the MEDICINE *of* LIGHT

Harnessing the Healing Power of Light-Based Therapies to Overcome Cancer, Pre-Cancer, and Chronic Diseases

Andrei V. Reshetnickov, PhD
and **Mark Nathaniel Mead, MSc**

Foreword by
Keith I. Block, MD
author of *Life Over Cancer*

"This is the natural health and healing way of the future."
—**Harrie Vink,** Chairman of The Natural Health Foundation

For all people with a life-threatening disease—
and for their friends and loved ones.

"For the rest of my life, I will reflect on what light is."

— **Albert Einstein**

Quoted in *Empire of Light* by Sidney Perkowitz

(Henry Holt & Co., 1999)

Disclaimer

This book is not intended as a substitute for the medical advice of your physician and cannot replace a one-on-one relationship with a qualified health care professional. The reader should regularly consult a physician in matters relating to his or her health and particularly with respect to any symptoms that may require diagnosis or medical attention. The information contained in this book is intended as a sharing of knowledge and information from published research and from the clinical experience of numerous health care professionals. The therapies, resources and products listed in this book are not intended to be fully systematic, nor does inclusion here imply any endorsement or recommendation by the Natural Health Foundation. The Natural Health Foundation makes no warranties, express or implied, about the value or utility for any purpose of the information and resources contained herein.

TABLE OF CONTENTS

ACKNOWLEDGMENTS

The Natural Health Foundation is grateful for the research contributions of many leading scientists in the field. The Foundation continues to provide support for their research and is dedicated to funding research projects aligned with this important medical endeavor. In particular, we would like to cite the work of the following individuals:

Dr. Olga Abakumova, for her early cytophototoxicity research of the effects of radahlorin active pharmaceutical ingredient on cancer cell lines, as well as advice and encouragement at V. N. Orekhovich Institute of Biomedical Chemistry of Russian Academy of Medical Sciences in Moscow, Russia.

Dr. Evgeniy Stranadko, currently the Head of the Department of Laser Oncology and PDT, of the State Research Center of Laser Medicine in Moscow for successfully treating the first patient (breast cancer) by PDT with photochlorin I as early as 1997 and informing the present book's author about its outstanding characteristics, setting the stage for further exploration and the eventual development of radahlorin.

Dr. Michael R. Hamblin, Associate Professor of Dermatology at Harvard Medical School and a Principal Investigator at the Wellman Center for Photomedicine in Boston, MA (USA) for pioneering research and exciting discussions regarding immuno-PDT.

Dr. Nikolay Vasiliev Dr. Nikolay Vasiliev of Research Design and Technology Institute of Biologically Active Substances in Novosibirsk, for his pilot clinical studies of PDT using Radachlorin® for lung cancer and tuberculosis, along with demonstrations of the efficacy of photoimmunotherapy at Novosibirskiy Regional Antituberculosis Dispensary, Russia.

Dr. Thierry Patrice, Scientific Head of the Laser Department, Neurosurgery, Laennec Hospital, in Nantes, France, for his leading-edge perspectives and *in vitro* and *in vivo* comparative studies of Bremachlorin® and chlorin e_6.

Dr. Stephen Bown of the National Medical Laser Centre at the University College London, UK, for his opinions and for hosting several presentations and discussions about PDT with Radachlorin®.

Dr. Olga Sergeeva, for her investigations of PDT of cholangiocarcinoma using Radachlorin®/Bremachlorin® and the therapeutic impact of immuno-PDT at the Russian Oncological Scientific Center (named after N. N. Blokhin) in Moscow.

Dr. Vladimir Romanov, for his pioneering research on stomach cancer PDT using Radachlorin®/Bremachlorin® at the Clinical Hospital 119, Novogorsk, Moscow Region, Russia.

Dr. Evgeniy Volkov of Sverdlovskiy Regional Oncological Dispensary in Ekaterinburg, Russia, for his 12-year study of Radachlorin®/Bremachlorin® PDT of patients having cutaneous melanoma and illustrations for the book.

Dr. Alexey Nasedkin, for his early pilot clinical studies of ear, nose and throat cancers using Radachlorin®, as well as phase II clinical trials of the antimicrobial PDT in sinusitis and tonsillitis at the V. F. Vladimirskiy Moscow Regional Clinical Research Institute in Russia.

Dr. David Dolidze, for his comparative clinical studies using Bremachlorin® PDT in combination with laserthermia to treat benign multiple adenoma of the thyroid at the S. P. Botkin Municipal Clinical Hospital in Moscow.

Dr. Valeriy Privalov, Head of General Surgery at Chelyabinsk Medical Academy (Russia), for his pioneering pilot clinical research in PDT, as well as phase I-II clinical studies of Radachlorin® PDT to treat superficial and nodular basal cell carcinoma at the Municipal Clinical Hospital 1 in Chelyabinsk, Russia

Dr. Alexander Lappa, Professor of the Chair of Theoretical Physics of Chelyabinsk State University, for his consistent support of Professor Privalov's work in the development of PDT using Radachlorin®.

Dr. Victor Sokolov, Head of the Department of Endoscopic and Physical Methods of Diagnosis and Treatment of Tumors at P. A. Hertzen Moscow Oncology Research Institute (Russia), for many years of encouragement and conducting phase I and II clinical studies of PDT of superficial basal cell carcinoma and cancers of the bronchi, esophagus, bladder, and prostate.

Dr. Marina Prokofeva, ophthalmologist, for her early initiative and interest in using Radachlorin® for PDT of eye diseases and conducting phase II clinical trials of cystic filtering blebs.

Dr. Clemens Lowik, Head of the Endocrinology Research Laboratory at the Leiden University Medical Center, in Leiden, The Netherlands, for Bremachlorin® fluorescence imaging and its fundamental research at the Center.

Dr. Dick Sterenborg, Professor of Photodynamic Therapy at the Medical Center of Erasmus University in Rotterdam, The Netherlands, for his innovative research on light delivery methods, fluorescent diagnosis and measurements of tissue oxygen, as well as his opinions and interest in Bremachlorin®.

A MESSAGE OF HOPE AND HEALING

My original vision in supporting this book's publication was to help create new life when another life, one very dear to me, had passed away. This was the life of my beloved wife Marijke. In the spring of 2003, we learned that Marijke had advanced lung cancer. Soon after her diagnosis, the oncologist informed us that she had precious little time left to live. The only established therapy available at the time, an intensive chemotherapy regimen, could perhaps prolong her life for a few weeks, but with a virtual guarantee of many severe side effects and the potential for major complications, some of which were themselves life-threatening.

We were both stunned. I tried my best to fight off the despair but felt numb with shock and disbelief. My dear, beautiful wife, now with cancer—this simply could not be happening. After receiving the news, she and I sat for 15 minutes in total silence. Each of us had always shared the belief that we could overcome any obstacle and that, together, we could face any challenge, no matter how difficult. But this diagnosis was the greatest challenge we had ever faced. Our world was falling apart. I could only begin to imagine what she was feeling.

Those were the longest 15 minutes I've ever experienced. It was Marijke who finally put an end to the silence. She stood up and, with a sparkle of determination in her eye, asked the physician for a copy of her medical records. She told him that she had no intention of giving up and submitting herself to a course of treatment that offered such a dubious chance of success, and that she would instead prefer to explore other possibilities for beating this disease.

After contacting everyone we knew who might have connections, and making many phone calls to clinics around Western Europe, we

reached a physician in Eindhoven, a large city in the southern part of the Netherlands. This doctor had lost his son to lung cancer a few months earlier, and he did not hesitate to offer us his firm opinion as to the most promising treatment strategy for Marijke.

"Your best option at this point is Photodynamic Therapy," he said. "With all the other therapies for advanced lung cancer, your prognosis is poor; your probability of survival is minimal. Photodynamic Therapy, in my opinion, offers you the best chance for beating this terrible disease."

Always in a winning mood, Marijke and I went on the Internet and visited many websites that focused on Photodynamic Therapy (PDT). We soon came across the name of Dr. Andrei Reshetnickov, the inventor of several photosensitizing drugs, such as radahlorin, now trademarked as Bremachlorin®. He is also one of the inventors of a patented clinical approach to Photoimmunotherapy, or PIT. Recent research suggests that PIT is a promising medical breakthrough for overcoming cancer. It helps better reveal cancer and infections to the immune system. (I strongly encourage everyone—particularly those from the medical-scientific community—to read the interview with Dr. Reshetnickov in Chapter 7.)

In reading about his work, we became excited about the possibilities for using this agent. As it happened, Andrei was to appear soon afterward at a seminar in The Hague. This was a meeting of the Dutch Association for Orthomolecular Oncology on PDT using Radachlorin® on August 23, 2003.

I resolved to go and meet with Dr. Reshetnickov. After hearing his presentation, I could see that this was a man who had something important to share with the world. I began to feel a renewed sense of hope. "If you will help us, I will help you," I told Andrei. That was how we began to interact with each other, and I have been communicating with this brilliant Russian scientist ever since.

Unfortunately, Marijke's tumor had already increased in size to the point where it was impinging on blood vessels to her heart. This was a dangerous situation, and the oncologists recommended that she undergo chemotherapy to help shrink the tumor as quickly as possible—and that this would be necessary before she began the experimental treatment. We did as they suggested. Although the treatments greatly suppressed her immune system and adversely affected her heart as well, it did reduce the size of the tumor so that she could start the PDT.

The light-based therapy took place over the next few months in Ireland. We saw with our own eyes how the treatment worked and how well Marijke responded. After a series of PDT sessions, her lung tumors were greatly reduced in size, and then continued to shrink well beyond what had been accomplished with chemotherapy.

By the time she started the light-based treatments, however, the tumor burden in her body was quite extensive. Although the PDT was effective in shrinking the cancer, the tumor broke down too rapidly, releasing a tidal wave of toxins. Because her heart and immune system had taken such a beating from the chemo, she could not cope with the tumor breakdown process. This led her to experience a great deal of fatigue and weakness. Her heart had become extremely weak, calling for electro-shock stimulation therapy as a desperate last measure.

Tragically, Marijke's body had become too weakened by the disease and the chemo treatments, and she was unable to endure the release of tumor toxins. On November 5th, 2003, she died at the tender age of 54.

In the months that followed, I reflected back on what we had witnessed during Marijke's encounter with PDT. It occurred to me that, had she been able to receive this powerful treatment option sooner, she might well have had a better chance of overcoming her cancer. Alas, she had come to the therapy too late in her disease process—when she was already at a point of critical tumor mass.

What appeared to be the end was, in fact, a new beginning. Since the passing of my beloved wife, I've met many cancer patients who used PDT as their primary treatment, but with much more favorable results. These individuals were more fortunate than Marijke because they had been introduced to the treatment much sooner in the course of their disease. In many cases, they were treated straight away with PDT instead of having the intensive conventional treatments first.

Through my subsequent discussions with Andrei, I could clearly see that Bremachlorin® was a promising tool for battling cancer. I learned that if you're able to break down the tumor using PDT—at a rate similar to that with which it grew in the body—there would be a much

greater probability of treatment success. This strategy, particularly when combined with targeted support for anti-cancer immunity, could prove to be the best way to overcome cancer, and there is a growing body of research to support this perspective. This is also why I believe we should support the development of photosensitizers that can detect cancer at a much earlier stage.

In the course of my discussions with Andrei, as well as meetings with other PDT experts and research scientists, I made the decision to set up the Natural Health Foundation here in the Netherlands. The original purpose of this non-profit organization was to promote and support the development of new photo- and radio-sensitizing agents to help doctors diagnose and treat cancer at a much earlier stage.

Presently, the NHF is striving to support holistic research for the prevention and treatment of cancer, as well as helping people find solutions for curbing and overcoming other chronic diseases. It is also my hope that the Foundation will help bring greater awareness to bear on the healing and curative powers of like PDT, PIT, and Systemic Light Treatment. With the help of such innovative photodynamic tools, as well as with the agents currently under development, physicians will be in a much stronger position to ultimately cure cancer.

It has been said that cancer is far more curable if detected early. To this end, the Natural Health Foundation has supported the research and development of a new photodynamic diagnostic test. This involves an innovative MRI contrast agent that selectively accumulates in tumors. The Foundation is also supporting new research and developments in PIT, an approach that trains the patient's immune system to better expose and ultimately eliminate cancer cells.

The purpose of this book is to help increase awareness regarding the healing powers of light, the natural healing pathway of the future. It is our hope that this book will inspire many people—patients, doctors, and scientists alike—to consider these wonderful therapeutic tools, which work in harmony with the body's innate healing mechanisms. In my opinion, this book should be on the desk of any physician interested in overcoming life-threatening diseases and in the future direction of medicine.

With your help and sponsorship, we will continue to guide and facilitate research and education efforts with the goal of helping all humankind and guiding the medical profession toward a better understanding of the usefulness of light-based therapies and other innovative, natural treatment options. Proceeds from the sales of this book will go to supporting studies of the light-based diagnosis and treatment of cancer. For more information or to offer support, please visit our website, www.naturalhealthfoundation.org.

Harrie Vink
CHAIRMAN OF THE NATURAL HEALTH FOUNDATION
23 August 2013

NHF
Supporting Health, Healing and Hope Around the World

FOREWORD

Since the 1970s, research and understanding of the biology, diagnosis, and treatment of cancer have grown exponentially. Despite this explosion in knowledge, cancer rates continue to rise, and many of the more common malignancies remain incurable. Novel approaches for overcoming the disease or further prolonging survival are urgently needed. Currently, the major therapeutic strategies against cancer all center on surgery, radiation treatment, and systemic chemotherapy, with molecular-targeted therapy gaining increasing traction as well. As the track record has shown, however, these modalities have come up short in the treatment of most advanced-stage cancers, and thus the need for integration and innovation has never been greater.

Photodynamic therapy, or PDT, is a clinically approved, minimally invasive therapeutic procedure that has demonstrated effectiveness in the treatment of various cancers, as well as macular degeneration, psoriasis, acne and localized infections. The treatment depends on a blending of three factors: light, a photosensitizer, and tissue oxygen (though the treatment effect can also happen without oxygen). The photosensitizer is a substance that transmits light's energy and uses it to destroy abnormal or unwanted cells.

All good photosensitizers have a remarkable ability to differentiate between normal and abnormal body cells. This special ability explains how PDT can selectively destroy tumor tissue with very little harm to the surrounding normal tissue. For this reason, PDT can be used in combination with the conventional trio of surgery, radiation and chemotherapy without adding to their downsides. The modality also offers several advantages over some of its conventional counterparts: First, as mentioned above, PDT is relatively non-invasive and accurately targets the cancer. Second, repeated doses can be given without the total-dose limitations linked with radiotherapy or chemotherapy. And third, the healing process takes place with little or no scarring.

In *The Medicine of Light*, you will learn about those attributes that help comprise the best photosensitizer and why this is so critical to the success of treatment. The book's first author, Andrei Reshetnickov, PhD, has developed chlorophyll-derived photosensitizers that concentrate selectively in tumor cells and effectively destroy those cells upon exposure to laser infrared or visible light. As a long-time student of botanical medicine, I was heartened to read about Dr. Reshetnickov's insights into the dynamic healing potential offered to us by the plant world.

At this time, PDT has been approved in many countries for the treatment of lung, esophageal, head and neck, bladder, and of course, skin cancers. It is receiving a great deal of attention in the European Union, Russia, Brazil and Southeast Asia, with slow but steadily increasing acceptance in North America as well. Clinical trials have proved it to be effective in the treatment of superficial basal cell carcinomas as well as several precancerous conditions—actinic keratosis, Bowen's disease, and Barret's esophagus (which can lead to esophageal cancer). Results from well-controlled randomized phase III clinical trials are becoming available for other cancers, and better photosensitizing drugs are in development.

Basal cell carcinoma is the most common cancer worldwide, accounting for 80 percent of all skin cancers and (ironically) being most prevalent in Australia and regions that receive intense sunlight much of the year. Though rarely fatal, this type of skin cancer does result in a great deal of morbidity and distress. Superficial basal cell carcinoma was the first cancer to be successfully treated with PDT back in 1913. Nevertheless, the competition posed by surgery proved too great at the time, and PDT was quickly pushed aside. It would be another 70 years before scientists around the world came to recognize PDT as a legitimate treatment option for skin cancer. We have now come full circle. Today, PDT is viewed as a viable, cost-effective alternative to surgery for superficial basal cell carcinoma (and even sometimes for the nodular form of this

skin cancer). It also results in a better cosmetic outcome, meaning a more pleasant appearance of the skin after the procedure. PDT can be done in an outpatient setting, is convenient for the patient, and has no serious side effects.

In the past two decades, PDT also has begun to show promise for treating tumors of the brain, lung, colon, rectum, esophagus, stomach, breast, prostate, bladder, liver, gall bladder, endometrium, eye, oral cavity, and thyroid gland. Indeed, though PDT already has proven value as a treatment for skin cancers and many of those cancers I just listed, it also has great potential for treating other types of cancer.

PDT is an especially attractive possibility for some aggressive cancers that have a poor prognosis. Two examples are inoperable cholangiosarcoma and hilar cholangiocarcinoma, both lethal cancers of the gall bladder and bile ducts that have responded well to PDT. Important evidence on the treatment's efficacy has come from small- to medium-sized clinical trials. Of course, larger trials are needed and require serious financial support, but the existing clinical data and lower risks associated with PDT suggest that it represents a novel cancer treatment option.

There are a few limitations of PDT worth mentioning. The first is photosensitivity, or skin sensitivity to light following treatment. This sensitivity is usually mild but can last for weeks depending on the photosensitizer. The second drawback relates to the fact that light must be able to reach the target area, with treatment being most effective for those cancers located close to the surface rather than deep in the tissues. Due to the limited tissue penetration of visible light, PDT has mostly been used for skin cancers. Third, for the most part, PDT has been used as a localized rather than as a systemic treatment—an essential concern when addressing advanced malignancy.

As you'll learn in *The Medicine of Light*, however, it's a mistake to assume that the efficacy of photodynamic treatments is limited to the local destruction of tumors. We now know that the more profound treatment effects of this modality are systemic. These whole-body effects are due to PDT's ability to induce a potent anti-tumor immune response, which in turn is linked with the treatment's ability to trigger the release of certain biomolecules from dead or dying cancer cells. In essence, dying cancer cells change their surface composition, and this

appears to be vital to stimulation of the patient's anti-cancer immunity, because the changes improve how cancer cells are recognized and eliminated by the immune system. Activated in this way, the immune system can then eliminate metastases and ultimately help thwart the more aggressive forms of cancer. The use of various immune stimulators or adjuvants appears to further augment these systemic effects.

