

CANCER AS A CHALLENGE

Scientific Discoveries and New Insights - A Source of Hope

Jacob Shoham, MD, PhD

CANCER AS A CHALLENGE

Scientific Discoveries and New Insights – A Source of Hope

Jacob Shoham, MD, PhD

Senior Editors & Producers: ContentoNow

Translation: Zvi Chazanov

Editor: Melinda Lipkin

Graphic Design: Naama Arinos

Cover Book: Benjie Herskowitz

Production Manager: Herela Hodaya Moise

Copyright © 2016 by Jacob Shoham

All rights reserved. No part of this book may be translated, reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, recording or otherwise, without prior permission in writing from the author.

ISBN: 978-965-550-558-0

International distributor: Contento Now
3 Ha'Barzel St., Tel Aviv, 6971007, Israel

www.ContentoNow.com
netanel@contentonow.com

CANCER AS A CHALLENGE
Scientific Discoveries and New Insights –
A Source of Hope

Jacob Shoham, MD, PhD

Disclaimer

This book was written with the sole intention of expanding knowledge and sharing information. It was not intended to promote or prescribe treatments, or serve as a manual for treatment or diagnosis. This book should not be used as a diagnostic tool or for self-treatment. In addition, this book should not be used as reference for accepting or refusing any given treatment, medical or otherwise. Please turn to your physician for diagnosis and or treatment. Both the publisher and the author, are not in any way responsible for the material presented in this book, legally or otherwise, and for any harm caused directly or indirectly as a result of the ideas or information presented in this book.

Table of Contents

Introduction	11
Chapter One What is Cancer?	18
Chapter 2 The Wonderfully Complex System of the Living Cell	36
Chapter 3 The Intricate Structure and Behavior of Cancer Cells	59
Chapter 4 The Genome of Cancer Cells: I. DNA Sequence Disruptions	82
Chapter 5 The Genome of Cancer Cells: II. Gene Expression Changes and Other Abnormalities	97
Chapter 6 The Genome of Cancer Cells: III. Searching For Cancer Causing Genes	109
Chapter 7 The Effects of Genetic Changes on Cell Behavior: I. Growth Factors and Their Receptors	122

Chapter 8	136
The Effects of Genetic Changes on Cancer Cell Behavior: II. Disruption of Intracellular Signaling Cascade	
Chapter 9	149
The Effects of Genetic Changes on Cancer Cell Behavior: III. Control of Cell Proliferation and Cell Death	
Chapter 10	163
Carcinogenesis As An Interactive Process: I. Factors Participating in the Cancer Process	
Chapter 11	175
Carcinogenesis As An Interactive Process: II. The Role of the Internal Environment in Carcinogenesis	
Chapter 12	189
Carcinogenesis As An Interactive Process: III. The Immune System and Cancer	
Chapter 13	203
Past and Present Cancer Treatment: A Story of Challenges, Achievements and Problems	
Chapter 14	219
Facing the Future: I. Approaching the Cancer Problem From A Complexity Science Perspective	

Chapter 15	238
Facing the Future: II. The Therapeutic Implications of Regarding Cancer As A Complex System	
Epilogue	262
Cancer As An Existential Human Experience: The Spiritual Aspect	
Suggested Reading	268

Acknowledgements

I wish to express my gratitude first and foremost to Dr. Avia Shoham, my wife, for her loving concern and support and for the inspiring discussions and critical reading of this book's chapters; to my children and their spouses – Tamar and Sergio, Asaf and Iris, Efrat and Yossi, for their support, love, and encouragement. To Avia's children and their spouses, for their concern.

To Dr. Yedida Sharaby, my senior assistant for years and to the many other researchers and students in my lab for the fruitful work together.

To Dr. Nechama Kossover of Tel Aviv University for the strict, thorough reading and important input.

To Dr. Yossi Yarden and Dr. Meir Shinitzky of the Weizmann Institute of Science, for their cooperation.

To Dr. Keith Block, of the Block Medical Center, Illinois, the leading pioneer of Integrative Oncology in USA, for true friendship, for serving as an example of full devotion to his humane and medical mission and for generously sharing with me his incredible knowledge and clinical experience. To Dr Penny Block for fruitful discussions.

To Dr. Lawrence LeShan, for opening the door to me to his unique and seminal work in psycho-oncology and for the many insightful and thought-provoking discussions we had.

To Dr. Ruth Bolletino, psychologist, LeShan's disciple, for leading and demonstrating an ingenuous, compassionate and

humble way of approaching the emotional and spiritual world of patients.

To the Talking Glossary website managers for the permission to use their illustrations as a basis for some of this book's illustrations.

Last, but not least, I would like to express my esteem and honor to the cancer patients I had the privilege to treat, guide, accompany and learn from. Many of them can serve as models of determination, courage, ability to change and take responsibility and penetrating, unique insights to the meaning of their life.

