, Pope depicts the subtleties of communication among cancer doctors. The doctors talk among themselves about cancer differently than they do to the patient or to the patient's family so as not to alarm the sensitivity of the layperson. In the hallway, the communication is considered scientific, blunt, and factual, while in the room it is considered more nurturing and emotional. Although many patients view cancer doctors as secular priests in today's society, the toxic therapies doctors use to treat cancer are often counterproductive to the long-term well-being of cancer patients.

The image in Figure 1.7 is an acrylic on canvas depicting a man lying underneath a radiation machine. Radiation therapy is given to many cancer patients. Radiation will kill both cancer cells and normal cells. Some normal cells that are not killed outright can be metabolically transformed into tumor cells. Moreover,

(a)



(b)

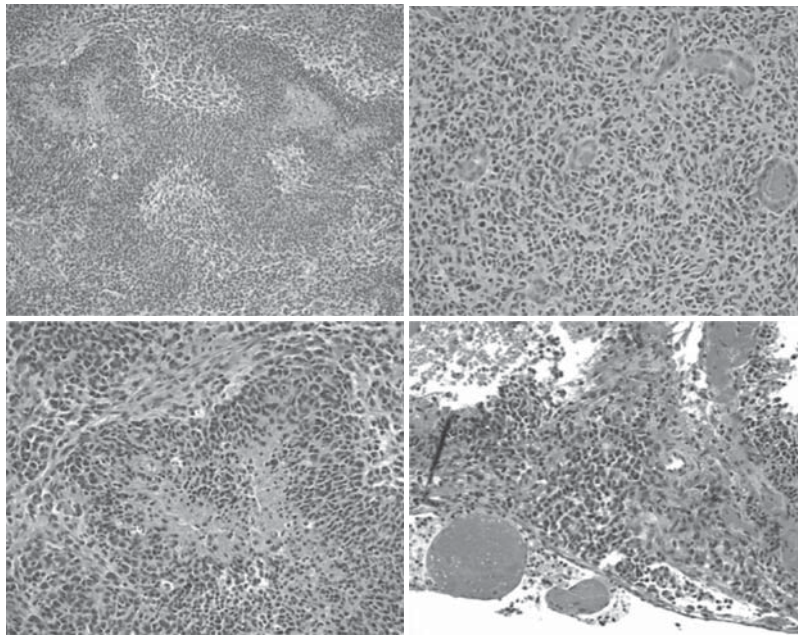


Figure 1.4 (a) Histological image of breast cancer. *Source:* Reprinted with permission from the NCI. (b) Histological images of glioblastoma multiforme. *Source:* Reprinted with permission from Reference 18. To see this figure in color please go to ftp://ftp.wiley.com/public/sci_tech_med/cancer_metabolic_disease.

those tumor cells that survive the radiation treatment will sometimes grow back as more aggressive and less manageable cancers in the future.

Figure 1.8 is also an acrylic on canvas that conveys the psychological impact of cancer drugs. The chemical in the syringe is Adriamycin (*doxorubicin*), which Pope received along with other drugs during his battle with cancer. In this painting, Pope depicts an older woman with lymphatic cancer who is getting chemotherapy. The woman is wearing a turban to hide her baldness caused from the drug treatments. Pope attempts to convey the patient's thoughts about the drug. The drug within the syringe elicits thoughts of either life or alarm. According to Pope, the painting shows the human encounter with poisonous drug therapy, an all-too-familiar scene for the cancer patient.