I believe that this more whole-body application, generally referred to as immuno-PDT, could have profound implications for integrative cancer care. It is widely known that chemotherapy, radiotherapy and major surgery tend to suppress or weaken the immune system. The ideal cancer therapy would not only target the primary tumor, but at the same time would bolster the immune system's ability to recognize, track down and destroy any remaining tumor cells, regardless of their location. PDT, perhaps in tandem with hyperthermia (heating up the body), appears to have such desirable effects on the immune system.

In the years ahead, I anticipate great advances in our understanding of combination therapies that can be used with PDT to enhance the anti-cancer immune response. It is hoped that such combinations might help us overcome the problem of local tumor relapses as well as micrometastases (microscopic clusters of cancer cells). Moreover, immuno-PDT can eliminate chemoresistant and radioresistant cancer cells—cells that manage to survive those conventional treatments and eventually cause a life-threatening relapse or recurrence. Thus, immuno-PDT could prove to be an effective way to help cancer survivors prolong their remissions for the indefinite future.

There is still much research to be done to optimize treatment outcomes, and *The Medicine of Light* lays out a great deal of the groundwork for that research. For example, as explained in Chapter 7, the optimal PDT regimen (e.g., specific dose and timing of light and photosensitizer) that produces a therapeutic impact at the local tumor site will be markedly different from the optimal PDT regimen for enhancing the immune response. Clinical trials for PDT and immuno-PDT strategies are underway, and I expect that such research will lead to better, more effective ways of combating advanced cancers and adding to the existing arsenal of cancer therapies. Due to its promising immune-therapeutic effects, PDT may play a salient role in addressing the problem of re-

lapses that so often steal away life and continue to stymie the best efforts of mainstream oncology.

PDT does involve some complexity compared to conventional surgery, including careful consideration of the photosensitizer, as well as optimal light delivery and good coordination between clinicians. Availability of the necessary light sources was a challenge in the past, but low-cost portable light sources are now more widely available. As our understanding of photodynamic principles has evolved, so too has the development of efficient, convenient, and inexpensive systems of light delivery.

Over the past few decades, I have been steadfast in my commitment to bring together different treatment approaches that have synergistic effects against some of our most deadly cancers. Such integrative thinking is the central theme of our journal, *Integrative Cancer Therapies*, and has served as the cornerstone for my approach to cancer care. *The Medicine of Light* makes it clear that, although PDT has some "alternative" applications such as those mentioned above, in certain advanced disease situations, it may best serve in tandem with conventional treatments, such as surgery, radiotherapy, chemotherapy, anti-angiogenic therapy, hyperthermia and laserthermia.

Improvements in tumor responses to PDT may be achieved by employing such combined modality regimens, and the authors do an excellent job documenting the power and promise of these therapeutic combinations. The key is not only targeting malignant cells directly, but also interfering with those processes and modifying those unique conditions that help drive the malignant process—the biochemical terrain of cancer. By attending to this terrain with the tailored use of diet, herbs, and other natural methods, I believe we can create the conditions that support optimal treatment outcomes and ultimately increase survival. You can read about some of these key terrain issues in Chapter 6 of *The Medicine of Light*.

The challenges of cancer are many and complex, and it's clear that a major paradigm shift is now in order. *The Medicine of Light* illuminates a revolutionary way of thinking about our approach to cancer and other diseases. Used in the right way, light therapy provides an important evolving intervention that can help us overcome a wide range of cancers, as well as to support the body's ability to resist disease and restore health. As we continue to unveil more ways to tap into light's profound healing potential, we can expect major changes in the ways that modern medicine approaches cancer, heart disease, HIV/AIDS, and other serious illnesses in the years ahead.

Keith I. Block, MD

MEDICAL DIRECTOR
Block Center for Integrative Cancer Treatment

DIRECTOR
Integrative Medical Education, University of Illinois
College of Medicine

EDITOR-IN-CHIEF
Integrative Cancer Therapies (Sage Science Press)

EDITORIAL BOARD *for Physician Data Query Cancer CAM*
National Cancer Institute, U.S. National Institutes of Health

SCIENTIFIC DIRECTOR
Institute for Integrative Cancer Research & Education

AUTHOR
Life Over Cancer: The Block Center Program for Integrative Cancer Treatment (New York: Bantam 2009)

CHAPTER 1

A New Light on Medicine

Imagine for a moment that you've stepped out onto a lush green meadow on a brilliant summer day. The world around you is awash in sunshine, casting a golden glow on the landscape. The sunlight warms your skin and lifts your mood. It literally lights up your day, even as it gives new life to the grasses and wild flowers around you. As you take in the radiant beauty of this pastoral scene, it seems wholly natural to feel wonder and gratitude for the life-giving gift of sunlight.

Now imagine that this sunlight is doing something even more wonderful: It reacts with a natural plant substance that has accumulated in abnormal or mutated cells inside your body. The reaction triggers the destruction of those aberrant cells, and by doing so helps ward off cancer and other kinds of disease while bolstering your health and longevity in the process.

Though this scenario may sound like some scientist's far-fetched fantasy—perhaps even harking back to the laser beams envisioned in science fiction novels—it now has considerable support from medical science. And believe it or not, a version of this same phenomenon already takes place in your own body every time you go out in the sun.

Here's how this occurs. Your body cells are normally producing a substance called protoporphyrin IX, or Pp-IX. This is a pigment derived from another compound naturally found in the body, one that goes by the name of 5-aminolevulinic acid (5-ALA). In addition to producing Pp-IX and other porphyrins, 5-ALA plays a key role in the formation of hemoglobin, the specialized protein that carries oxygen throughout your body.[†]

Now, as your blood circulates through your liver and skin, it leaves Pp-IX in those tissues. What makes this substance so valuable is that it's constantly working on your behalf to protect your health. It does so with nothing more than the sun's rays. Simply put, Pp-IX absorbs the sun's energy, then transmits that energy to oxygen molecules, which, in turn, kill any undesirable microbes that happen to have sought refuge in your skin.

It is largely thanks to this natural compound—along with some essential help from the sun—that your skin is able to clear itself of potential disease-causing factors on a constant basis.[††] Given that the skin is the body's largest organ, it makes good sense that we humans would have evolved such a protective mechanism.

Now, under healthy conditions, your body generates just the right amount of Pp-IX, and this in turn absorbs just the right amount of energy from sunlight in order to keep your skin free of infections. As it turns out, various types of skin cancer also can be eliminated with the combination of Pp-IX and light. In Chapters 3 and 4, we'll show you how, by exploiting this elegant principle, various skin cancers can be cured without the need for surgery.

Indeed, it was this understanding of Pp-IX that led medical scientists in the 1980s to develop an effective treatment for two of the most common forms of skin cancer in the West, basal cell carcinoma and squamous cell carcinoma. The scientists learned that if they applied a cream that increased the skin's production of Pp-IX, they could ef-

† As you will see shortly, ALA has held a central place in the evolution of light-based treatments and diagnostic methods. For example, after 5-ALA is administered to a cancer patient, Pp-IX accumulates in the malignant tumors, and this is the basis for its phototherapeutic and photodiagnostic potential.

†† By the way, if you happen to accumulate too much Pp-IX, your skin becomes far too sensitive to light, resulting in considerable pain and discomfort. In fact, this is the basis for a rare inherited disorder known as Erythropoietic Protoporphyria. Treatment for the disorder includes avoiding regular exposure to sunlight, wearing protective clothing, and using special sunscreens that block out the longer wavelengths of light (the shorter wavelengths are what cause sunburn and can be protected against with the help of normal sunscreens).

fectively eliminate these skin cancers.† Even in those early studies, the complete response rate for basal cell carcinoma was found to be 90 percent after a single treatment.[1]

The Power of Photosensitizers

Thanks to the study of Pp-IX and other light-sensitive substances, or *photosensitizers*, we now know that the healing benefits of light extend far beyond the well-known connections between sunlight and vitamin D.[2] The term *photosensitizer* comes from the Greek word *phōs*, meaning "light", and the Latin *sens*, meaning "to feel". Thus, a photosensitizer is a substance that "feels the light". These special compounds literally sensitize the targeted cells to light, rendering them vulnerable to the destructive power of light's energy.

So how does a photosensitizer accomplish this marvelous feat? To begin with, it captures and absorbs the light's energy. This is very similar to what happens in green plants through the process of photosynthesis: The chlorophyll molecule that accounts for the green color of plants captures the sun's energy and then converts this energy into a usable, chemical form. Sunlight strikes the chlorophyll molecule, and the magic of photosynthesis unfolds from there.

In a similar way, the photosensitizers used for healing purposes are able to harvest the energy from light. They then transfer and convert that energy into a form that can knock out cancer cells, bacterial cells, and other abnormal cells linked with disease.

Now, as you might expect, photosensitizers are naturally abundant in the plant world. This makes sense on an intuitive level, since all green plants and algae are constantly absorbing and transferring the sun's energy throughout the day. As we mentioned above, plants already use chlorophyll (and other natural pigments) to accomplish this fundamental light-harvesting process, which forms the basis for our entire food chain as well as the source of all the oxygen we breathe.

† The rate of synthesis of Pp-IX is determined by the rate of synthesis of the substance called 5-Aminolevulinic acid (ALA), mentioned earlier in this section. Thus the medical cream that is used to increase production of Pp-IX for skin cancer treatment contains ALA.

With the discovery of photosensitizers, scientists have taken this life-giving principle of light energy transfer and applied it to the realm of medicine. One of the earliest photosensitizers came from the study of Pp-IX, the natural skin compound we introduced earlier. But many other light-sensitive substances have been discovered and used with ever-greater therapeutic effectiveness. The best photosensitizers build up quickly in abnormal or diseased tissues and leave normal, healthy tissues largely untouched.

THE POETRY OF LIGHT

"What light is light, if Silvia be not seen?"—Shakespeare

"From within or from behind, a light shines through us upon things, and makes us aware that we are nothing, but the light is all." —Ralph Waldo Emerson

"To me every hour of the light and dark is a miracle." —Walt Whitman

"But I also say this: that light is an invitation to happiness, and that happiness, when it's done right, is a kind of holiness, palpable and redemptive." —Mary Oliver

"Beauty is not in the face; beauty is a light in the heart." —Kahlil Gibran

"Light, be it particle or wave, has force: you can rig a giant sail and go. The secret of seeing is to sail on solar wind…" —Annie Dillard

"The light of the morning, Heaven's mountains adorning: In particles bright, the jewels of light." —William Blake

The Science of Light Medicine

For cultures the world over, light has been a symbol of beginnings and rebirth, as well as of cleansing and healing. In western poetry and phi-

losophy, light is a symbol of love, hope, and wisdom. In Buddhism, the "enlightened" state of being has been described as one of insight and compassion.

And yet, our knowledge of the physical properties of light, as well as what it can do for the human body, is a relatively new science. Even as we continue to understand how light and other forms of energy can impact our health, there is still much to be learned about how this magnificent element can be harnessed to bring about therapeutic results and prolong life after a diagnosis of cancer or other serious disease.

Efforts by scientists to create new light-sensitive compounds from plants and other natural sources have fueled a whole new direction in medicine, one that has come to be known by various names: photodynamic therapy, photochemotherapy, and photoimmunotherapy (see glossary for definitions). These approaches are increasingly recognized as promising options for the treatment of cancer and other major health challenges.

What these approaches all have in common is the use of a photosensitizer that becomes selectively concentrated in mutated or unwanted cells, with minimal if any effects on normal, healthy cells. In the presence of light and oxygen, a reaction is triggered inside the abnormal cells, ultimately causing their demise. Different types of indoor light source—LEDs (light-emitting diodes), infrared, or ultraviolet lamps—have been used in order to achieve specific therapeutic effects.

The light-based approach already has proved effective against several cancers for which conventional treatment has largely failed. (In Chapters 2 and 4, you'll have a chance to learn about which cancers in particular have responded best to light-based therapies.) The advantages are obvious. First, as a consequence of the accumulation of certain plant compounds within abnormal cells, the cancer cells are selectively targeted and often destroyed or modified upon light exposure, while normal tissues are largely spared. A report in the 15 March 2013 issue of *Current Medicinal Chemistry* cited a number of natural plant compounds that could accomplish this impressive therapeutic feat.[3] This tumor-specific effect stands in sharp contrast with that of chemotherapy, which tends to create much indiscriminate damage, harming healthy and unhealthy tissues alike.

Moreover, when properly administered, light-based therapies are virtually free of toxic side effects. This too poses a dramatic contrast with modern chemotherapy and radiation treatments. With chemotherapy, for example, cancer patients often suffer even more from the toxic side effects of the drugs than from the disease itself. It is an added burden that can greatly compromise one's quality of life, ultimately limiting the ability to maintain good health and immunity.

Another key benefit of this light-based approach is that the immune system is activated in specific ways so that it can recognize the presence of cancers and infections. Just as importantly, the immune system now becomes far more active against these diseases, providing an indirect way to eliminate the abnormal cells—or to eliminate any residual cells that may be left over after the more direct lines of attack are tried. By clearing the body of cancer and other abnormal cells, this approach can help stave off the return of more aggressive disease later on.

We've just provided you with a glimpse of some of the ways that light-based therapies are already beginning to transform the field of medicine. We believe this treatment strategy will help overcome certain pressing problems that now baffle many medical experts, such as resistance to antibiotics and chemotherapy drugs. In time, the strategies we describe in this book should greatly reduce the already colossal financial burden posed by cancer as well as many infectious diseases.

And as you'll see in later chapters, there are other exciting ways to tap into the medicine of light. For example, once the photosensitizer has accumulated in abnormal cells, those cells will actually "light up" or gleam brightly upon exposure to certain types of light. This phenomenon can be used for the purposes of both diagnosis and monitoring of the disease. When a surgeon goes in to remove a tumor, the area around that tumor can be "lit up", enabling the surgeon to more completely cut out or excise any diseased tissue that would otherwise be hidden from view.

Last but not least, recent studies suggest this approach can be effective in reversing the all-too-pervasive problem of clogged arteries, thus helping to ward off cardiovascular disease, the number one killer disease in the European Union, Russia, the United States and many other westernized countries.

Light Therapy From Ancient to Modern Times

We are creatures of light. From the time the morning sun rises in the East, light exerts a profound influence on our health and well-being. According to medical records from ancient India, Egypt and China, humans have been cognizant of the healing powers of light for more than 5000 years. It's quite possible that these healing energies were understood and appreciated long before then, though available documents can only shed light on our recent history.

As implied above, our primary focus in this book is on how certain substances, when taken into the body, can amplify or enhance the healing effects of light. This area of medicine is broadly referred to as *photomedicine* or light medicine. As a medical science, photomedicine officially began in the 1880s. This field encompasses the positive and negative effects of light on human health and functioning. Its more recent evolution has included the use of light for diagnostic purposes, and the use of both lasers and non-laser light for therapeutic purposes.[4]

Our primary focus throughout this book will be on an application of photomedicine known as photodynamic therapy. As already mentioned, *photo* comes from the Greek word for light. The *dynamic* part refers to the therapy's ability to transmit light energy for the ultimate destruction of abnormal cells. Thus photodynamic therapy, or PDT, can be viewed as a targeted approach to light-based therapy, whereby the light is able to selectively strike and destroy mutated cells (either precancerous or cancerous cells) as well as microbes linked with infectious disease. In its very first usage in the early 1900s, the term was specifically applied to light's ability to immobilize living organisms (protozoa).

The historical basis for PDT actually dates back at least 3000 years, when healers in ancient Egypt and India used plants to enhance the healing effects of light. In those early days, individuals with vitiligo-like skin lesions were treated with a plant compound that scientists now refer to as *psoralen*.† Abundantly found in vegetables like celery, parsley and parsnips, psoralen is a weak photosensitizer that sensitizes the skin to the sun's rays. When the ultraviolet radiation of the sun strikes the psoralen in the skin, the white patches and other skin problems disappear.

† In more specific terms, psoralens are a group of natural furanocoumarins. These days, they are commercially derived from Ammi majus, a plant native to Egypt.

UV LIGHT AND PSORALEN:
Oldest Medical Treatment on Record?

Thousands of years ago, humans learned that consuming certain plants (e.g., parsley, parsnip, carrots and celery), followed by sun exposure, could produce a skin reaction similar to sunburn. Those plants were rich in the natural compound psoralen, and the reaction produced in the skin is now understood to be a photodynamic reaction.

Even today, psoralen plays a role in the treatment of vitiligo, an ancient disease in which white patches or white spots appear on the skin, due to a loss of normal pigment. This is a distressing and potentially disfiguring condition, especially for individuals with darker skin. Currently affecting about 1-3 percent of the world's population, vitiligo's overall appearance and unpredictable course can be socially and psychologically devastating.

Due to the complexity of the disorder, a variety of light-based treatments have been recommended for vitiligo following the observation that sun-exposed lesions on the skin often acquired a more normal appearance during the summer months. Today's physicians continue to use a combination of psoralen and ultraviolet-A (UV-A) light therapy to treat the localized forms of this condition. The approach is known as *photochemotherapy*—quite a fancy term when you consider the treatment's ancient, humble origins. The first modern application of psoralen-based photochemotherapy was in Egypt in 1948, using a purified 8-methoxypsoralen followed by sunlight exposure.

For the more diffuse manifestations of this skin disease (i.e., those affecting larger areas of the body), ultraviolet-B (UV-B) light therapy is considered to be the "gold standard" treatment of choice.[5] Both UV-A and UV-B can be obtained by sunbathing; however, whereas the UV-A can be transmitted through glass, UV-B requires direct, outdoor exposure to the sunlight.

The more recent practice of *heliotherapy*, or sun therapy, probably had its roots in early Greek medicine, around 400 BC. *Helios*, the

Greek word for "sun" or "sunlight", was the most ancient of the sun gods.† The Greek physician Hippocrates, widely regarded as the father of western medicine, actually recommended heliotherapy for a range of physical and mental ailments. Though we lack detailed records of how Hippocrates used the sun for medicinal purposes, it seems that he did at least recognize the importance of sunlight for emotional well-being and possibly even for combating some skin infections.