Introduction

Cancer is one of the major challenges facing science and medicine. This challenge has two aspects: one, understanding the nature of the cancer process, which poses a key question in life sciences; two, finding an effective therapy for cancer, a disease that still constitutes a most difficult medical problem. While cancer poses a complex biological and medical challenge, it is first and foremost a highly human, personal, and social challenge, which raises fundamental existential and spiritual questions. However, in this book the focus is on an introductory scientific description of cancer as a biological process. This exposition of the subject, albeit simplified, is based on an enormous amount of scientific discoveries in cancer research, some of which led to the development of various means of treatment. Furthermore, general insights as to the nature of the cancer process suggest new avenues to cancer treatment, allowing room for more hope. Some of these insights and their medical implications are described in the book's final chapters. The issues of cancer as a human challenge extend beyond the scope of this book, and they will be addressed only briefly, in the closing parts of the book.

Cancer is a subject matter to which everybody is exposed in his or her circles. It seems threatening and scary. Most people have fragmentary knowledge regarding this disease — at times due to witnessing the suffering of cancer patients who are relatives or friends, and at other times due to news about patients struggling for the right to receive the most innovative treatment.

The frequency of being exposed does not help clarify it or make it easier to accept; on the contrary, it only intensifies the feeling that cancer is a medical problem that is difficult to solve and whose prevalence is only growing.

However, there is another important aspect to this subject which bears a comforting message: In the past few decades cancer research has constituted the battlefield of scientific investigation in biology. Consequently, an immense amount of information has been accumulated regarding cancer, its development process, its sources, and its characteristics.

This information is important in itself, as it enhances our understanding regarding some of the most basic life processes taking place in each cell and in the organism as a whole. The healthy whole organism is comprised of a huge amount of cells that interact intensely with each other to create an orchestrated, properly functioning organism. Cancer cells violate the most fundamental rules of cells' behavior both as single cells and as part of a multicellular organism. These rules include those associated with cell life, growth, differentiation, and death, and those associated with proper conduct in a large society of cells, i.e. conveying the right intra- and inter-cellular signals, preserving tissue structure and size, etc. Knowledge of rule violation facilitates a better understanding of the violated rules and consequently the way normal cells behave. Thereby, the study of cancer promotes the biological research as a whole. A considerable part of this book will be devoted to a concise description of this knowledge.

However, it is clear that the practical implications of this knowledge are of more immediate relevance to our life than its theoretical value. Much money has been invested in cancer research, especially since 1971, the year when then U.S. President Richard Nixon, announced the war on cancer (The National Cancer Act of 1971). This intensive research has yielded highly important findings regarding cancer biology, allowing the

development of more accurate diagnostic and monitoring means. More importantly, certain aspects of this research resulted in the development of innovative biological treatments. Some of those developments will be mentioned in the book in the relevant context.

Yet, it is not enough to perceive cancer as a mere matter of objective knowledge. Rather, cancer creates strong emotional reactions, such as fear or anxiety.

Why does cancer arouse emotions more intense than other, commonly known diseases that bear a great risk, such as heart diseases? There may be two causes: the nature of the disease and the type of treatments offered for it at present.

Cancer may creep quietly, in many cases without any warning symptoms. In the mind of many people, it is associated with a state of prolonged suffering, pain, a decline in functioning, lowering of self-image, a feeling that one's body has betrayed him, increased dependency on others, and fear of death. You may add to this image of cancer the information regarding the increased prevalence of cancer in the Western world, with more and more cases of younger people being diagnosed with types of cancer formerly found more typically in older adults. However, the good news is that the knowledge accumulated regarding the causes of the disease may enable individuals and society to reduce disease prevalence (see Chapter 10 for details).

The sensations of fear and anxiety, however, are not only the consequences of the disease's image and its increasing prevalence. Unfortunately, the medical treatments for cancer entail many adverse reactions and health-damaging effects, some of them severe and long-lasting. Furthermore, in many cases, these treatments are of limited, temporary value. The economic aspect to individuals and to society, including the extremely costly, new, and innovative biological treatments for cancer in the medical arsenal, should not be underestimated. In the last few chapters

I will propose another way of addressing the cancer problem, which may offer a path of hope down which we may be heading.

I approach this subject from two perspectives. The first is as a physician specialized in internal medicine who studied medical oncology at a leading cancer institute in the United States and then integrative cancer medicine at a medical center, in the United States as well. I have treated numerous cancer patients. The second perspective is that of a cancer researcher, who focused upon studying cancer cell behavior in the past and now focuses on the immune and inflammatory reaction to this disease.