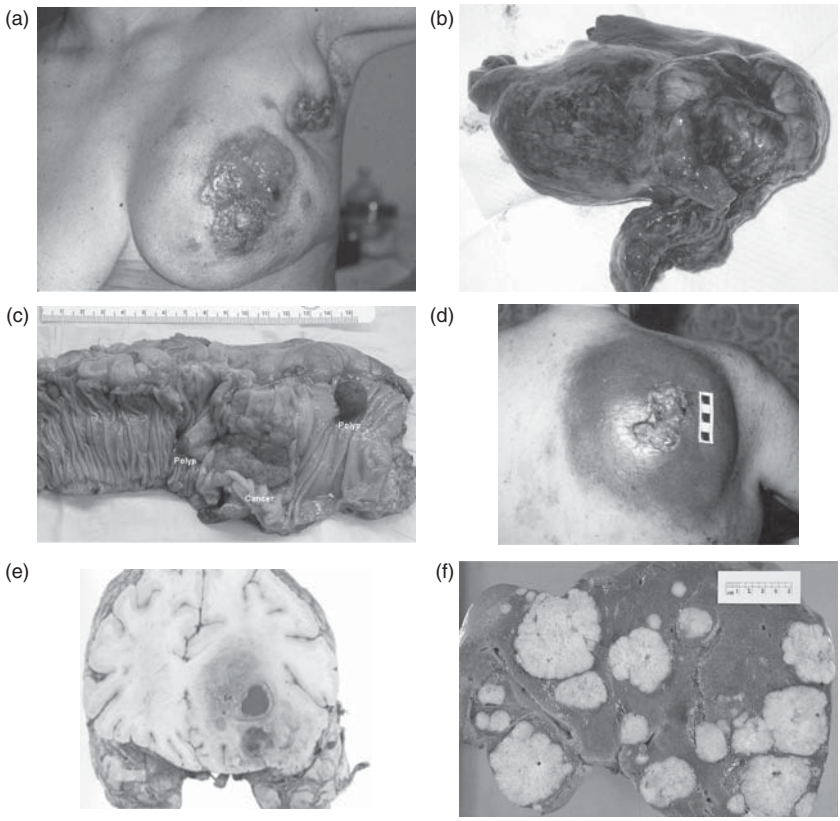


Figure 1.5 (a) Breast cancer, (b) lung cancer, (c) colon cancer, (d) melanoma, (e) glioblastoma, and (f) liver cancer. See color insert for (a, d). To see figures (b, c, e, f) in color please go to ftp://ftp.wiley.com/public/sci_tech_med/cancer_metabolic_disease.

Figure 1.6 The Conference. *Source:* Reprinted from Pope (p. 113) with permission. See color insert.

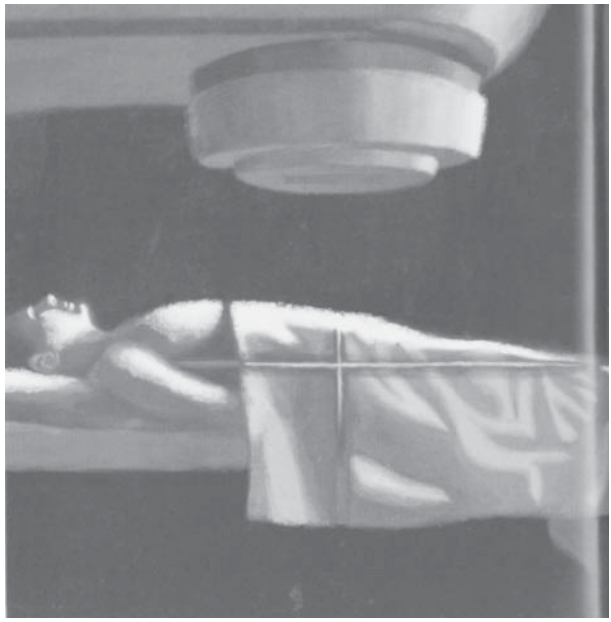


Figure 1.7 Radiation. *Source:* Reprinted from Pope (p. 52) with permission See color insert.

Figure 1.8 Chemotherapy. *Source:* Reprinted from Pope (p. 47) with permission. See color insert.

The ink on paper image in Figure 1.9 depicts the suffering of a woman receiving her scheduled chemotherapy. Pope recalled that the injection days were the worst days of his life. The woman pictured winces in pain as the poisonous drug is administered. In contrast to the treated patient, the mask and gloves protect the nurse from the toxic effects of the chemotherapy.

Figure 1.10 is also an ink on paper image that conveys Pope's memories of his sickness from chemotherapy treatment and the responses of his father (driving) and brother (in back seat) to Pope's suffering. Many cancer patients and their family members continue to experience these emotions. Indeed, these sufferings have become even worse with some of the newer drugs available (15, 22).

Figure 1.9 Chemotherapy injection. *Source:* Reprinted from Pope (p. 62) with permission.

Figure 1.10 Three men. *Source:* Reprinted from Pope (p. 89) with permission.

Figure 1.11 Mastectomy. *Source:* Reprinted from Pope (p. 101) with permission.

Another ink on paper image in Figure 1.11 conveys a woman's emotional trauma associated with mastectomy, which involves the surgical removal of a breast to prevent the spread of cancer.

Figure 1.12 is a charcoal on paper image that conveys the suffering of a young girl from the ravages of chemotherapy. She gently touches the instrument of her suffering, while her doll in the background and the metal pan in foreground are reminders of the comfort and pain in her life.

Figure 1.13 depicts a son's artistic impression of the neurological devastation of glioblastoma in his father.