Heliotherapy's modern resurgence took place in the 1800s, when European doctors started using red light therapy. This approach, the first well-documented exploration of what came to be known as *phototherapy* or light therapy, was carried out in rooms with red glass windows, mostly for the treatment of itchy eruptions of rubella and other skin disorders. Individuals suffering from depressive disorders also seemed to respond well to red light therapy.††

From the late 1800s to about 1940, heliotherapy became popularized throughout Europe as a treatment for tuberculosis—especially when the disease also affected the bones, joints and skin. We now know that prolonged exposure to sunlight can lead to the destruction of the bacteria that cause tuberculosis, but in those early days the offending organisms hadn't yet been identified. Nevertheless, TB-infected children were sent out to special hospitals and encouraged to spend as much time outdoors as possible. Many of these children came from dark and dingy city slums, so that exposing their skin to sunshine would have helped them eliminate the bacteria. In a book titled *The Sun Cure* (*La Cure de Soleil*, in French), French physician Dr. Auguste Rollier claimed that heliotherapy's success in these cases depended on the duration and intensity of sunlight, as well as the specific condition being treated.

Of course, in the northern latitudes and colder climates, sunlight

† Apollo, another sun god for the ancient Greeks and Romans, drove his chariot of fiery horses across the sky to give light to the world. He was also the god of medicine and healing. As with the sun gods of the Aztec and Inca empires of the Americas, Apollo could bring sickness and deadly plagues but also had the ability to cure.

†† Light therapy is now an established treatment for depression, regardless of the season (meaning people also have Seasonal Affective Disorder, or SAD). One advantage this therapy has compared with antidepressant drugs is that the benefits tend to appear more quickly. Also, the combination of light and medication has proven to be more effective and faster than either alone.

is often limited. For this reason, artificial light sources (some of which are referred to these days as "sunboxes") were sought that could closely approximate the sun's rays and beneficial effects. Among the best-documented early examples was the Finsen lamp created by physician Niels Ryberg Finsen of the Faroe Islands (near Denmark). This ultraviolet lamp allowed treatment throughout the year; moreover, its rays could be focused on specific parts of a patient's body. The lamp's greatest success was in the treatment of tuberculosis of the skin (lupus vulgaris), for which Finsen won the Nobel Prize in 1903.

In the early 20th century, sun bathing was deemed to be the best treatment modality not only for tuberculosis, but many other infectious diseases as well. Other conditions successfully treated with heliotherapy included acne, eczema, anemia, colitis, sciatica and asthma, among others. With the discovery of penicillin in 1938, however, big business rushed headlong into the mass production of antibiotics, and heliotherapy quickly became a thing of the past.

Photodynamic therapy was discovered quite by accident at the end of the nineteenth century. In 1898, a Munich university student named Oscar Raab was observing the effects of light on paramecia, tiny organisms that are naturally present in fresh water and clearly visible only with a microscope. Here's what he observed:

- Upon exposure to light, and in the presence of the dyes, the paramecia would begin to slow down in their movements.
- Some died prematurely when the light exposure was prolonged, but again only in the presence of the dyes. Without those dyes, the tiny creatures were unaffected by the light.
- In the absence of light, the dyes had no effect whatsoever. This so-called "dark experiment" proved that it was neither the light nor the dye alone, but rather their combination that made the difference.

Raab's professor, Herman von Tappeiner, later identified the orange dye acridine and the pigment eosin as the substances that sensitized cells to the destructive effects of light. He subsequently demonstrated that their cell-killing power also required the presence of oxygen. Just as fire requires oxygen to exist, it seemed that light required oxygen to exert its special effects on these living cells.

This was the conclusion von Tappeiner offered in his classic 1907 treatise on PDT in which he referred to the light-based effects on infections and cancers as *Photodynamische Wirkung*. When the photosensitizer was combined with light and oxygen, a toxic reaction resulted in the exposed cells. He proposed that this reaction could be the basis for treating various diseases—including infections, skin tumors, and some non-cancerous skin conditions.

Porphyrins: From Ancient Healing to Modern Medicine

Earlier in this chapter, we mentioned the amazing compound called protoporphyrin IX, or PP-IX, which is produced in the body and constantly eliminates harmful bacteria and cancer cells with the help of sunlight. PP-IX belongs to a group of natural photosensitive compounds known as *porphyrins*, intensely colored compounds whose name is drawn from the Greek word for purple (*porphura)*.

Long before humans roamed the planet, porphyrins were serving as oxygen carriers for all warm-blooded creatures and played an indispensable role for plant and animal life alike. In humans and other mammals, porphyrins are generated as the body builds hemoglobin, the compound that carries oxygen in blood cells. The first compound in the porphyrin synthesis pathway is 5-ALA, which we alluded to earlier. This important pathway leads to the production of *heme* in mammals and *chlorophyll* in plants (see sidebar, "The Big Picture: Shedding Light on Porphyrin's Structure and Significance").

Though you may never have heard of them previously, porphyrins do play a number of important roles in medicine today. Small amounts of various porphyrins normally appear in the urine and can be measured to provide insight into a range of health issues. This is because the relative amounts of porphyrins found in the urine can be affected by certain hereditary diseases and by nutritional and environmental factors, such as mercury and other heavy metals.†

The main application of porphyrins in modern medicine has been as a diagnostic tool in the form of *fluorescence imaging*: The light-sensitive molecules accumulate in areas of infection and cancer, causing those areas to literally "glow" a reddish or purplish color upon exposure to light. This can be quite helpful in surgical situations in which the surgeon is unable to see whether the margins—that is, the periphery of the surgical site—are "clean" or free of cancer. In this way, the porphyrins help guide the surgery and other treatments, ultimately making them more effective.

THE BIG PICTURE:
Shedding Light on Porphyrin's Structure and Significance

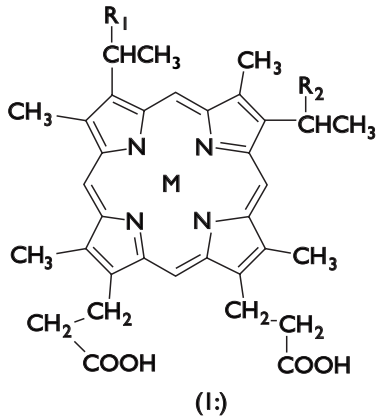
The chemical structure of a porphyrin is quite distinctive. It consists of four ring compounds (*pyrroles*) and these are joined together, forming a structure that can hold a metal ion in its center (see Figure I). Let's consider two well-known examples from the animal and plant kingdoms: the hemoglobin found in red blood cells, and the chlorophyll found in green plant cells or chloroplasts.

In the case of hemoglobin, the metal is iron, and the porphyrin together with the iron is called heme. In the case of plant cells, the metal is magnesium, and the respective porphyrin holding that metal is called chlorophyll. Thus, in plants, porphyrins are essential to the process of photosynthesis. In humans and animals these molecules serve mainly to keep the body well-nourished with life-giving oxygen, while also helping to remove the carbon dioxide "exhaust" that results from each living cell's metabolic activities.

Speaking of treatment, porphyrins also have a central place in the use of PDT for various medical conditions—not only cancers, but also many skin conditions and age-related macular degeneration, an extremely common form of blindness. Other key medical and biological roles include antiviral, antimicrobial and antibacterial applications such as the sterilization of blood plasma and water.

† When high levels of porphyrins appear in the urine, this is known as porphyria. The classic cases of hereditary porphyria resulted in highly colored urine and skin eruptions, as well as neurological symptoms of mania and "madness." Some medical historians believe that the famous vampire Dracula could have been someone suffering from the extremely rare congenital condition known as erythropoietic porphyria. Symptoms of this condition include the following: 1) pale, yellowish skin and other skin aberrations; 2) protruding reddish teeth, 3) avoidance of sunlight; and 4) blood thirst, often accompanied by psychotic attacks.

Now, PP-IX is just one of several porphyrins that have captured the attention of medical science, most recently as a light-sensitizing vehicle for cancer treatment. Another very popular porphyrin is called hematoporphyrin-IX. In 1908, an Austrian scientist named Walther H. Hausmann isolated the compound and was able to show that hematoporphyrin-IX (see Figure 1) had powerful photodynamic effects in microscopic organisms. He later demonstrated these same effects in animal experiments using mice, and this eventually led to its use in humans.



(I:)

R1=R2=-OH, M=2H

Figure 1: *The chemical structure of hematoporphyrin IX.*

Several years later, it was discovered that the porphyrins could also kill microbes on human skin exposed to light. These observations would quickly spawn efforts to use PDT to kill bacteria associated with human disease. In 1913, the Austrian physician Friedrich Meyer-Betz performed the first human study of porphyrin-based PDT. This research took place in the medical clinic of Konigsberg (now Kalininigrad in Russia). The previous year, Dr. Meyer-Betz had observed the phototoxicity of hematoporphyrin in mice in the laboratory of his colleague Hans Fischer in Munich.

In a remarkable self-experiment, Meyer-Betz injected himself intravenously with 200 mg of hematoporphyrin. The first day after the injection was cloudy, but two days later it was sunny, and the Austrian physician observed a definite photosensitive reaction: a prickling and burning sensation only in those regions of his body that had been exposed to sunlight. Photographs clearly showed reddening and swelling (erythema and edema, respectively) only in those areas that had been exposed to sunlight.

Studies in the 1930s went on to show that hematoporphyrin-based PDT could be effective in eliminating bacterial infections and some skin cancers. Nevertheless, when antibiotics came into use in the 1940s, the medical establishment's interest in PDT suddenly waned. Antibiotics seemed to offer a more practical and profitable approach than PDT, as the patient could simply pop a pill to eradicate the infection. Antibiotic drugs were touted as "magic bullets" that could eradicate any infection, and of course their introduction spelled explosive profits for the medical and pharmaceutical industries. (We now know that antibiotics are fraught with problems, such as creating antibiotic-resistant bacteria and helping to spawn fungal infections such as *Candida*. In contrast, the use of PDT has none of these problems.)

Meanwhile, in the area of oncology, chemotherapy and radiation treatments were being developed as the answer to cancer, and here too the photodyamic approach was unable to make much headway. In the 1940s, researchers had shown that hematoporphyrin-IX had some affinity for cancerous tissues. As the porphyrin accumulated in the tumor, those malignant tissues would "glow" under a specialized light called the Woods lamp. As with infectious disease, many scientists began to explore PDT as a possible treatment for certain cancers. Throughout the early 1900s, PDT was successfully used to treat people with various skin cancers. Nevertheless, it was soon rejected as a treatment because porphyrin accumulations resulted in extremely sensitive skin when exposed to sunlight. This uncomfortable skin sensitivity, or *photosensitivity*, typically lasted for several weeks.

The evolution of PDT as a medical treatment languished until the 1960s and 1970s, when scientists began to uncover ways to greatly reduce the photosensitivity problem. Most of this resurgence can be credited to an American scientist named Thomas Dougherty and his

colleagues at Roswell Park Cancer Institute, in Buffalo, New York. He and the other Roswell researchers went on to develop a commercially suitable photosensitizing drug called Photofrin® II (Porfimer Sodium), the first widely used PDT drug.†

Photofrin® II showed a good ability to accumulate more rapidly in tumors than normal tissues. Nonetheless, it also had some disadvantages, such as causing damage to the skin (swelling, blistering, redness) and eye sensitivity to light with repeated exposures to sunlight over the course of 30 days or more. The drug also required up to three months —sometimes even longer—to be cleared from the body, and during that time the skin reactions could be triggered even with fairly brief exposures to sunlight.††

From the beginning, it was clear that Photofrin® could achieve some impressive therapeutic results, especially with superficial tumors or those located close to the surface of the body. In 1978, Dougherty's research team published some dramatic findings based on the use of Photofrin® I (a predecessor of Porfimer Sodium) to treat cancer, reporting that they had observed a total or partial elimination of 111 out of 113 malignant tumors.[6] For these early efforts, Thomas Dougherty became known as "The Father of PDT," though in fact he was just one of several leading scientists whose pioneering work in the sixties, seventies and eighties would eventually establish PDT as a bona fide cancer treatment.

Scientific interest in PDT continued to flourish throughout the 1970s and 1980s, but the real clinical breakthroughs occurred in the 1990s. The first of these breakthroughs was that Dr. Dougherty managed to get Photofrin approved for use in several countries, beginning with

† In an attempt to resolve the hypersensitivity issue, Dr. Dougherty and other PDT researchers focused on a complex group of photosensitizers known as hematoporphyrin-IX oligomers. This represented a major departure from the previous focus on single molecules, and it formed the basis for developing Photofrin® II.

†† Other disadvantages included: 1) a low therapeutic ratio, equal to 0.8 for the skin overlaying a tumor, 1.1 for the skin surrounding the tumor, and 2-5 for muscles; 2) a low PDT efficacy connected with low yields of singlet oxygen as a consequence of poor light penetration (630 nm) to tissues; 3) a strong affinity for epithelial tissues, resulting in the reddening of skin during and after treatment along with increased sensitivity to the light; and 4) the need for a pause of 24-72 hours between Photofrin® II introduction to a patient and irradiation, during which the patient had to stay in a darkened room.

Canada in 1993 for the treatment of bladder cancer. In 1994, the drug received approval in Japan for treating early-stage lung cancer. In 1995, Photofrin® was approved in the United States for treating esophageal cancer, and this was followed by approval for treating early non-small cell lung cancer a few years later.

During this timeframe, the second major breakthrough took place. Dr. James Kennedy, a physician and professor at Queen's University in Canada, proposed a new method using a cream now called Levulan® Kerastick®. This medication contained 5-ALA, the natural compound we introduced earlier that helps the body build blood. The U.S. Food and Drug Administration approved the therapeutic use of 5-ALA in 1999, and with that approval, hundreds of studies of PDT would be launched to explore its potential as a way to improve the treatment of many malignant and infectious diseases.

Remember that our cells can convert 5-ALA into Pp-IX, the compound naturally present in our body cells that can damage bacteria and other unwanted cells upon exposure to light. Working with chemist Roy Pottier (then a professor with the Royal Military College in Kingston, Ontario), Dr. Kennedy demonstrated that the 5-ALA approach was very effective against common skin cancers and various skin conditions, including acne and actinic keratosis.

Of all the countries that have pursued PDT research in the past few decades, Russia has been among the most prolific. For example, the composition of Photofrin® II and its mechanism of synthesis can be traced back to research conducted by Dr. Gelii Ponomarev in the early 1980s. In addition, the Photofrin® II analog named Photogem was developed in Russia during that same early period; it was approved in 1999 for stage I superficial tumors and advanced-stage tumors that were considered to be either inoperable or resistant to chemotherapy and radiation treatments.

Clinical drawbacks of Photofrin® II and its analogs (drugs with similar structure or constituents but different effects) would eventually lead to an intensive search for new-and-improved medicines, the so-called *second-generation photosensitizers*. Among the most salient features of these light-sensitive drugs is the ability to accumulate in a highly selective way in tumor tissues. These second-generation photosensitizers also

have a very low toxicity in normal tissues when given at therapeutic doses

From 1984 onward, a flurry of studies focused on these second-generation agents, mostly conducted in Japan, Canada and the United States. These landmark discoveries led to the development of other light-sensitizing drugs with such complex-sounding names as benzoporphyrins, phthalocyanines, porphycenes, and, of course, chlorins. It is this last group of compounds that led to the discovery of radahlorin† by one of the authors of this book. You can learn the story behind this remarkable chlorin agent in Chapter 7.[7]

Over the past four decades, numerous animal studies and clinical trials have demonstrated that these light-sensitive drugs can be used to eliminate cancers of the breast, lung, bladder, prostate, esophagus, brain and of course, the skin. For example, drawing from the ALA-based approach discovered by Drs. Kennedy and Pottier, other powerful PDT drugs have emerged. These have included two drugs, Metvix® and Hexvix®, which were developed by a research team based in Oslo, Norway, led by Drs. Johan Moan and Kristian Berg.†† Dr. Moan is greatly respected for his contributions to understanding the principles and applications of PDT in Europe. Thanks to these and other innovations, PDT has emerged as an established treatment option for many cancers. And yet, as you'll learn in the chapters ahead, the medical community has only begun to appreciate its true potential.

† Radahlorin is the international non-proprietary name of an active pharmaceutical ingredient.

†† Metvix-PDT has emerged as an alternative to surgery for the treatment of Actinic Keratoses and certain types of basal cell carcinomas (BCC) on the scalp and face. See Chapter 2 for our discussion of these conditions. Hexvix® was hailed as the first significant advance for the improved photo-detection of bladder cancer, the most costly of all cancers due to its high recurrence rate. It can also be used as part of PDT for bladder cancer, which is quite common but notoriously difficult to detect. See Chapter 4 for our discussion on the photodynamic treatment of bladder cancer.

CYCLES OF LIGHT, CYCLES OF HEALTH

All human life has revolved around the daily 24-hour cycle of light and dark. This cycle reflects the time it takes for the Earth to spin completely around on its axis, exposing us to different amounts of sunshine in the process. It is this cycle that helps regulate the timing and coordination of nearly every biological function in the human body!

Here's a very simple example: When you step outside in the morning to greet the morning sun, you're actually triggering a series of reactions that result in better sleep that night. This circadian benefit is a byproduct of sunlight passing through your eyes and programming your body's "internal clock," which is located in the pineal gland.† In addition, getting some sun exposure in the middle part of the day actually helps revitalize us by increasing our mental alertness. And by taking in the twilight at dusk, you can shift your body's wake-up time so that you don't wake up too early in the morning.

Light affects our health and quality of life in many other ways as well, most of which we take for granted. For example, if you're exposed to bright lights within two hours of bedtime, this can disrupt your brain's production of melatonin, a neurohormone that helps regulate the body's internal clock. With too little melatonin, your body will have trouble falling and staying asleep at night.[8]

Also, too much light at night tends to increase your body's production of the infamous stress hormone, cortisol. An imbalanced ratio of cortisol and melatonin is associated with sleep disturbances and energy problems, possibly even promoting exhaustion.[9] Cortisol is associated with chronic anxiety and depression. This hormone can suppress your immune system, elevate blood sugar, and generate more fat around the abdomen. So simply by submit-

† The term circadian refers to the 24-hour light-dark cycle and its effects on human health and functioning. It's interesting to note that the circadian health benefits of opening your eyes to the morning daylight are actually reduced or prevented by wearing sunglasses. However, you should also avoid looking directly into the sun, as this can damage your eyes.

ting ourselves to night-time artificial lighting—conditions that are biologically incompatible with at least 99.9 percent of human evolution—you may be increasing your risk to such common diseases as diabetes, obesity, heart disease and cancer.