This book's goal is to provide the knowledge-seeking public with some of the most up-to-date scientific information regarding cancer as a biological process and its causes. During the writing of this book, I made a conscious effort to simplify complex biological information and make it suitable for the wide public. Hence, several of the topics associated with cancer research are addressed here in a nutshell, without portraying the full scope of the discussed phenomena or their fine details. Moreover, some issues will be mentioned merely in passing or not be addressed at all. However, this concise description will be enough to serve as a basis for discussing some of the theoretical significance and the practical, therapeutic implications this information bears.

The book's outline:

Chapter 1 will focus on the general definition and description of the cancer process, presenting various viewpoints from which it can be explored. This chapter also includes a short review of cancer research development and the research methods involved.

Chapter 2 will present basic concepts regarding cell structure and function. The cell is the most basic life unit, in both the normal organism and in cancer. The information included in

this chapter provides sufficient background and basic biological terms for readers who have never studied biology. I do not intend to use scientific jargon in the book, but complete avoidance of specific biological terms is impossible. Such terms and concepts are therefore to be explained in Chapter 2.

Chapters 3-9 will be devoted to an up-to-date, yet not comprehensive description of the knowledge on cancer as a highly complex biological process. The main motif upon which this part is based is the genotype-phenotype relationship – a key issue in biology, not only in relation to cancer. Hence, it is important to precede and clarify those terms. The genotype represents the genetic makeup of a cell or a whole organism, such as a human being, while the phenotype represents the observable characteristics of an organism (physical, biochemical, morphological, etc.), and the way in which it expresses itself or behaves. Although the two are related, it is not a one-for-one relation. Not every defined quality, which is part of the phenotype, is a consequence of the information contained in one particular gene, which is part of the genotype. Some qualities reflect the combined expression of many genes, brought about through a complex interactive activity, and vice versa – one gene may participate in shaping many qualities. The environment has a significant role in these interactive processes. Molecular biology has contributed greatly to our understanding of the subject matter, but the way in which the transition from genotype to phenotype occurs is still far from being fully understood. The first chapter of this part (the book's third chapter) will address the nature of cancer cells and their behavior, i.e. their phenotype, which is different from that of normal cells. We shall also note how some of those data serve in cancer diagnosis.

Chapters 4-6 will be devoted to the other aspect of the matter, namely, the genotype, the nature of damages and changes in the

cell's genome, and the specific genes involved in the carcinogenic process.

Chapters 7-9 will explain how both aspects may be connected, namely, the way in which damages to the cell genome (the genotype) are expressed as modified qualities and disturbed behavior of the cancer cell (the phenotype).

Chapters 10-12 are devoted to the interaction of the cancer and its environment. This matter is of highly practical significance. Causes and conditions that may initiate the cancer process, allow and nourish its existence, and speed up its development will be addressed. They include both factors in the external environment and in the individual's internal environment, namely, his various body systems, including his hormonal, immune and inflammatory systems and his mental condition. In this context, modes and means through which those risks may be eliminated, prevented, or reduced will also be mentioned.

Chapters 13-15 review the development of the medical approach to cancer treatment to date and the prospect of further development in the future. Chapter 13 presents a brief description of contemporary cancer treatment. Chapters 14 and 15 offer a different outlook on cancer, based upon Complex Systems Theory. This theory has become central in current biological thinking, and it consequently bears significant implications on the way we should approach cancer research and cancer treatment.

As stated, cancer poses not only a biological and medical challenge but also a highly significant emotional and spiritual personal one. This challenge will be briefly discussed in the Epilogue.

The book may be read on three levels:

- A reader interested in the sections dealing with practical implications only may read Chapter 1, the short summary concluding Chapters 2-9, chapters which require more thorough reading, and go on to Chapters 10 -15.
- A reader interested in understanding both the biological aspects and the practical implications is welcome to read the whole book.
- A reader striving for a thorough exploration of the subject matter may rely upon this book as a foundation for a journey to be continued in the reading list suggested at its end. Furthermore, each term mentioned in the book may be used as a keyword for the search of further information through the Internet.

I hope this book will allow the reader a glance into the complex world of life sciences in general and of cancer in particular, inducing in them the desire to further delve into the issue both in its theoretical and research aspects, as well as its practical aspects. The reader who is not interested in further exploring this field should at least assimilate the main practical lessons to be learned: There are concrete ways to reduce the likelihood that this disease will strike us. Furthermore, despite the complexity of the cancer problem, one may find effective modes to cope with it, even if it has struck. I believe we are embarking on an exciting time in the field of cancer research and treatment, bearing a true promise for controlling and overcoming this devastating disease.

Chapter One

What is Cancer?

In order to address this question, the cancer process will be briefly described. We shall further delve into many details of this short description later in this chapter and in the chapters to follow. The description is focused on cancer in humans, although this process may occur in all living beings.