In addition to these pictorial images of cancer, we can also obtain a literary image of cancer from a paraphrase of Herman Melville's "Moby-Dick," when captain Ahab (played by the actor Gregory Peck) utters these words:

> *Look ye, Starbuck, all visible objects are but as pasteboard masks. Some inscrutable yet reasoning thing puts forth the molding of their features. The white whale tasks me; he heaps me. Yet he is but a mask. 'Tis the thing behind the mask I chiefly hate; the malignant thing that has plagued mankind since time began; the thing that maws and mutilates our race, not killing us outright but letting us live on, with half a heart and half a lung.*

More personal accounts of cancer images can be found in the 2010 HBO movie, *Wit*, starring Emma Thompson, and in the popular books by physicians

Figure 1.12 Erica. *Source:* Reprinted from Pope (p. 80) with permission.

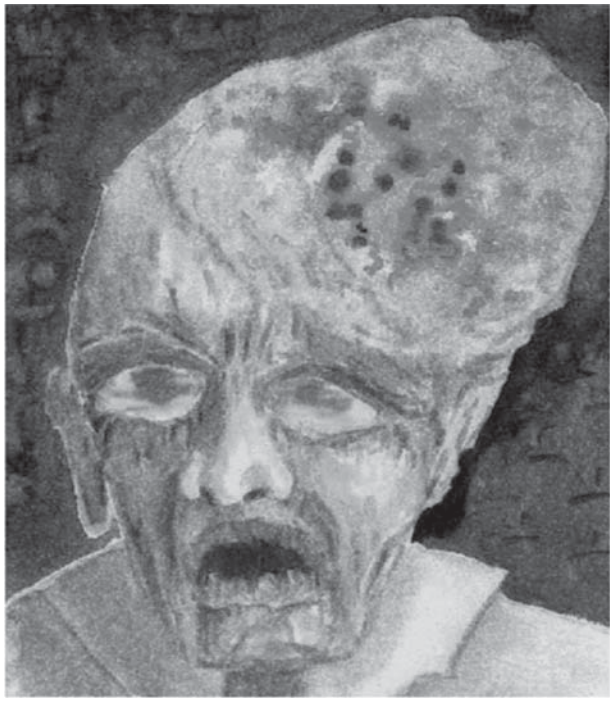


Figure 1.13 Fading away. *Source:* Reprinted with permission from Gupta and Sarin (23). See color insert.

David Servan-Schreiber ("Anticancer: A New Way of Life") (24) and Siddhartha Mukherjee ("The Emperor of All Maladies: A Biography of Cancer") (25).

Synopsis

The images of cancer have changed little for more than a hundred years. If anything, they have become worse in this new century. The data in Table 1.1 show that we are not winning the war on cancer, regardless of what the pundits say (8). The promises of new drugs based on improved understanding of cancer genetics and biology have not materialized (26–28). As each new "miracle" cancer drug is discontinued due to no efficacy or unacceptable toxicity, a new "miracle" drug with similar disappointing effects quickly takes its place (15, 29). The media feeds into this process, providing false hope and misinformation (30). When will this continuum end? It will end, in my opinion, only after we come to recognize cancer as a metabolic disease that can be effectively managed with nontoxic metabolic therapies (31). My goal is to provide scientific evidence supporting this view.

Table 1.1 Cancer Statistics from 1990 to 2010

Year	Number of new cases	Number of deaths per year	Number of deaths per day
1990[a]	1,040,000	510,000	1397
1996[b]	1,359,150	554,740	1520
2002[c]	1,284,900	555,500	1522
2003[c]	1,334,100	556,500	1525
2004[c]	1,368,030	563,700	1544
2005[c]	1,372,910	570,280	1562
2006[c]	1,399,790	564,830	1547
2007[c]	1,444,920	559,650	1533
2008[c]	1,437,180	565,650	1549
2009[c]	1,479,350	562,340	1541
2010[c]	1,529,560	569,490	1560

The data show that the number of new cancer cases and deaths per year is increasing, while the number of deaths per day has remained fairly constant from 1996 until 2010. The numbers clearly indicate that the war on cancer is not going well. Indeed, the number of new cases, deaths per year, and deaths per day for cancer in 2010 was greater than the number of total casualties (1,076,245), total deaths (405,399), and deaths per day (416) suffered by all US military forces during the Second World War (1941–1945; data from http://en.wikipedia.org/wiki/United_States_military_casualties_of_war). What does this say about the leadership of those who are directing the war on cancer? The persistent high number of cancer deaths per year is especially disheartening considering that the budget for the National Cancer Institute (NCI) increased from $4.12 billion in 2002 to $5.10 billion in 2010. The 24% increase in the NCI budget is comparable to the 19% increase in new cancer cases.

[a] Data from Silverberg et al., http://caonline.amcancersoc.org/cgi/reprint/40/1/9.

[b] Data from Parker et al., http://caonline.amcancersoc.org/cgi/reprint/46/1/5.

[c] Data from Jamal et al. (4, 5, 7, 9–11).