And as we all know by now, sunlight is the primary source of vitamin D, typically providing 50 to 90 percent of the body's needs. Upon exposure to sunlight, cholesterol molecules in the skin are able to manufacture the vitamin in fairly large amounts—between 10,000 and 20,000 units in just 15 to 20 minutes for a light-skinned person, and roughly half that amount for a dark-skinned person. The vitamin then undergoes further changes in the body in order to support the health of the bones, joints, muscles and brain, as well as all kinds of important functions.†

Vitamin D production in the skin stops entirely during the winter months and is also virtually absent in the higher latitudes such as Canada and northern Europe. In general, as humans move farther from the equator, the deficiency becomes increasingly common. So it is that light affects our health on a daily basis, seasonal basis, and geographic basis, all depending on the availability of UV-B radiation from direct sunlight. If we ignore the impact of light on our health, we set ourselves up for a lifetime of disease and dysfunction. The cycles of light and dark are no less important to our wellness and vitality than the air we breathe, the water we drink, and the food we eat.

† Vitamin D is widely regarded as a pre-hormone because, once produced in the skin in response to the sun's UV-B radiation, it undergoes various transformations that lead to its production as a steroid hormone—that is, it acts as a hormone by binding to and activating receptor molecules that serve to regulate gene expression (at least 229 genes are known to be activated by vitamin D). More specifically, vitamin D is classified as a secosteroid, a molecule that is similar in structure to a steroid, except that two of its four B-ring carbon atoms (C9 and 10) are not joined together. Vitamin D is considered to be the most important secosteroid in the human body. In humans, the vitamin D receptor is expressed in almost all tissues, enabling effects in multiple systems of the body; note that these effects can be endocrine, paracrine and autocrine.

How Photodynamic Therapy Works, In a Nutshell

Photodynamic therapy requires three basic ingredients for its success: light, oxygen, and a photosensitizer. Everyone understands what we mean by the first two ingredients, light and oxygen, but what in the world is a photosensitizer? Breaking the word down, we can see that it refers to a light sensitizer, a substance that sensitizes tissue to light. The photosensitizer we favor for PDT is the porphyrin-type photosensitizer described earlier.†

There are three steps involved in the process of PDT. In the first step, the photosensitizer—let's say, a chlorophyll compound—is administered to your body. This can be done in basically three ways: (1) as a topical cream or ointment applied directly to the skin; (2) as a drug or dietary supplement taken through the mouth; and (3) by injection or intravenous infusion, so that the photosensitizer enters the bloodstream directly and travels to the target cells.

Step two involves the target cells just mentioned. Target cells refer to cells that are undesirable or potentially burdensome, such as the abnormal or precancerous cells that have formed on your skin, the malignant cells that comprise a tumor, or perhaps a cluster of disease-causing bacteria or virus-infected cells.

The photosensitizer compound must be taken up by the target cells in order to selectively accumulate in those cells. Chlorophyll compounds have been shown to do just that—they become far more concentrated around cancer cells than in normal, healthy tissues.†† This is part of

† Although we will only focus on porphyrin compounds in this book, other compounds too have been used as photosensitizers. We will explain shortly why porphyrin, and, in particular, chlorophyll derivatives are really the photosensitizers of choice.

†† You may be asking yourself how the chlorophyll compound "knows" to seek out and accumulate around those "bad" cells or pathogens. This is part of the magic of a good photosensitizer, and it most likely has to do with evolution. All animals on the planet—including humans and other primates of course—have coevolved to some extent with the plant world, which preceded the animal world by many millions of years. Animals have helped plants by spreading their seeds and providing fertilizer in the form of animal droppings. Thus, it makes sense that certain compounds would have favored the survival of animals, and chlorophyll is just such a compound. Many studies have demonstrated that chlorophyll can avert or reverse mutations and thus may help prevent the development of cancer and birth defects. We now know that even the dinosaurs had cancer, and of course the dinosaurs too depended heavily on the plant world.

what makes the chlorophyll compounds such good photosensitizers.

The third and final step involves the activation of the photosensitizer inside the target tissue, using light as the source of the activation. In more technical terms, we know that a specific wavelength of light must be directed toward the tumor, localized infection, or other target tissue. By this time, thanks to step two, the photosensitizer has already accumulated in the target tissue. Once it becomes activated, and in the presence of oxygen, it destroys the cancer cells or other abnormal cells.

This, in a nutshell, is how PDT works. Because the photosensitizer "prefers" to accumulate in the cancer or other diseased tissues, the light source will directly target that tissue, while nearby healthy tissues or adjacent body structures are only minimally affected. This is what we mean when we say that PDT is a "targeted approach" to cancer treatment.

Limitations of the PDT Approach

Though PDT has several major strengths, it also has some limitations. To begin with, the light source must have access to the cancer or diseased tissue. In other words, the cancer must be in a location where light can reach it and activate the agent that has accumulated in the cancer cells. Cancer located deep in the tissues is much less accessible to light. So, for example, using PDT on brain tumors can only work during surgery, when the skull has been opened up.

A related limitation of this "direct action" principle of traditional PDT is that cancer cells not exposed to the light source may escape—similar to how cancer cells not in the vicinity of radiation treatment can escape that treatment. For this reason, the early PDT procedures sought only to treat tumors that were clearly visible and readily exposed to the light source. The treatment had no effect on clusters of cancer cells that might be in other areas of the body. (As you'll see, however, certain photodyamic strategies also can bolster the immune system and thus have therapeutic effects that go beyond the local destruction of the tumor.)

Also, as with cancer chemotherapy, the treatment is only as good as the agent used. Though the photosensitizer agents do selectively attach to cancer cells, some of the agent also gloms on to healthy cells. Thus, when the tumor or target tissue area is sensitized by light of a certain frequency, some healthy cells will be killed or damaged along with the cancerous or diseased cells. This means that irritation and even burning may occur in the area adjacent to the target tissue. Over the last few decades, this fact has helped fuel the search for much more selective or targeted photosensitizers.

Another limitation is that the agent may stay in the body for a period of time, and during that time the body remains sensitive to light sources—again, the problem known as *photosensitivity*. Different photosensitizers can take anywhere from a few minutes to a few months to clear from the body. In some cases, patients will need to avoid direct sunlight, as well as spotlights or other strong artificial lights, for a period of time after the initial treatment.

Finally, although much scientific research has informed the evolution of PDT, it should also be viewed as a kind of medical art. Until standard PDT methods for the treatment of specific types and stages of cancer have been developed, your physician's skill, clinical experience, and overall approach to you as an individual will play major roles in the success of your treatment, especially when it comes to aggressive cancers or other challenging conditions.

The good news is that PDT applications have been improving by leaps and bounds over the years, and in some cases the limitations have been turned into strengths. For example, the fact that some photosensitizers stay in the body can actually be exploited to help eliminate skin cancers: When you go out in the sun, the photosensitizer can "light up" a patch of mutated cells, thus triggering the destruction of any cancerous or precancerous tissue found near the skin's surface.

In addition, various light delivery systems have been developed that allow for more versatility in treatment options. Whereas light-emitting diodes, or LEDs, have been used on skin cancers, lasers are being used to treat deeper or less accessible tumors. Using an endoscope, the laser can be directed through fiber optic probes, as is the case with esophageal, stomach, nasopharyngeal, and lung cancer.

One of the leading innovators in this area is Professor Dick Sterenborg of Erasmus University Medical Center in Rotterdam (The Netherlands). Dr. Sterenborg has perfected a method for the delivery of light to the nasopharyngeal cavity using optical fiber probes for diagnosis and to monitor treatment effects.[†] This ingenious system enables

the user to monitor, regulate, and display laser output and fluence rates at preselected locations in the nasopharyngeal cavity during PDT treatment. Such devices have been extremely helpful in the image-guided surgery of head and neck cancers.

How Light Signals the Immune System to Eliminate Cancer

By the time cancer is detected and diagnosed, in most cases it is not just an isolated disease. Though the tumor may be the only visible sign of the disease (based on standard diagnostic scans and perhaps surgery as well), isolated tumor cells already may have spread to other parts of the body. Those disseminated cells can later multiply and create more aggressive cancer. But with proper priming of the immune system, those cells can be eliminated, and the catastrophe of aggressive cancer averted. This is where light-based therapy may have its most profound impact on the disease.

Indeed, one of the fascinating effects of PDT is that it can stimulate the immune system to become highly active against cancer. This takes place in the following way. An infrared laser is focused on the tumor area using an approach known as laserthermia. This results in greatly increased temperature in the tumor tissue—in essence "cooking" and directly killing the tumor. As the tumor cells swell up and die, they release key proteins, the so-called tumor antigens, which in turn can stimulate the body's anti-cancer immunity.††

Within the immune system is a group of star-shaped cells known as the dendritic cells. You might think of these cells as the immune system's "sentinels", because they are constantly on the lookout for cancer and other trouble. The dendritic cells are able to capture the tumor antigens and then migrate to lymph nodes, where they interact with T-cells to trigger an aggressive immune response against the cancer.

You may be asking yourself, why doesn't the immune system manage to get rid of cancer more often? The problem is that these dendritic

† Dr. Sterenborg is also known for his research involving measurements of tissue oxygen and the crucial role this plays in the efficacy of PDT.

†† It appears that Chinese doctors were the first to use laserthermia, with the earliest recorded use being for the treatment of liver cancer in 1991.

cells are often "asleep" when cancer is present. That is, they tolerate the existence of the tumor, as if it were simply part of the body. With PDT and certain other cancer therapies (mentioned below), specific molecules are generated as the tumor is dying. These molecules have been referred to as *danger signals*, and they essentially "wake up" the immune system.

In other words, these special signals alert the system to the fact that a real and present danger exists in the form of cancer. When the dendritic cells are exposed to both the danger signals *and* the tumor antigens at the same time, the rest of the anti-cancer immune response springs into action, and the remaining cancer can be effectively eliminated.[10]

One example of these "danger signals" that has been very well studied in the context of PDT is a group of proteins called thermally induced heat shock proteins, or HSPs [11]. Huge amounts of these HSPs are also released as part of the body's natural stress response during either laserthermia or hyperthermia (heating up the body), which is another strategy that has been used together with PDT. When you combine PDT with laserthermia or hyperthermia, the production of these proteins is even greater, and thus your immune system becomes far more engaged in fighting cancer.

There is evidence from both animal experiments and human clinical studies that this approach, known as low-power laserthermia, offers a promising treatment option for cancer patients.† Though considered to be an experimental treatment, it has been used to treat malignant tumors in various organs including the liver, breast and lungs. Preliminary findings from a study in Sweden indicate that the laserthermia approach may be helpful in women with invasive breast cancer.[12] A case report suggested efficacy for the treatment of a woman whose breast cancer had metastasized to the eye (choroidal metastasis).[13]

To take these treatment effects a step further, scientists have discovered that adding interferon and other immune-modulating substances (generally referred to as immune adjuvants) can further improve the outcome of light-based therapies. Such an approach has already been explored for the treatment of warts, actinic keratosis and basal cell car-

† This approach has also gone by several other names, including laser thermotherapy, thermal ablation, and laser photocoagulation.

cinoma, the most common form of skin cancer. And recent studies suggest that it shows excellent potential for the treatment of advanced cutaneous melanoma, even when used on a stand-alone basis—that is, without the addition of conventional treatment.

When we go from infrared lasers to visible light or PDT, we see that the same types of immune system activation also occur. Leading scientists such as Dr. Michael Hamblin from the United States and Dr. Mladlen Korbelik from Canada have been instrumental in demonstrating how PDT can bring about an effective anti-tumor immune response. For example, in his work at the British Columbia Cancer Agency, Dr. Korbelik has shown that PDT can result in the rapid destruction of tumors. As the tumor cells are dying, the signals they release provoke the body to launch protective actions for dealing with a threat to tissue integrity. This leads to a strong acute inflammatory reaction, which in turn propels a vigorous whole-body immune response against the tumor.

Working out of the Wellman Center for Photomedicine in Boston, Massachusetts (USA), Dr. Hamblin has observed that the powerful acute inflammatory response prompted by PDT causes neutrophils and other inflammatory immune cells to accumulate in large numbers at the light-treated site, ultimately resulting in the tumor's complete eradication. Moreover, he and his colleagues recently demonstrated for the first time that a single PDT treatment could not only destroy the primary tumor, but also induced a whole-body immune response capable of destroying distant metastases.[15] These findings have profound implications for the future of cancer medicine.

It is only natural to think of laser therapy as focused on a specific part of the body. Nevertheless, the research of Hamblin, Korbelik, and others indicates that using lasers as part of immuno-PDT results in a whole-body approach because it harnesses immune mechanisms that have access to the entire body. Immuno-PDT involves the very same photosensitizers used in PDT. The central difference is that the immunologic approach combines the laser-based treatment with specific support for the immune system—that is, strategies to enhance the system's functioning so that you can treat cancers or infections that may be in other parts of the body, well beyond the reach of the laser.

Such elegant applications of PDT have already begun to result in therapeutic outcomes that far surpass what can be accomplished with the simpler forms of this light-based modality, and they could soon prove to be superior to many conventional cancer treatment approaches as well. Certainly the biological rationale behind the immuno-PDT strategy—that is, getting the immune system to attack rather than tolerate the cancer—is a perspective that should illuminate a whole new way of thinking about what constitutes truly effective cancer treatment.

Why You Need This Book

Our purpose in writing this book is to unveil a powerful method by which physicians and their patients can harness the healing energies of the natural world. Although the approach sounds novel, it is actually based on an integration of ancient healing insights and cutting-edge medical technology. As scientific support for this approach continues to mount, it seems clear that this new wave of understanding is on track to transform the practice of medicine as we know it.

Before going further, here's why we feel this new direction in health and healing is so desperately needed: Our modern healthcare system is now in crisis. In most westernized countries, medicine is too caught up in the business of disease management—that is, helping people reduce the symptoms of such chronic diseases as heart disease, diabetes, cancer, arthritis, hypertension and stroke. Modern medicine would have you believe that the answer to these very common health problems is to develop ever-more powerful drugs and invasive surgeries. However, we believe there is a better solution.

The problem of cancer is particularly serious. Modern medical systems prefer to treat cancer with surgery, radiotherapy, and chemotherapy, as well as various molecular targeting approaches when there is sufficient research to support those treatments. Many of the treatments favored by high-tech medicine either are too toxic, too invasive, or too expensive. Not surprisingly, these same treatments also have limited efficacy over the long term. Some chemotherapy drugs are so toxic that they frequently must be discontinued before the patient can receive the full treatment plan. Radical surgery and intensive radiation treatments tend to grind the human body down so that it loses vitality, resilience and immune competence.

Though such treatments may stop cancer, in many cases the malignancy develops resistance to the drugs and radiation, and thus the treatment removes most of the visible signs of disease, but leaves some "treatment resistant" cancer cells behind. Those same cells can then multiply and develop into a more aggressive form of the disease later on. With many cancer relapses or progressive disease situations, it is not long before the oncologist declares that the patient is "untreatable" or "terminal". Patients and their families are then told that nothing more can be done and are advised to "get your affairs in order".

A very similar scenario has emerged in the treatment of certain infectious diseases. Infections caused by resistant bacteria or other microorganisms do not completely respond to the conventional antibiotic approach, and this results in prolonged illness and a heightened risk of death. The once miraculous power of antibiotics has become increasingly limited by the worldwide development of antibiotic resistance, and thus antibiotics are viewed as an excessively used medical treatment whose days may be numbered.

Here are some key facts from the World Health Organization (WHO) concerning the scope of this problem, with reference to organisms that have developed resistance to multiple antibiotics, or what scientists now call multidrug resistance:

- Each year, according to WHO figures, there are about 440,000 new cases of multidrug-resistant tuberculosis, resulting in at least 150,000 deaths.[16]
- Resistance to earlier generation antimalarial drugs (e.g., chloroquine and sulfadoxine-pyrimethamine) is common in most malaria-endemic countries.[17]
- A high percentage of hospital-acquired infections can be traced to highly resistant bacteria, notably methicillin-resistant Staphylococcus aureus (MRSA).
- In 2005, an estimated 478,000 hospitalizations were linked to Staphylococcus infection in U.S. hospitals—including about 278,000 hospitalizations related to MRSA.[18]
- Within Europe, MRSA rates have been increasing in Germany, Belgium, Ireland, the Netherlands, and the United Kingdom. Far more MRSA cases have been reported in southern and western Europe than in northern Europe.[19]
- Even outside the hospital population, a significant percentage of people suffering from either acute or chronic sinusitis (sinus infection) have positive MRSA cultures.
- As the WHO states, "Inappropriate and irrational use of antimicrobial medicines provides favorable conditions for resistant microorganisms to emerge, spread and persist."[20]

What these troubling facts and figures tell us is that we can no longer continue to use the same approach to the problem of infectious disease. Antibiotic abuse may very soon be reaching a critical threshold. The good news is that there are far more natural methods available to us that can circumvent the problem of antibiotic resistance, yet still overcome the infectious disorder.

This brings us to the area that many healthcare professionals now refer to as "complementary and alternative medicine" (CAM), or integrative medicine. CAM therapies are those that can be used in conjunction with conventional methods, and which, in some cases, can even supplant those methods—such as in the above-mentioned case of resistance to either chemotherapy or antibiotics. Well-known examples of CAM therapies include massage, acupuncture, homeopathy, herbs and nutritional supplements. Turmeric, rosemary, and many other herbs have shown great promise in the laboratory in terms of eliminating various types of disease-causing bacteria—and possibly even reversing antibiotic resistance—though clinical research is needed to confirm these observations.[21]

For decades, now, the well-educated public has been clamoring for a medical orientation that does not poison the body in the process of treatment and that honors and supports the body's natural capacities for overcoming disease. Internet usage reflects this hunger for better information on what people can do for their own health. For example, in May 2002, according to the Pew Internet & American Life Project, the number of Americans seeking health information on the Internet was approximately 73 million, with 93 percent using the Internet for information about a particular illness or condition, 65 percent using the Internet to access information on nutrition and weight control, and

48 percent—about half of all Internet users—looking for information about CAM therapies.