Cancer is a dynamic process which begins with a single cell (Figure 1-1). The initiation of the process is manifested by a change in the genetic information in one cell of a certain tissue in the human body. It usually occurs through the formation of a specific mutation, which allows growth and uncontrolled divisions of the cell. Hence, this cell is given the advantage of proliferative ability over normal cells. The cell serving as a source of cancer development may be a stem cell of the same tissue. The cancer initiating mutation may be caused by a carcinogen, a mutation causing agent; but sometimes, particularly during cell replication, a spontaneous mutation can take place. The replication stage is particularly sensitive to disruptions.

A cell which underwent such a specific mutation becomes autonomous in terms of its growth and development abilities. It ceases to obey the body's rules and ignores signals limiting cell division. However, it continues to receive its nurturing from the body and employ or divert many of the body's mechanisms for its many needs. When this cell divides, the daughter cells stemming from it inherit this quality, and they, in turn form a clone.

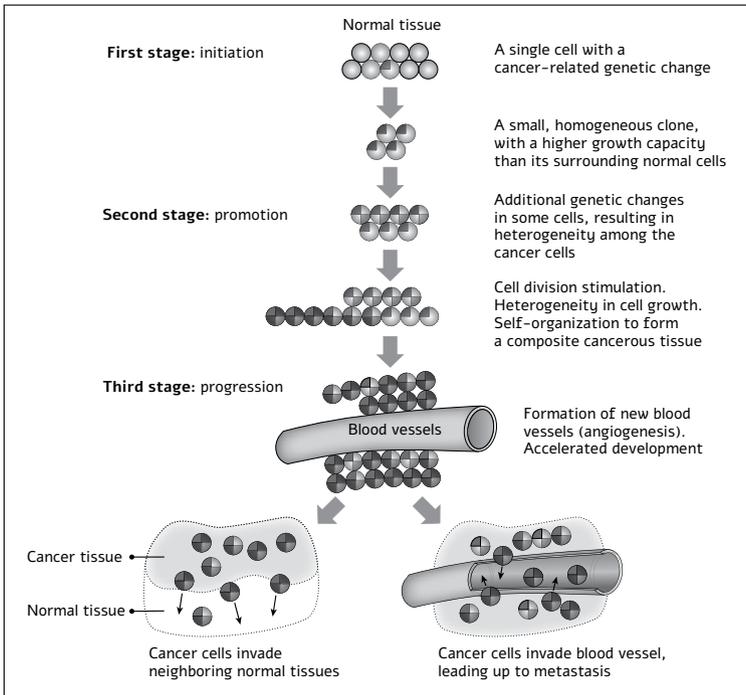


Figure 1-1: A general outline of cancer development.

Every circle stands for a cell. Every shade of grey within a circle stands for a mutation.

In biological terms, a clone is a group of cells which developed from one cell, bearing an identical genetic setup. The clone may remain dormant, or begin forming a complex cell system which will continue developing and growing. In such case the cells in a clone must acquire the ability to violate the conduct rules of the individual in whose body they grow, the rules which are essential for close control of cell division. Furthermore, they exploit the internal human environment for growth and development. This is the promotion stage of the cancer process. The cells in the clone gradually accumulate further disruptions in the structure

and expression of various genes responsible for cell life and replication. These events neutralize more and more mechanisms which were designated to prevent cancer development and by doing so intensify cancer violence. The genetic disruption process is not equal for all clone's cells. Each cell may undergo a different set of accumulative disruptions. Hence, every cell which has undergone a different set of changes can form a new clone with unique characteristics, within the developing cancer tissue. Consequently, cancer becomes heterogenic, namely, comprised of a wide diversity of clones, representing various qualities and different levels of malignancy and violence. This situation forms the basis for a natural selection process, by which cancer cells or clones that have developed the highest survival and multiplication abilities will be selected.

One of the basic conditions for enhancing cancer survival and growth is the development of an ability to induce blood vessel formation. The blood vessels nourish the tumor, thereby facilitating a constantly growing tumor tissue. This is the progression stage, in which the growing tumor undergoes a self-organization process with an inner "labor division". This process includes also the development of mechanisms which deceive the body's resistance and defense mechanisms, even exploiting them for their advantage, further enhancing tumor viability, growth and expansion. Additionally, some of those cells, within the heterogenic cancer tissue, may develop features allowing them to invade their near environment and migrate through the blood and lymph vessels to peripheral tissues, where they will form metastasis. The two latter processes, invasion and metastasis, are those which particularly threaten the survival of the cancer-bearing individual. Thus, we witness a dynamic process of changes, which augment the malignant features of the cancer, increasing the threat faced by the cancer patient.

There is a rather wide range of tumor malignancy, from tumors whose behavior is benign, to highly fatal tumors. Differences