Unfortunately, because CAM therapies are not part of standard medical training, many physicians—particularly those in the United States, but also some European countries—continue to overlook or ignore the potential of natural medicine and CAM therapies. These physicians feel that they have studied hard enough in medical school, and that the tools they learned about in school are the only tools that have any merit. Even though their patients are requesting information on natural CAM options, they dismiss these options as "lacking evidence of efficacy" or probably not worth pursuing.

In order for us to solve the current crisis in healthcare, a more open-minded attitude toward these options is needed. We need to start taking responsibility for our bodies and minds. Beyond changing our daily habits to include a more nutrient-rich diet, regular physical activity, more relaxation, and more nurturing relationships, we need to think creatively and holistically about solutions to common health problems. We need to be open to novel methods for treating cancer—especially those methods that have minimal side effects yet have shown clear evidence of efficacy in the clinical setting.

This book reflects the efforts by the Natural Health Foundation to shift the focus toward such innovative thinking and cutting-edge methods. To overcome cancer and other diseases while at the same time promoting good health, we can no longer afford to dismiss the healing powers of nature, or to overlook the value of non-toxic, non-invasive therapies. It is time to shine a new light on medicine.

CHAPTER 2

Let There Be Light

The sun, our planet's primary source of energy, is also a source of awesome beauty, inspiration and imagination. Beyond the often picturesque sunrises and sunsets that grace our skies on a daily basis, the sun supports almost all life on Earth through photosynthesis, the process by which plants capture sunlight and convert its energy into chemical forms that, in turn, actually enable plant growth and generate oxygen as a byproduct. The sun also drives the planet's climate system along with its myriad cloud and weather patterns.

Solar radiation refers to all the energy emanating from that brilliant yellow orb at the center of our solar system. This energy arises from nuclear fusion reactions deep within the sun's core. The radiation reaches our planet in a variety of forms, including gamma rays, x-rays, microwaves, radio waves, and infrared radiation. As it turns out, visible light is just a small percentage of the full range of solar radiation. Most of the radiation is invisible, and some of that is in the form of ultraviolet (UV) rays.

Two forms of UV rays reach the surface of the Earth, and we refer to these as UV-A and UV-B. It is the latter that causes sunburns, as well as the mutations that lead to pre-cancerous skin conditions and, in some cases, to cancer. Chronic exposure to UV rays also results in tanning, which is a kind of protective mechanism that helps shield the skin from the ravages of sunburn. But too much of this sun exposure will, over time, result in premature aging—as testified by the leathery, wrinkled skin of many old farmers and construction workers, as well as surfers and other sun worshippers.

HERE COMES THE SUN

Below are some fun facts about our sun:

- Our sun has been shining for about 4.5 billion years, and is expected to continue to radiate "peacefully" for another 5 billion years, becoming twice as luminous during that time.
- In about 1 billion years, it may become too hot for life on Earth to continue, though this possibility would be precluded if our planet happens to assume a more distant orbit.
- The sun contains more than 99.8 percent of the total mass of the Solar System; also, compared to other stars in our galaxy, it is considered to be in the top 10 percent by mass.
- By most estimates, about a million planet Earths could fit inside the sun.
- Although once viewed as a star of modest brilliance, our sun is now thought to be brighter than about 85 percent of the stars in the Milky Way galaxy.
- Although the sun is 93 million miles from Earth, it takes only about eight minutes for the sun's light to travel to Earth.
- Earth's surface and atmosphere absorb more than two-thirds of the sun's radiation; the rest is reflected back to outer space.

In short, sunlight is a mixed blessing. Though too much sun can cause skin cancer, too little sun can seriously compromise our health and render us more vulnerable to a host of chronic diseases. Aside from the fact that we would all perish without the sun's energy (the ultimate source of our food and oxygen), we also need direct encounters with sunlight to trigger the skin's production of cholecalciferol, more commonly known as vitamin D3. Sunlight is also essential to the 24-hour circadian rhythms that govern the immune and hormonal systems, affecting all variety of key processes throughout the body.

Given that sunlight serves such a vital need, it seems paradoxical that precancerous skin lesions—and the cancers that follow—are a frequent consequence of overexposure to the sun. Why would soaking up solar radiation lead to so much skin cancer and premature aging?

The answer is fairly straightforward: Chronic exposure to UV radiation results in inflammation and oxidative stress, which is to say an excessive amount of free radicals, highly unstable molecules that can cause DNA damage. Too much sunlight also suppresses the immune system in the skin, thus allowing those mutated cells to propagate with ease. In short, the surfeit of UV radiation creates the perfect storm for the genesis of skin cancer.

Then again, as they say on the dance floor, it takes two to tango: To a large extent, the sun only inflicts its damage with the help of a biologically vulnerable body. Frequent or chronic exposure to UV rays causes the most damage in those individuals whose bodies lack protection against the effects of inflammation and oxidative stress. Though this is partly due to genetics, diet and lifestyle habits play a more relevant role for the simple reason that they're within our control.

Targeted Light-Based Therapy for Skin Cancer and Pre-Cancers

It's interesting to note that skin is our body's largest organ, and at the same time, skin cancer represents the largest group of all human malignancies.† One reason we don't hear as much about skin cancer as we do about other cancers is that most skin cancers are not deadly. Nevertheless, they are enough of a problem to send many people to their dermatologists on a frequent basis. And the incidence of malignant melanoma, the deadliest of all skin cancers, has approximately tripled in recent decades.

During this same period, PDT and laserthermia have emerged as highly successful, targeted strategies for treating skin cancers and precancerous skin conditions. The treatment achieves excellent cosmetic results as well. Indeed, in many instances, the recipients of such treatment end up looking *better* than they did before the diagnosis.

† Indeed, statistics for the total number of cancers in a particular region separate nonmelanoma skin cancer from other cancers because the disproportionate number of skin cancers would greatly skew any public health official's estimates of a single population's total cancer burden.

CULTIVATING A HEALTHY RELATIONSHIP WITH THE SUN

How can your diet and lifestyle help protect your skin from the more damaging effects of the sun? This protection derives mainly from specific plant nutrients and other natural compounds called phytochemicals (*phyto* means "plant"). There is evidence that these dietary factors are constantly interacting with your genes, thus helping to regulate their expression and ensuring a higher level of protection against many diseases.[22] In particular, the consumption of a large group of plant substances known as polyphenols—abundant in green tea, soy, milk thistle, berries, grapes and grape seed—can confer protection against the damaging effects of excess light exposure and thereby prevent skin cancers from taking root in the first place.[23] The scientific use of these and other natural products to help sun lovers ward off various types of skin cancer is known as *photochemoprevention*.[24]

Back in our hunter-gatherer days, we were consuming a lot more berries and other plant foods that were replete with UV-protective plant compounds, and thus the human body's defenses against the sun's rays were much stronger than they are today. Another recently identified group of "photoprotective" nutrients is omega-3 fatty acids, which come from fish, algae, nuts, seeds and wild game.[25] Against this evolutionary backdrop, it makes sense to emphasize healthy foods and supplements that load up the body with these sun-protective compounds. In this way, we can still benefit from the sun's more salubrious side while also getting some protection against its more harmful side.

So again, rather than advise you to shun the sun entirely, we recommend a more balanced approach. In addition to eating a plant-based diet, it's important to learn good sun protection habits, such as wearing clothes that cover your arms and legs to avoid excessive sun exposure. Wearing a hat to shield your head from intensive sunlight is also very helpful—especially if you're light-skinned or tend to get sunburn a bit too easily.

People who don't get enough sun during the summer months are invariably vitamin D deficient by winter. Therefore, during the summer months, use a good sunscreen lotion after about 15 to 20 minutes of unprotected mid-day sun exposure (dark-skinned people will need twice this amount). When you're not getting out in the sun, we recommend that you supplement your diet with products rich in vitamin D3, such as sun-dried Shiitake mushrooms, mackerel, wild salmon, herring, sardines, tuna, cod liver oil, and free-range eggs.

Children and toddlers, too, should use sunscreens, especially since most of our lifetime sun exposure occurs before people reach age 18. If skin cancer seems to run in your family, or if you've already had a bout with skin cancer, then you'll need to be far more rigorous about sun protection strategies. This means wearing sun-protective clothing and hats, as well as using sunscreens far more often.†

If you do adopt these sun-protective habits, however, you will need to be far more consistent with vitamin D-rich nutrition or consider whole-body treatment with narrowband UV-B light three times a week. The UV-B light treatment is even more effective than taking a daily vitamin D3 supplement.[26] It can help improve your vitamin D balance during the winter, and your body's response will still be evident two months after completing the treatment.

† Note that sunscreens lose their potency after about one year, so if you're using something from last year, it already may have lost its protective power. Also, the use of sunscreen tends to block the ultraviolet-B waves responsible for your skin's production of vitamin D.

In 2010, a comprehensive review of the scientific research concluded that PDT is a well-accepted option for the treatment of many skin cancers, both benign and malignant.[27] In this chapter, we'll address some of the key research support for this assertion, and explain why we believe that PDT and laserthermia are indeed the answer to skin cancer.

While it's true that many skin cancers do respond quite well to PDT, the therapeutic benefits go well beyond that superficial level, even seeking out and destroying abnormal cells that are lodged deep within

organs and tissues throughout your body. Far from being a treatment that's only "skin deep", the therapeutic potential of PDT may extend to the whole body, at least when performed under the right conditions.

Let's take a look at a number of skin conditions and cancers that have been treated with targeted light-based therapy. Where appropriate, we will provide research citations so that our more inquisitive and skeptical readers can look up the studies themselves. We'll start with a very common precancerous skin condition known as Actinic Keratosis.

Actinic Keratosis

Actinic keratosis, or AK, is an irritating skin condition that also goes by two other names: (1) *solar keratosis,* due to its connection with chronic sun damage; and (2) *senile keratosis* because it becomes more common as people age, usually beginning after age 30. Of course, what all these labels have in common is the term *keratosis,* referring to small yet obvious red, brown, or skin-colored patches that occur most commonly on the head, neck, forearms or hands. Usually rough in texture, these patches are itchy, burning, or stinging. Fair-haired, pale-skinned, light-eyed people are the ones most often affected by AK.

Though you may not have heard of AK, tens of millions of people in Europe and the United States are affected every year and end up seeking treatment from dermatologists and primary care physicians. What makes this condition important is the fact that it can progress and transform into non-melanoma skin cancer. Some scientists even regard it as an early stage of cancer. In any case, the successful treatment of AK may offer an opportunity to cut short the development of such common skin cancers as basal cell carcinoma and squamous cell carcinoma.

Given the sun's causal connection to AK, it may seem odd that light-based therapy could help people with this condition. But there's little doubt that PDT can be a very effective treatment option, and a very practical one as well.[28] PDT is currently approved for the treatment of AK in the United States, Canada, and the European Union. At this writing, at least 20 randomized controlled trials have evaluated the light-based treatment for AK. Thanks to all this gold standard research, PDT is widely considered to be among the top treatment options for the bothersome skin condition.

KEYS TO THE SUCCESS OF PDT FOR CANCER

PDT has been approved in many countries for the treatment of lung, esophageal, skin, bladder, and head and neck cancers. Research is underway to determine whether PDT and laserthermia can be helpful in cases of breast, brain, cervical, ovarian, and prostate cancer, and we'll be addressing much of this research in Chapter 4. PDT is regarded as an experimental treatment for many cancer situations, though the main problem in most developed countries is limited availability of the treatment with the exception of dermatology clinics.

This low-invasive procedure takes place in three basic stages: (1) administration of a photosensitizer; (2) accumulation of the photosensitizer in tumors; and then (3) illumination of those tumors with visible light. The reaction between the light and photosensitizer inside the tumor cells results in biochemical reactions that trigger the destruction of those cells.

In general, the effectiveness of PDT depends on the following factors:

- The type of photosensitizer drug used, its dose and ability to selectively penetrate diseased tissue, and how long it is retained in those target tissues.
- The specific light source (usually a laser), its ability to penetrate through to the desired target or diseased tissue, and the duration of light exposure.
- The type of target cells and their oxygenation status, or how much oxygen is in the vicinity when light activates the photosensitizer.[29]
- To be truly effective, the damage resulting from PDT must surpass the cancer cells' ability to repair themselves. This feature is referred to as the *minimum photodynamic dose* or threshold of injury.[†]

† The PDT induces intense inflammation associated with the cytokines, chemokines and other immunologic proteins released by the injured and apoptotic cells. Again, the degree of injury must exceed the inherent repair capacity of the damaged cells.

The treatment involves applying a photosensitizer cream or ointment to the affected area, and allowing the cream to be absorbed over a period of one to three hours prior to light exposure.[30] After a single treatment, at least seven out of ten cases of AK will be fully cleared; and with some topical applications, due to better penetration of the skin, the success rate is as high as 100 percent.[31] Although such impressive-sounding results are similar to those reported with other mainstream treatments, the difference is that PDT has far fewer side effects and results in a speedier recovery.†

Organ transplant patients represent a group that tends to be even more susceptible to AK as well as skin cancers in general. The difference here is that the immune system becomes profoundly suppressed after transplant surgery, and thus the extent of treatment (i.e., frequency and duration of PDT sessions) is usually longer. Nevertheless, PDT is safe and effective for the treatment of AK in transplant patients and may substantially lower the risk of developing invasive squamous cell carcinoma, as we discuss later in this chapter.

In the June 2012 *Journal of the European Academy of Dermatology and Venereology*, researchers at the Bispebjerg University Hospital in Copenhagen confirmed that PDT is an attractive option for treating AK and other non-melanoma skin cancers because one can treat large areas of the body all at once. Nonetheless, the Danish authors also point out that the treatment can result in long visits to the clinic and discomfort during therapy. They propose a very practical and elegant solution: Get a topical photosensitizer cream at the proper dose, then go out in the daylight and let the sun do the rest (see sidebar, "Photorejuvenation: Applying the PDT Principle to Skin Care and Skin Health).

This sensible-sounding approach, known as daylight-mediated PDT, is a far more tolerable treatment procedure. It is nearly pain-free and more convenient for both you and your physician. The only hitch is that you should use an appropriate sunscreen if you're getting substantial sun exposure. At this writing, several randomized controlled studies already have confirmed that daylight-mediated PDT is an effective treatment for thin AK.[32]

† Topical use of 5-aminolevulinic acid (ALA) and methyl aminolevulinic acid (MAL) has received U.S. Food and Drug Administration approval for the treatment of actinic keratoses. Other photosensitizers will soon follow suit.

Remember that this could be an especially good fit for you if you have AK over large portions of your body, or at least over portions that can easily be exposed to daylight. Also note that it's usually unnecessary and often ill-advised to get your sun exposure in the middle part of the day—unless your primary goal is to boost vitamin D production. But for the purpose of successful PDT, the sunlight from the morning or late afternoon is often more than sufficient to activate the photosensitizer synthesized in your body from the ALA cream that you previously applied to the skin.

PHOTOREJUVENATION:
Applying the PDT Principle to Skin Care and Skin Health

Aging is an ongoing process, and one of the clearest expressions of this process is what happens to our skin as a result of repeated sun exposure. Such exposure to the ultraviolet rays of the sun eventually results in *solar elastosis,* the medical term for the chronic skin damage (deep wrinkles, vertical creases, and loose or sagging skin) that happens in elderly people following sun exposure over the long term. A number of factors—pollution, cigarette smoke, alcohol and caffeine abuse, cold weather, stress, lack of sleep and broken circadian cycle, nutritional imbalances, and insufficient physical activity—can accelerate premature aging of the skin and contribute to unhealthy skin in general.

Given the "photodamage" that results from excessive exposure to sunlight, it seems ironic that light also plays such a pivotal role in reversing this aging process. Photorejuvenation was recently defined in the medical journal *Dermatologic Clinics* as "the process of using laser and other light sources for restoring skin to a more youthful appearance."[33] This application of PDT has been shown to improve or reduce skin roughness, lentigines (small dark spots on the skin), sallow complexion and fine wrinkles.[34]

Thankfully, your skin has an amazing ability to regenerate, meaning that it can replace damaged or dying cells with completely intact, healthy cells. Young children have a phenomenal capacity for skin regeneration, but the ability is amply retained throughout

adulthood and well into the golden years of life. In essence, with photorejuvenation, you're using light to speed up the regenerative process, perhaps even turning back the biological clock.

So how does this occur? The precise mechanisms are still being mapped out. We now know that photorejuvenation is associated with an increase in the formation of type I collagen in the skin.[35] Collagen is the main protein in connective tissue and the most abundant protein in humans, comprising about one-quarter of your body's entire protein supply. Along with soft keratin, collagen is responsible for skin strength, elasticity, and suppleness, and its breakdown or deterioration leads to wrinkles that accompany the aging process.

As an aside, it's interesting to note that intense pulsed light therapy, or IPL, can by itself *reduce* the signs of photodamage or photoaging of the skin. By using a specific photosensitizer cream (in this case, topical 5-aminolevulinic acid), IPL's beneficial effects on skin health and appearance were significantly improved.[36] Once again, this demonstrates the power of the photodynamic principle.

In our Moscow laboratories (www.lortie.ru), we have found that certain plant compounds, including Chlorophyll-Lipoid Complex®, "Phycoprotein®" and "Active Water-Soluble Chlorophyll®", can enhance the skin's ability to renew itself in response to light. Derived from blue-green organisms called *Spirulina* (scientific name: *Spirulina Platensis*), these patented compounds stimulate the replacement of aged or damaged skin cells by new healthy cells. Cosmetic creams that contain these photosensitizer compounds can help bring about the photorejuvenation process anytime you step out into the sun.

The spontaneous regeneration of the human skin takes place throughout life. As mentioned above, the process is far more active in early life, then slows down during adolescence and continues to do so with increasing age. This helps explain why acne is so common in teenagers, and why skin cancers and precancerous conditions are more common in older adults. Of course, older adults are more likely to experience a wider range of age-related skin problems, most of which respond beautifully to the photorejuvenation approach.

Summer is an ideal time to experience the benefits of photorejuvenating cosmetics (photosensitizer gels) as the days are much longer, and daylight is abundant. Since most people go on vacation in the summertime, this makes it easier to combine leisure time with photorejuvenation and achieve good results without spending months in professional treatment or dermatology salons. This strategy simply means spending a good amount of time out in the open air, such as at the beach or in the yard or garden.

Mornings or evenings are the best times for photorejuvenation during the summer, because the sunlight is less intense at those times. Usually two to three weeks of this practice are all that's needed to achieve significant results using the gels from the professional series, such as the JUVENON® and MORION® gels by J. Hewitt Inc (www.jhewitt.co.jp). The basic strategy is as follows: Before going to bed, you can apply either gel on your skin instead of using a skincare cream. The next morning, you wash off the residual cream and go outside to expose your now "primed" skin to the morning sun. Alternatively, if you happen to be busy in the morning, you can apply the gels for a couple of hours in the afternoon and expose your face to sunlight after 5 p.m.

Photorejuvenation is an anti-aging technological breakthrough with proven effectiveness in terms of accelerated skin healing, rejuvenation, and preventive medicine. For example, some studies indicate that the use of these topical photosensitizers can be effective against acne vulgaris.[37] There is some soon-to-be-published research on the accelerated skin healing afforded by VIRTA-VITALIZER®, anti-wrinkle action of VIRTA-REVIVE® (both by Brema Pharma B.V., www.bremapharma.com), anti-acne effects of MORION®, and the face-rejuvenating effects of JUVENON® (both by AREV PHARM LLC, www.arev.biz).

Finally, it's worth reiterating that there's a solid rationale for using the photorejuvenation approach to help prevent or treat actinic keratoses and Bowen's disease—both precancerous skin conditions.[38] Thus, the ultimate benefit of this approach is not just to promote healthier skin, but also to help ward off superficial basal cell carcinoma and other non-melanoma skin cancers.[39]

Basal Cell Carcinoma

We noted earlier that skin cancers are the most common form of cancer worldwide. Basal cell carcinoma (BCC) is the most frequently diagnosed form of skin cancer, at least among white people or those of mixed European descent. This slow-growing disease starts in the top layer of the skin and is usually painless. It tends to affect people who have had frequent exposure to sunlight or tanning beds. Older individuals may develop BCC on the top of the head, or scalp. Though BCC occurs more often in people over age 40, it can strike younger people as well.

Your chances of getting basal cell skin cancer increase if you have one of the following:

- Pale, light-colored or freckled skin
- Numerous moles
- Blond hair or red hair
- Blue, gray or green eyes
- Family members who have or had skin cancer
- Long-term daily exposure to the sun
- Many severe sun burns during childhood or young adult years
- Frequent exposure to x-rays or other forms of radiation

One of the challenges of detecting BCC is that it may not look all that different from your normal skin's appearance. In some instances, the skin may be slightly raised, or you may have a skin bump or growth that is pearly or waxy, light pink or whitish, brown or flesh-colored. Other characteristics of BCC cases are as follows: a scar-like sore, sometimes with a depressed (sunken) area in the middle; a sore that does not heal; a sore that bleeds easily; oozing or crusting spots in a sore; or irregular blood vessels in or around the spot. It's best to consult a dermatologist in order to assess the size, shape, color, and texture of any suspicious areas.

Superficial BCC was the first cancer to respond to PDT, with the first success story documented in 1903. It would take another 70 years before the promise of PDT for the treatment of cancer really was realized. Due to the ease of exposing the skin to light, non-melanoma skin cancers have received the lion's share of PDT research attention since the 1970s.

At the present time, PDT is approved in Canada and the European Union for the treatment of BCC (superficial and nodular forms). A number of randomized clinical trials have reported favorable results using PDT for the treatment of both nodular and superficial BCC, as well as mixtures of the two forms.[40] For superficial BCC, clinical studies indicate the complete response rate is over 90 percent in the first six months, with a recurrence rate of about 20 percent within five years of initiating treatment.[41] Complete response rates of up to 100 percent are easily achieved with this light-based treatment of BCC, though some long-term studies also reported high regrowth rates. Our own experience in treating BCC with the use of PDT and photosensitizer "Radachlorin® is illustrated in Figures 2 and 3.[42]

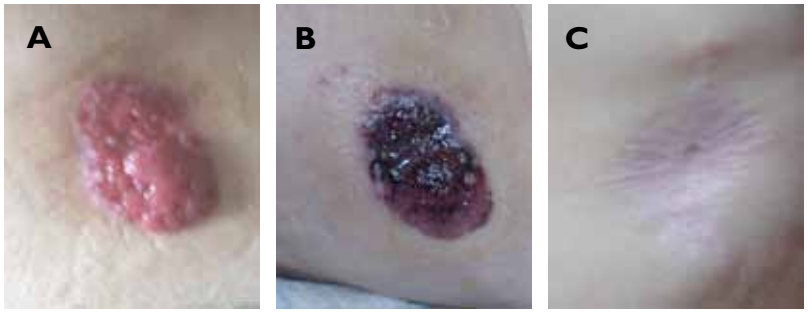


Figure 2: *Basal cell carcinoma of thigh skin. Tumor size 4.5 x 2 cm. (a) Before PDT. (b) 1 day after PDT. Dry necrosis. (c) 4 years after PDT No recurrences. (Courtesy of Prof. Valery Privalov, Chelyabinsk Municipal Clinical Hospital Nr. 1, Russia).*

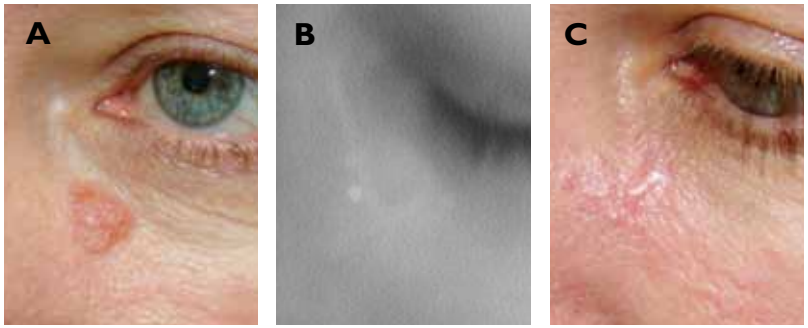


Figure 3: *Basal cell carcinoma of face skin. (a) Before PDT. (b) Flourescence diagnosis: the rim of the tumor can be seen. (c) In 3 months after PDT. Complete response. (Courtesy of Dr. Evgeniy Volkov, Ekaterinburg Region Oncologic Dispensary, Russia).*

A recent clinical study compared cryotherapy with PDT for the treatment of superficial BCC. Cryotherapy involves repeatedly freezing the area of diseased skin, and it is one of the most widely used methods of treating superficial skin cancers. For superficial BCC cases, the three-month complete clinical response rates were similar for PDT (97 percent) and cryotherapy (95 percent).

After five years of observation, both treatments showed similar results: About 75 percent showed complete elimination of the lesions, and recurrence rates were around 22 percent for lesions that had initially cleared following treatment. In sharp contrast, however, PDT led to superior cosmetic results, with a good or excellent outcome reported in 87 percent of those in the PDT group, compared to only 49 percent of those in the cryotherapy group.[43] So if you'd prefer to look better after the procedure, PDT is clearly the treatment of choice.

Squamous Cell Carcinoma of the Skin

Squamous cell carcinoma is a type of cancer that forms in the squamous cells—cells that are flattish and even resemble skin when viewed under the microscope. There is a squamous lining to the mouth, the upper parts of the airways and esophagus, the lower part of the cervix, the anus, and several other body parts. If cancer develops in such a lining, it is called squamous cancer or squamous cell carcinoma. These cancers commonly affect the mouth, throat, lung, cervix and skin, all of which can be treated with PDT.

Let's start with squamous cancer of the skin, or what oncologists refer to as cutaneous squamous cell carcinoma (cSCC). This skin cancer looks slightly different from basal cell carcinoma (BCC), which we discussed in the preceding section. The two types of skin cancers also behave differently. Compared to BCC, cSCC is more likely to spread to distant parts of the body, particularly if it starts in skin areas not previously exposed to sun. Also, the latter occurs predominantly in people in their late sixties and early seventies.

As with BCC, the main risk factor for cSCC is excessive exposure to ultraviolet radiation, either from sunlight or tanning beds. The risk is greatest for people who have a history of heavy sunbathing, interspersed with frequent visits to the tanning salon in the "off season".

Why should you care about this type of cancer, especially if you have never had it? To begin with, SCC is the second most common of all human cancers, at least among white people of mixed European descent. What's even more concerning is that having this type of cancer increases your risk of developing any other type of cancer (the same holds true for BCC as well).[44] Moreover, the incidence of such non-melanoma skin cancers has dramatically increased in the past few decades.[45]

The treatment of cSCC can involve surgical and nonsurgical methods such as PDT. Nevertheless, the results of PDT for this particular skin cancer, using the first generation photosensitizers as an ointment, have generally been disappointing. The main problem is an unacceptably high recurrence rate, typically over 50 percent. On the plus side, though, PDT is associated with much faster recovery following treatment, as well as excellent cosmetic results. Once again, you end up looking much better after PDT than you would with surgery or radiation treatments. Our experience in treating SCC by PDT and the photosensitizer Radachlorin® is illustrated in Figure 4.

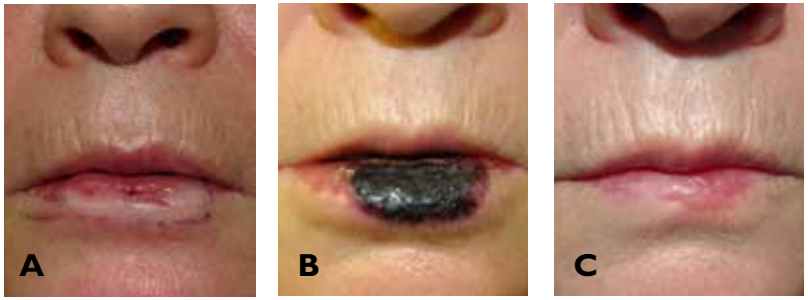


Figure 4: *(a) Squamous cell carcinoma before PDT. (b) Squamous cell carcinoma 4 days after PDT. (c) Squamous cell carcinoma 6 weeks after PDT. Complete response.*

At this point, we should conclude that PDT serves much better as a preventive strategy—reducing the number of new lesions that may develop in patients at high risk of skin cancer, such as organ transplant recipients, Bowen's disease patients (discussed in the next section), or individuals with various strong risk factors, notably actinic keratosis and a history of frequent sun exposure.

Bowens' Disease

Bowen's disease refers to early-stage squamous cancer of the skin, and its more technical-sounding name is *squamous cell carcinoma in situ*. If you've been diagnosed with Bowen's disease, you may have been offered cryotherapy, surgery, or radiotherapy, or some combination of these. More recently, however, PDT has demonstrated success as a treatment for this condition. The photosensitizers can be activated with either coherent light (lasers) or non-coherent light sources (lamps and LEDs), all of which seem to have about the same effectiveness.

At this writing, at least ten controlled clinical trials have focused on the use of PDT for Bowen's disease. In most studies, PDT was combined with other treatments, and then different combinations were evaluated. For example, when researchers compared PDT with cryotherapy to PDT with 5-FU cream, they found that the response rates were substantially higher for the PDT-cryotherapy combination—even as high as 100 percent in some studies![46] Certainly at this point, we can say that PDT is an excellent first-line treatment option for Bowen's disease.[47]

On the other hand, we really don't know which PDT regimens and complementary strategies are optimal for achieving the best long-term outcomes.[48] It seems logical to suggest that cancer-repelling dietary habits and other lifestyle factors—such as good sun protection and minimizing exposure to toxic chemicals, cigarette smoke, and alcohol—are sensible things to consider if you wish to reverse a pre-cancerous condition and hopefully steer clear of cancer in the future.

Our preliminary research in this area has been promising. With the intravenous form of the second-generation photosensitizer Radachlorin®, a complete eradication of a stage 1 SCC lesion (Bowens' disease) was achieved, and the patient was cancer-free for the three-year follow-up period.[49] Based on such well-documented case reports, we anticipate that future clinical studies will show favorable outcomes with second-generation photosensitizers (such as those discussed in Chapter 7). It is hoped that these agents will help cure SCC the same way they worked on BCC—that is, with excellent cosmetic results and long-term remissions.

Malignant Melanoma

Melanoma, or malignant melanoma, is a type of skin cancer that starts in the cells that make the pigment or coloring of the skin. These cells, known as melanocytes, are found below the surface of the skin. They produce a dark brown pigment called melanin, which accounts for suntans and dark skin. The melanocytes can create colored lesions called moles, the majority of which are completely benign and do not carry any increased risk of melanoma. Nevertheless, a few unusual types of moles do carry a higher risk. The risk of developing melanoma is increased by regular exposures to sunlight, though genetic factors and lack of dietary antioxidants may also play a role.

Melanoma is much less common than the other types of skin cancer we addressed earlier in this chapter, but also far more deadly, accounting for 80 percent of deaths from skin cancer. In its metastatic form, melanoma is the most lethal type of skin cancer because of its aggressive behavior and ability to spread to the organs and lymphatic system. Moreover, the incidence has been steadily increasing in most parts of the world over the past few decades, doubling about every ten years. Extremely rare in childhood, malignant melanoma strikes men and women alike in their forties.

As just mentioned, some melanomas are quite aggressive. Nevertheless, most cases can be cured by surgery if the disease is diagnosed at an early stage and has not spread deeply into the skin or to the lymph nodes. Once the disease becomes metastatic, however, chemotherapy and radiation treatments are largely ineffective and result in too many adverse side effects. Instead of these conventional strategies, a stronger emphasis must be placed on harnessing the anti-cancer immune defenses, since malignant melanoma is among the most immune-responsive of all cancers. A high-dose immunotherapy approach that includes interferon and interleukin-2 is thought to be the most effective. This is where immuno-PDT and related strategies come into play.

Our experience with PDT of melanoma involves using the second-generation photosensitizer Radachlorin® in combination with surgery in a number of patients. For example, complete responses were reached in three out of four cases with stage I and II melanomas who received

PDT prior to surgery.† The follow-up period was 9 and 12 months.[50] These cases are illustrated in Figures 5-7.

Compared to earlier-stage melanomas, patients with stage III and IV melanomas and skin involvement have very poor survival rates. In our clinical practice, laserthermia has shown some promise against malignant melanoma. For example, we used laserthermia to treat stage III melanoma of the soft palate along with metastases in the lymph nodes of the neck. An example is shown in Figure 8 (pg. 70). Following laserthermia, the patient underwent radical surgery (including removal of the regional lymph nodes) and PDT of the tumor bed. A recurrence occurred at 1.5 years, and the patient eventually died from distant metastases after living considerably longer than the average survival time. This is an example of a combined approach that entailed three different treatment strategies.

Even as far back as the 1970s, scientists studying PDT were able to obtain a 50 percent response rate in malignant melanoma; this early research used a photosensitizer together with red light from a xenon arc lamp.[51] Since that time, several clinical studies have demonstrated favorable results with PDT, indicating a promising role as an adjuvant treatment for advanced-stage melanoma (stage III and IV). In animal experiments, PDT triggered the death of both human and mouse melanoma cells, as well as blocking tumor growth and prolonging the survival of the animals.[52]

Immunotherapy, the use of treatment strategies that harness the immune system against disease, has become a mainstay of treatment for malignant melanoma. At this time, however, most oncologists rely on a relatively small number of immune-enhancing strategies. In the United States, for example, interleukin-2 and interferon-alfa 2b are the only approved immunotherapeutic drugs for melanoma treatment. These agents can result in remissions that sometimes last for years. Their use also has been studied in combination with tumor vaccines as well as with different chemotherapy drugs.

Recognizing the central role of the immune system for the control of some cancers, scientists have begun investigating the use of PIT as a new therapeutic approach to malignant melanoma. In our approach

† These melanoma patients were classified using the 2nd and 3rd invasion levels by Clark.

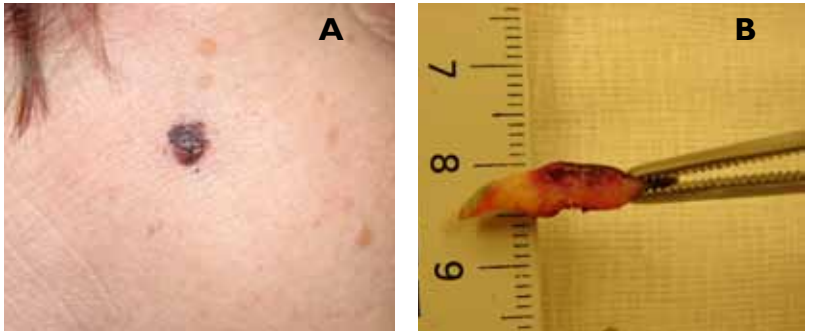


Figure 5: (a) *Melanoma of the skin before PDT with photosensitizer Radachlorin as an adjuvant to surgery.* **(b)** *Melanoma after removal: the depth of 662 nm laser light penetration and corresponding infiltrate are shown to be around 6 mm.*

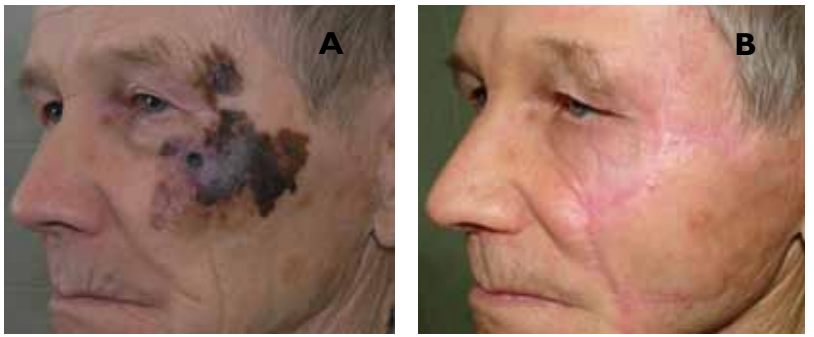


Figure 6: (a) *An 80-year-old patient having melanoma of the skin with a 30-year history of Dubreuilh's melanosis.* **(b)** *One year after PDT combined with resection and plastic surgery. Cancer free after 3-year follow-up. Surgeon Dr. Evgeniy Volkov.*

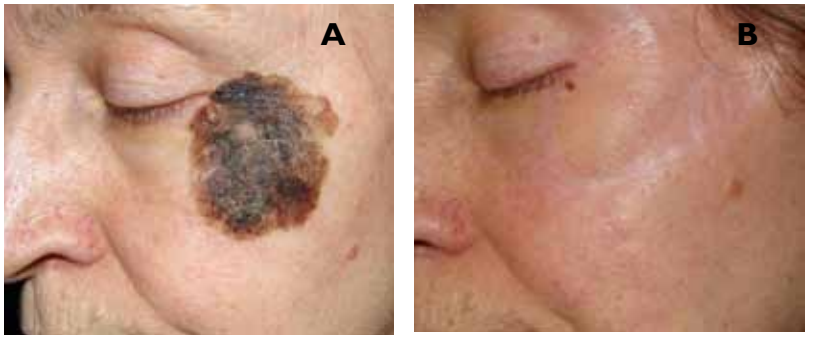


Figure 7: (a) *Before PDT.* **(b)** *Ten months after PDT combined with resection and plastic surgery. Surgeon: Dr. Evgeniy Volkov.*

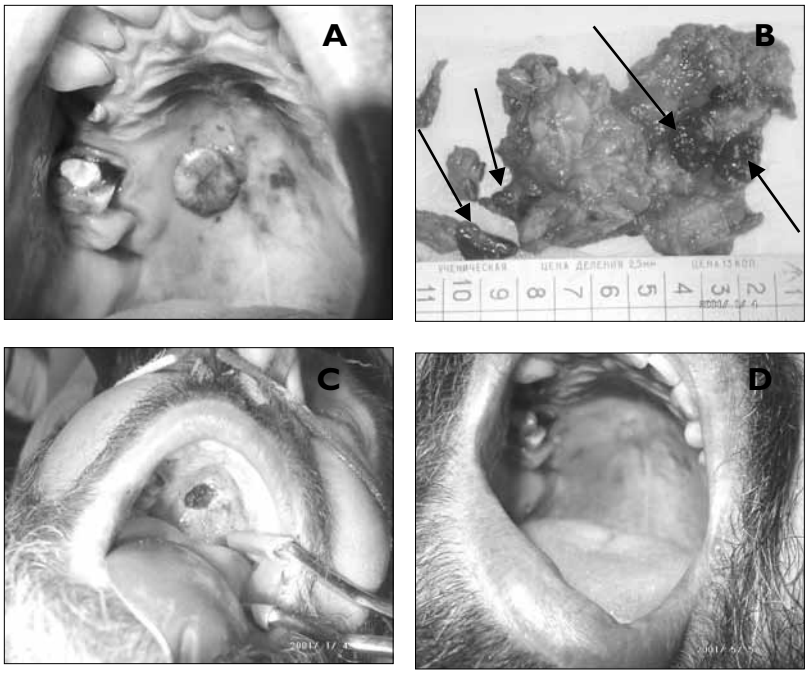


Figure 8: *Soft palate melanoma with metastases in lymphatic glands of the neck on the right side (3 N2 M0).*
(a) *4 Jan 2000. Soft palate melanoma before treatment. On the soft palate, there was a round tumor-like formation of blue-black color rising above the surrounding mucous membrane with satellite tumors along inner semi-circle of the melanoma. PDT was performed at the light dose of 500 J/cm^2. Immediately afterward, laser ablation was done using 980 nm-diode laser at 30 Watt output.*
(b) *Photosensitizer Radachlorin was administered 3 hours prior to surgery (100 mg). The ablated neck cellular tissue with melanoma metastases is indicated by arrows. A Crile's type operation was performed with the ablation, as a single block of cellular tissue of submaxillary and side neck triangles on the right, together with jugular vein, sub maxillary salivary gland and lymphatic collector along the carotid. Urgent histological investigation revealed the melanoma metastases in the neck lymphatic glands. Irradiation of the post-operative wound was performed at the light dose of 200 J/cm^2.*
(c) *Melanoma after PDT and the laser ablation. Replacing the melanoma is a crater-like depression of soft tissues covered with dark scab. The necrotic mass gradually cleared and was totally epithelized by the sixth week.*
(d) *16 weeks after the treatment. Total epithelization of the scar and complete absence of melanoma. The patient was subjected to two courses of polychemotherapy. After 1 year, there was no recurrence or evidence of metastases.*
(Courtesy of Prof. Valery Privalov, Chelyabinsk Municipal Clinical Hospital Nr. 1, Russia).

to PIT, the photosensitizer is delivered through an infusion and treated with light as it is being infused into the body.[53] Thus the photosensitizer is already activated before it becomes concentrated in the melanoma cells, causing specific light-induced changes in their membranes (photomodification) and eventual destruction though light treatment.

Some clinical reports suggest that this approach can lead to the regression of choroidal melanoma and skin melanoma metastases. The antitumor effects result not only from the activation of an immune response, but also from the destruction of the tumor's blood vessel supply and light-induced damage to the cancer cells themselves—thus having both direct and indirect tumor-killing effects.[54]

Another strategy uses near-infrared laser energy to induce temperature increases in target tissue, again directly killing tumor cells. As the tumor cells swell and are disrupted due to the temperature increase, they release proteins (antigens) that subsequently help generate a strong anti-tumor immune response.[55]

Also released in this process are heat shock proteins (HSPs) that further amplify the immune response. We introduced you to these special proteins in Chapter 1, and we'll be returning to them later on. The combination of the antigens and HSPs seems to optimally boost the various key immune cells' activity against advanced melanoma and other types of malignancies.[56]

To further enhance the immune system's stimulation within PDT, a drug called Imiquimod has been used (though mostly for the treatment of warts, actinic keratosis and superficial BCC). Used as a cream, Imiquimod has been effective in cases of advanced metastatic melanoma, even when used on a stand-alone basis.[57] In addition to activating the production of various immune-enhancing chemicals called cytokines, this drug activates a number of key immune cells—namely natural killer cells, macrophages and B lymphocytes. This overall combination of immune-enhancing effects makes Imiquimod a strong option for integrating into the PDT approach.

In a small clinical pilot study, Imiquimod was added to the PIT/photothermal therapy protocol to invoke an effective immune response against malignant melanoma cells that may have spread to other parts of the body.[58] Six out of 11 patients with advanced metastatic melanoma

showed a complete response, and the overall survival rate after one year was 70 percent. The main side effect was irritation and sometimes intense itching at the photothermal laser treatment site. This pilot study suggests that this unique approach, which includes a laser thermal effect (heat), could be effective in late-stage melanoma patients for whom reliable treatment options are very limited at this time.

Imiquimod is just the tip of the iceberg when it comes to further bolstering the immune system's response to melanoma and other cancers. As we discuss in the last chapter of this book, there are other immune-enhancing natural products that can be useful as well in this context. These supplements include various immune-stimulating herbs, mushroom compounds, and nutraceuticals such as inulin, a natural plant-derived compound used for boosting intestinal health and immunity. In animal experiments, inulin significantly delayed the recurrence of melanomas following PDT, an effect further enhanced by injecting the drug interferon beforehand.[59]

Why should we be interested in ways to further bolster the anticancer immune defenses if light-based therapies (PDT, laserthermia, PIT) are already working to stimulate the system? There are several reasons, which can be listed as follows:

- The immune system may be substantially damaged by chemotherapy and radiotherapy received *before* someone with late-stage melanoma receives PDT.
- Those conventional treatments typically result in the development of cells less sensitive to chemotherapy and radiation treatment, and those same treatment-resistant cells may be less easily recognized by the immune system. (In some cases, however, a more active immune response may occur following lower doses of certain chemotherapy agents. This approach is known as Chemo-Immunomodulation, though its success may still depend on the use of other immune-enhancing agents.[60])
- Chemo and radiation treatments also tend to directly blunt the immune system's ability to respond, due to their toxic effects on the bone marrow; this makes it even more likely that at least some melanoma cells will survive the effects of PDT when used without additional immune strategies.

- As a general rule, the immune system of late-stage melanoma patients is less responsive than early-stage patients, thus warranting an even more innovative and aggressive approach. (In contrast, the smaller tumors of early-stage cancer tend to produce fewer immune-suppressive factors.)

Such limitations could account for PDT's occasional inability to produce a complete remission in patients with advanced melanoma. Future studies of PDT effects should take into account which patients have previously received conventional treatments, and which patients have not. It is probably the case that those melanoma patients who have not previously undergone chemotherapy or radiation treatments will respond even better to PDT and other modalities.

Regardless of these limitations, it's obvious that PDT has many advantages over conventional treatment. To begin with, it is far more tolerable than conventional chemotherapy and has a much more favorable impact on one's quality of life. Also, unlike chemotherapy and radiotherapy, PDT can be used repeatedly with relative safety, even in patients who are weak or who have other conditions such as diabetes, advanced age or cardiovascular disease. Moreover, PDT is readily available through outpatient treatment facilities, unlike most of the conventional treatments for malignant melanoma.

At this time, we believe that PDT, PIT and laserthermia should be viewed as viable treatment options, especially when used in combination with surgery for metastatic malignant melanoma.[61] At this time, a great deal of scientific attention is being focused on targeting the melanosomes, tiny organelles found within cells of the melanocyte lineage that produce the compound, melanin.

Another exciting focus of research is to determine whether PDT-generated anti-tumor vaccines can further improve the immune responses to malignant melanoma. That is, the vaccines themselves are being generated by PDT treatment of surgically removed melanomas and then used to treat patients with advanced-stage melanoma. Those PDT-generated vaccines could prove to be more effective than other vaccines in helping to prevent the progression or relapse of advanced melanoma.[62] (For more details about PDT vaccines, please see our discussion in Chapter 7.)

IN SITU PHOTOIMMUNOTHERAPY:
Blending Light and Heat to Cure Melanoma

Mention the phrase *cancer therapy* and most people will think of the standard trio of chemotherapy, radiation and surgery. Trouble is, these treatments all tend to suppress the immune system—not a good idea in the case of malignant melanoma, a disease that's highly responsive to the immune system when properly activated.

An ideal approach to cancer therapy would not only destroy the tumor, but at the same time would fire up the immune system to detect, track down and destroy any remaining tumor cells. PDT, as well as another innovative treatment known as *Photoimmunotherapy* (PIT), seem to have these immune-activating properties.

Another novel approach called *In Situ Photoimmunotherapy* (ISPIT) also bears mentioning here. This approach brings together the elements of light and heat to eliminate tumors.[63] ISPIT uses laser radiation in a pulsed fashion to expose tumor proteins, or antigens, to the immune system's key sentinels, the so-called dendritic cells. Those cells then undergo a process that enables them to present the antigen to other parts of the immune system, notably the macrophages and T-cells, which are then activated to help eliminate the tumor.

By the way, PDT and PIT trigger these same cancer-repelling effects within the immune system. With laserthermia and ISPIT, however, there is the added element of heat, an element made possible by the unique biology of melanoma.

It turns out that melanocytes—as well as their mutated counterparts in melanomas—are uniquely responsive to this approach because the laser light causes them to heat up more than other cells. This is due to the fact that melanomas contain an abundance of light-absorbing molecules in the form of melanin, the dark pigment we mentioned earlier. Laser triggers the so-called *photothermal effect*—very much like the effect of various photosensitizers that are used in PDT.

Thus, when the melanoma tumor is "zapped" with laser sources, local temperatures in the tumor can rise to 130 degrees Centigrade. This very localized heating triggers a series of chemical and mechanical changes within the tumor, changes that ultimately result in its destruction. Thus, in addition to directly assaulting the tumor, the ISPIT approach coaxes the immune system into eliminating any malignant cells that may have spread to other parts of the body. Sound logic and mounting clinical evidence indicate that this novel approach offers us a powerful way to treat advanced metastatic melanoma.[64]

Benign Tumors

Aside from treating malignant tumors, a combination of PDT with immune-based laserthermia can be helpful for eliminating benign tumors. An example of this is the use of PDT to effectively treat benign thyroid nodules.[65] The use of laserthermia at 808 nanometers (nm) enhanced the effectiveness of PDT treatment for multiple benign adenomatosis of the thyroid gland using the second-generation photosensitizer Bremachlorin®. This, in turn, enabled a substantial lowering of the red light dose.[66] The pulse laser treatment strategy led to significant reductions in pain and tissue damage (necrosis), as well as a complete tumor response in five cases and partial responses in three other cases after a 5-year follow-up.†

Finally, the combination of PDT, PIT or laserthermia with various immune-enhancing agents—either drugs or natural products, or both—might further increase the efficiency with which those light-based treatments can destroy the initial tumor as well as any hidden metastases, thereby greatly reducing the chances of a relapse later on. We are very excited about the possibility that FloraDynamica®, the supplement we introduce in more detail in Chapter 7, will provide a

† This pilot study enrolled 8 patients who received 2 treatments at 6-month interval and a 5-year follow-up. This method also allowed for decreasing the infrared laser power to as low as a minimally damaging 1W. With the pulsed regimen, the PDT light dose was lowered by twofold compared to the continuous one, and the effect of the treatment was kept the same. Coupled red and infrared illumination in a pulse mode in one fiber in a painless low-power regime was more effective than single-wavelength therapies even at higher doses.

very practical way for people in these situations to help stay cancer-free for life.

Now that we've shared with you the better-known applications of PDT, we turn our attention to the big picture. In the next chapter, we'll explain the overall rationale for photodynamic cancer treatment. We'll explain how PDT could be used to supplant surgery in some situations, and how photodynamic principles can be applied to enhancing the anti-cancer immune defenses in such a way as to help patients prevent and overcome the deadly scourge of metastatic cancer.

CHAPTER 3

Shining a Light On Cancer

We fear cancer more than any other medical condition. For many people, the diagnosis is synonymous with death itself. It evokes feelings of hopelessness and helplessness, often intermingled with panic, terror, and paralysis. The fear seems totally justified given the dismal statistics on surviving metastatic cancers and the devastating effects that cancer and its treatments can have on one's physical and emotional well-being.

Of course, the disease we call cancer does have some inherently frightening aspects, beginning with a propensity to steal away life. Cancer is a major cause of death worldwide. At this writing, it accounts for nearly eight million deaths annually, according to the World Health Organization. Among all cancers, those of the lung, breast, stomach, liver, and colon are thought to cause the most deaths per year. Based on current projections, an estimated nine million people will die annually from cancer in 2015, and about 13 million cancer deaths are predicted to occur each year by 2030.

One of the hallmarks of malignant cells is their penchant for multiplying in an out-of-control fashion, without the normal regulatory controls that keep healthy cells from proliferating on and on. Two other hallmarks are the potential to invade other tissues and spread beyond the tumor—which is to say, invasion and metastasis, respectively. The latter process, metastasis, accounts for most cancer-related deaths.

According to mainstream oncology, cancer cells arise from mutations within normal cells that originate in our own normal tissues. The mutated cells were once an orderly part of the body politic, but at some

point they went renegade. As they continued to mutate, their behavior became more erratic, chaotic, and aggressive. Eventually their sheer numbers and strategic locations began to sap the body's energy and interfere with normal functioning.

Though we tend to think of cancer as a single entity, in fact there are over 200 distinct types of cancer. These diseases vary greatly in their potential for causing harm. Some cancers have a strong proclivity for spreading to distant parts of the body, making them especially dangerous and often lethal. Other cancers are less life-threatening for the simple reason that the cells do not multiply rapidly, nor do they spread throughout the body. Those types of cancer are far more likely to be cured with single treatments, such as surgical removal of the tumor.

In a best-case scenario, cancer is identified very early on in its development. Oncologists consider these early-stage cancers to be easiest to treat, resulting in a "cure" in the majority of cases. The thinking is that the sooner we can detect the disease, the better our chances will be of clearing it from the body. As you'll see shortly, however, the way we choose to clear it from the body is equally critical for the long term.

Unfortunately, many cancers are discovered too late—at a point when they've already become too aggressive. The treatments chosen in these cases are often drastic and have severe toxic side effects. Though life may be prolonged, late-stage cancers often gain the upper hand, and treatment ultimately proves powerless against the disease.

Our purpose in writing this chapter is to lay out the broader argument for using PDT and immuno-PDT in the context of cancer medicine. We will explain why these light-based therapies make sense, both biologically and medically. Knowing that you have effective tools available to potentially eradicate the disease can afford some measure of hope and peace as you move forward to meet the challenge.

Putting the Disease in Context: Cancer as a Natural Process

Cancer, a byproduct of mutations, has been a fact of life long before we humans began roaming the planet. In fact, researchers discovered in the late 1990s that cancer existed as far back as the Jurassic period, in the age of the dinosaurs. In studies conducted at Northeastern Ohio Universities College of Medicine (USA), tumors in dinosaurs were found to be very similar to those found in human patients, indicating that cancer has been around long before the arrival of humans. The first report of metastatic tumors in dinosaurs was published in a 1999 issue of the British medical journal, *The Lancet*.[67] The most common cancers found in dinosaurs were benign blood vessel tumors known as hemangiomas; these are present in about 10 percent of humans.[68]

Written records concerning cancer date back to ancient Egypt, but it's quite likely that malignant diseases have always been with us. According to one hypothesis, the earliest use of fire by our human ancestors nearly one million years ago led to smoke inhalation that helped spawn the first wave of lung cancers.[69] Whatever the case, cancer is certainly an old story, albeit far more common these days, thanks in large part to widespread pollution and unhealthy dietary and lifestyle habits.

You may be asking yourself, why should we be interested in the ancient origins of this terrible disease? One reason is to convey the idea that, however cruel its manifestations can be, cancer is a natural process arising from mutations or damage to the DNA. Such damage, too, may have been with us for millenia due to natural background radiation levels and natural carcinogens.† As an aside, this would help explain why cancer increases as a function of the aging process: As people grow older, their DNA damage increases while DNA repair mechanisms (and internal antioxidant power) decrease; these dual effects result in an ever greater risk of developing cancer.[70]

Some scientists have proposed, moreover, that cancer may be nature's way of selecting out individuals who have acquired too many mutations, thus essentially helping to save the species.[71] Though benign tumors and small amounts of cancer in the body reflect a low level of mutation, malignant tumors and a larger overall burden of the disease reflects a much higher degree of mutation.†† Natural selection could exploit cancer as a

† In the case of the dinosaurs, these mutations were traced to the consumption of carcinogenic substances naturally found in certain tree species (conifers).

†† By the way, another powerful protector of the gene pool is miscarriage, or spontaneous abortion, which prematurely ends one in every four pregnancies. This, too, is a way to select out individuals who may have acquired mutations that could be harmful to the next generation.

way to weed out those individuals who may have exceeded their mutation quota, thus lowering the risk to future generations.

So where does this idea of cancer as a natural process leave us? Over millions of years of evolution, the human body has acquired a great deal of biological intelligence and resilience. Adaptation, the ability to adjust to changing conditions, has largely enabled our survival as well as that of countless other organisms on the planet.

Following this line of biological reasoning, there is a distinct possibility that the formation of a tumor itself is a kind of adaptation—namely, the body's attempt to isolate or wall off the malignant cells and keep them from moving throughout the body. Alternatively, the tumor could be regarded as an organ-like structure in the body, a collection of anatomically discrete cells with well-defined functions, all of which interact with the body's biochemical environment.

Why would your body—primarily the immune system—attempt to isolate or contain the cancer? To begin with, cancer cells are very much like adolescent misfits, criminals or sociopaths. They behave in immature, selfish ways—for example, by continually siphoning off large amounts of glucose, the body's primary source of energy. At the same time, tumor cells are quite adept at generating pollution in the form of lactic acid and other toxins, as well as inflammatory chemicals and growth-stimulating factors that further bolster the tumor's aggressive behavior.

Initially, the immune system is able to contain the proliferating cancer cells. After the tumor has reached a certain size, however, certain immune cells often seem to switch allegiances and instead tend to support the tumor's growth. Macrophages—immune cells that are often described as the body's garbage collectors—can become inflammatory and tumor promoting, thus helping the disease become more aggressive.

It's almost as if the body has "decided" it's time to let nature take its course, and the immune system is no longer serving in a truly protective capacity. (As we'll see, however, it's also quite feasible to shift the macrophages into a tumor-killing mode, using targeted light-based therapy and other natural methods. We'll come back to this idea in a moment.)

How Surgery "Angers" Cancer

The oldest known use of surgery to treat cancer dates back to approximately 1600 BC in ancient Egypt. Of course, surgery today is far more humane than in those early days, thanks to the development of highly sophisticated surgical tools and procedures, as well as anesthesia, sterilization (antisepsis), and antibiotics. At first glance, the use of surgery to cut out an existing tumor, the most visible sign of cancer, seems like the most sensible-sounding strategy one could imagine, a prescription of unquestionable value, a logical first-line strategy that's even considered "curative" for many early-stage cancers (we'll return to this point shortly).

The truth is, cancer surgery's track record is not quite what you might think. Let's consider the case of breast cancer. From the early 1900s to the late 1970s, radical mastectomy was performed on virtually every woman who presented with breast cancer, regardless of the degree of disease severity at the time of diagnosis. This surgery involved complete removal of a breast and the underlying muscles, as well as the underarm lymph nodes. The surgery was not only disfiguring but caused profound pain, debility, and emotional distress. Other operations even more extensive than the radical mastectomy were also performed at the time. This vast, torturous experiment resulted in untold physical and emotional suffering for many thousands of women.

Despite all these surgical endeavors and the misery they created, 75 percent of node-positive patients (those with cancer in the lymph nodes) who underwent surgery later developed distant metastases and died from their disease. For those without visible cancer in the lymph nodes, 30 percent died despite the aggressive surgery.[72] Because of these dismal statistics, in the last four decades we've witnessed a steady decline in the extent of such surgery, with breast-conserving surgery (lumpectomy) becoming more popular.

Let's take a closer look at why surgery's effects on the disease process may be less than benevolent. We'll then explain why targeted light-based approaches offer the ideal solution to this problem.

First of all, we have to understand that by the time a tumor is discovered, it has already released some tumor cells into the circulation. Those cells have entered blood or lymphatic vessels, traveled and then

taken up residence elsewhere in the body—perhaps in the bones, brain or liver. These microscopic clusters of cancer cells, or *micrometastases*, are so small that they will not show up on any scans.

Second, those same micrometastases now enter into a quiescent phase called *dormancy*. This means that the cells are still multiplying, but they're also dying at about the same rate. Thanks to dormancy, the micrometastases remain silent and hidden from view. They may not pose any malignant threat or cause any symptoms for a very long time, possibly even decades.[73]

This brings us to the final and most controversial point: Surgical removal of the tumor can end the dormancy phase! During surgery, cancer cells as well as key immune cells are activated to release factors that stimulate the formation of new blood vessels. This process, known as *angiogenesis*, causes the micrometastases to grow and morph into full-blown metastases, thus setting up a potentially deadly disease situation.

Another means by which surgery can trigger the metastastic process is as a byproduct of the wound healing process. Wound healing involves angiogenesis, which again seems crucial to tumor growth. Fluids from wounds have growth-stimulating effects on tumor cells and have been shown to stimulate microscopic tumors even when the surgery itself did not involve removal of a tumor.[74]

Where does this bring us? It seems that the primary tumor exerts a controlling influence on the tumor cells that originated within it. If we think of the primary tumor as an organ-like structure, we can regard those distant clusters of cells, the micrometastases, as extensions of the tumor, which somehow keeps the metastases from growing or becoming active. To fully embrace this way of thinking, it may be helpful to remember that the tumor is not an alien entity, but rather a malformation originating in your own body's tissues.

Furthermore, this theory is supported by reams of scientific data showing that surgery can and does serve as a vehicle for speeding up the deadly process of metastasis. The earliest studies of this phenomenon began to appear about a century ago, with rodent experiments conducted in Europe.[75] This research showed that laboratory animals that received implanted tumors rarely showed any sign of metastases. However, these same animals frequently developed metastases if most of the primary implant was then surgically removed. In similar experiments, the metastases that arose in tumor-bearing animals after surgery were larger and more numerous compared to the control group, which did not undergo surgery.[76]

Scientific interest in this topic surged again in the 1970s and 1980s. In 1981, for example, Japanese researchers reported on animal experiments showing that surgical removal of the primary tumor frequently gave rise to visible metastases.[77] The following year, German biologists confirmed those findings and concluded that "surgical removal of the primary tumor either induced or markedly enhanced the outgrowth of macroscopic metastases."[78]

Since that time, the evidence has continued to mount in support of the tumor dormancy theory. These findings largely have gone unchallenged, suggesting that what was once a sure-fire way to treat cancer is open to serious scrutiny. Consider these very striking statements from some of the most recent scientific reports:

- "[Research suggests that] surgery to remove the primary tumor often awakens distant dormant micrometastases. Accordingly, over half of all relapses in breast cancer are accelerated in this manner." [*International Journal of Environmental Research & Public Health*, June 2009] [79]
- "It is well known that cancer surgery can actually promote the growth of some tumors by a variety of mechanisms. There are observational data suggesting that surgery *per se* can increase the risk of cancer among individuals without a history of clinical cancer." [*QJM*, September 2011] [80]
- "Many patients with solid tumors already have micrometastases at the time of detection and surgical removal of their primary tumors. Primary tumor resection is believed to stimulate angiogenesis, initiating the proliferation of latent micrometastases." [*Oncology*, November 8, 2011] [81]
- "[Research suggests that] surgical trauma can facilitate the metastatic spread of experimental tumors… Moreover, it seems that mechanisms through which the metastatic process can be enhanced include inflammation, angiogenesis, secretion of growth factors and immunosuppression." [*Anticancer Research*, March 2012] [82]

This last statement, excerpted from an article titled "Is surgical trauma prometastatic?", provides a nice snapshot of the "perfect storm" created by surgery in terms of its potential to fuel more aggressive cancer. First, surgery produces inflammation, a key condition for the growth and spread of cancer. Next, it stimulates the formation of new blood vessels (angiogenesis). The inflammatory process also entails the secretion of growth factors as part of the wound healing response after healthy tissues have been cut or damaged. By definition, of course, growth factors stimulate growth, including that of cancer. And finally, the immune system is often suppressed by surgery.

In recent years, a few clinical studies have also suggested that while surgical removal of the primary tumor does seem to improve the prognosis for some patients, it may also trigger and hasten the development of metastatic disease in others.[83] We also know that both before and especially during surgery for breast cancer patients, epithelial cells (shed from the tumor stroma) are released into the circulation. After even complete surgery of small tumors, these cells can remain in the circulation over long periods of time. Such cells may remain dormant but might settle and later grow into metastases, possibly years later.[84]

Interestingly, when a large tumor is removed, there's a much higher chance of having a sudden and dramatic exacerbation of the disease. In a recent clinical study of colon cancer, when laparoscopy (using a scope instead of opening the body) was compared to open abdominal surgery, tumor recurrence and mortality were significantly worse in those patients who underwent the latter surgery.[85] This suggests that more extensive tissue damage may help spur on the development of metastasis.

It could also be that larger tumors, and the surgeries involved to remove them, tend to directly suppress the immune system. Remember that it's partly the body's anti-cancer immunity that keeps those more remote clusters of malignant cells from growing and causing a relapse later on.

At this point, you may be wondering why surgery has been considered so successful and even "curative" for many cancer patients. Part of the reason is that the micrometastases may continue to stay dormant after surgery. In the interim, the patient is pronounced as "cured" for a simple mathematical reason: Being five years in remission is the official benchmark for a cure, at least in the United States and some European countries. However, the disease may come back again *after* five years, sometimes decades after the operation and *after* someone has been told they're cured.

Breast cancer, for example, can have an especially long dormancy period. Many of the recurrences that follow mastectomy, the standard surgery for breast cancer, tend to occur around eight years after the operation. Some breast cancers have recurred twenty or even thirty years after the surgery. When the cancer does come back, it's often more difficult to treat when compared to the original primary tumor.

So where does this leave us? Many cancer patients with solid tumors already have micrometastases by the time their tumor is detected and then removed. Surgical removal of the primary tumor is believed to stimulate the process of angiogenesis, which in turn serves as the primary stimulus for micrometastases to exit their "silent" or dormant state.

Now, it's very likely that your oncologist will react to this theory with vehement denial, perhaps even outrage. Such a reaction would be understandable, especially given that surgery has been the number one cancer treatment since the 19th century. Nonetheless, oncologists who reject this theory should be aware of the well-documented biological consequences of surgery. Moreover, just because the treatment has successfully eliminated the most visible manifestation of cancer—the tumor—this does not mean that its overall and long-range effects are entirely benign or desirable.

This idea of surgery-driven escape from dormancy is now widely accepted among cancer researchers. The theory is so compelling and well substantiated that many researchers have begun arguing vigorously for research on strategies that can inhibit angiogenesis after surgery.[86] But while this is considered to be a very rational approach, the results thus far have been disappointing, and the approach itself has yet to truly bear fruit.

Immuno-PDT: An Ideal Alternative to Cancer Surgery?

In Chapter 2, we explained that PDT is often a better option than surgery when it comes to certain skin cancers because the light-based approach will not damage the skin or other structures. Surgery, on the

other hand, can result in substantial morbidity, typically leaving the skin scarred and damaged. We also noted that PDT has better cosmetic results in the event of treating skin cancer and other skin conditions. But as we just saw in the preceding section, the argument that PDT is the ideal alternative to surgery goes far beyond the cosmetic level.

With targeted light-based methods (PDT, PIT, and laserthermia), you can accomplish the same outcome as that accomplished by surgery, yet still avoid all the problems that could potentially make surgery so problematic. The most important problem, of course, is the one we illuminated in the preceding section—that of "switching on" the latent micrometastases, so that the metastatic potential of the disease actually may increase in the wake of surgery.

When tumors are treated using PDT, PIT, or laserthermia, a process is set in motion that triggers the steady destruction of the cells within the tumor, primarily through various cell-death processes.† At the same time, the blood vessel supply to the tumor is greatly reduced, and consequently many tumor cells begin to die off through the process known as *necrosis*. Other tumor cells undergo a kind of programmed cell death or cell suicide (*apoptosis*), while still others die as a result of being broken down or "digested" by their own enzymes (*autophagy*). Of these three types of cell death, it is necrosis that is most critical to attracting the immune cells that will ultimately help eliminate the tumor. ††

Now, as a tumor starts to break down, it releases proteins called tumor antigens, which eventually are transported to cells of the immune system called dendritic cells. The dendritic cells take in these antigens, and then present the antigens to other parts of the immune system.

† It's a bit simplistic to say that they are simply being destroyed upon exposure to the light-based therapy. Many of the cancer cells are actually undergoing changes in their surface composition, or is called photomodification (photochemical modification).

†† This mix of different kinds of cell death is a unique aspect of PDT. It also helps explain how this form of treatment is able to activate the anti-cancer immune defenses even as it directly breaks down the tumor. When cancer cells die by apoptosis (the main form of cell death caused by high-dose chemotherapy and radiation treatment), they specifically block the immune responses. In contrast, however, cell death caused by necrosis (one of the main forms of cell death linked with PDT) promotes a short burst of inflammation and activates the innate immune response against any remaining cancer cells, including metastases.

This sets the stage for possibly alerting the entire immune system to the fact that cancer is present. But here's the fascinating part, and it's a point we touched on previously in this book: The dendritic cells will not carry out this essential role unless certain other factors, called "danger signals", are also present.

In Chapter 1, we explained how PDT creates the ideal conditions for releasing both the tumor antigens and the danger signals needed to make the immune system aggressively seek out and destroy cancer. Among the danger signals are the *heat shock proteins*, or HSPs (also mentioned in Chapter 1). These proteins are generated during PDT, and paradoxically they can increase the tumor's resistance to the treatment. At the same time, however, these HSPs are critical to helping the immune system perceive that cancer is present.

One of the most important HSPs is known as heat-shock protein 70 (HSP70), which is associated with a strong immune system response to cancer. According to Dr. Michael Hamblin and his colleagues at the Wellman Center for Photomedicine, HSP70 helps form a stable complex with tumor antigens inside the cancer cell. These antigens can then either be expressed at the surface of the cancer cells or are released from the dying necrotic cells to interact with the body's dendritic cells and macrophages. Those immune cells, in turn, help bring about a potent anti-tumor immune response.[87]

A rise in body temperature due to fever or hyperthermia treatment also will generate HSP70 and other danger signals. As mentioned previously, hyperthermia is an experimental cancer therapy that further enhances the effectiveness of PDT. In fact, much research has demonstrated a synergy between PDT and hyperthermia for brain tumors, colon cancer, osteosarcoma and other cancers that tend to be highly resistant to conventional treatments.[88]

In summary, even though PDT attacks the tumor directly, its more important effects may in fact be indirect—that is, educating the immune system to recognize and eliminate any microscopic clusters of cancer cells (micrometastases) that have moved to other parts of the body. Those clusters provide the seeds for growing metastases in the future. Particularly when PDT is combined with other immune-enhancing strategies, its overall effects are not limited to breaking down

the tumor, but also to controlling cancer that has spread to other parts of the body. By supporting this ability to purge the body of micrometastases, we can help prevent the progression of malignant disease to a more advanced and lethal form.

A Radical Proposition

Given the potentially adverse impact of surgery on micrometastases, an argument could be made for *not* doing surgery for all early-stage cancers, especially those that do not involve an aggressive tumor. Many breast and prostate tumors, for example, either remain dormant or regress on their own.† These tumors would never develop into an aggressive disease, and therefore many thousands of people go through unnecessary surgery every year because of screening practices that detect these tumors.[89]At the very least, it may be best to postpone surgery, and instead try the photodynamic and photo-immune methods, PDT, PIT and SYLT, which cause the slow yet inexorable destruction of the tumors we described in the preceding section.

Some tumors will need to be surgically removed for specific situations, such as brain cancer (see our discussion on fluorescence guided surgery for brain tumors in Chapter 4). Other tumors may benefit from the more gradual approach offered by PDT. One might reasonably speculate that if a tumor takes many years to develop, then we should be similarly slow and deliberate in its eradication. By gradually dissolving the tumor using immuno-PDT, or breaking it down with classical PDT, there may be a greater likelihood of totally eliminating the disease and achieving better long-term remissions.

Keep in mind that we are not by any means rejecting surgery as a treatment option. Surgery still plays a particularly critical role for cases involving large tumors (debulking, removing the bulk of the disease) or those in which a vital organ is being impinged upon, perhaps compromising one's ability to function normally. But there may be many situations for which PDT (as well as immuno-PDT, PIT, SYLT) may be sufficient, particularly given the fact that the treatment also harnesses the anti-cancer immune defenses even as it's breaking down the tumor. As we mentioned earlier, a salient focus of our light-based treatment approach to cancer focuses on "educating" or retraining the immune system so that a recurrence in the future is far less likely.

Again, it's important to keep in mind that PDT is unique among other approved therapeutic approaches in its ability to support anti-cancer immunity for the entire body.[90] This awareness has helped foster growing interest in two promising modalities based on PDT, notably photoimmunotherapy (PIT) and PDT-based cancer vaccines. Though the lion's share of scientific attention has focused on PDT, there is increasing research interest in these other forms of targeted light-based therapy and how they can complement PDT as well as other treatment approaches.

In the next chapter, we will unveil some of the more exciting applications of targeted light-based therapy for cancer, with a primary focus on PDT. As you will see, PDT for many of the more common cancers is increasingly supported by scientific research. Though some cancers have less impressive research support, they still show considerable promise based on preliminary studies and given the fact that the efficacy of conventional treatment options for many advanced cancers tend to be extremely limited.

† These tumors are also referred to as indolent, inactive, or clinically insignificant. There is a definite lack of conclusive data demonstrating a definitive mortality benefit from earlier diagnosis and treatment of both breast and prostate cancers. This fact is likely due to the treatment of a large proportion of indolent or dormant cancers that would have had little adverse impact on one's health or lifespan if left alone. According to most estimates, for example, between 30 and 50 percent of all breast cancer detected by mammography would never develop into an active or clinically significant disease.

CHAPTER 4

Lighting Up the Most Common Cancers

In the preceding chapter, we laid the groundwork for a new way of thinking about cancer and overcoming the disease. In this chapter, we'll explain how targeted light-based therapy can help you overcome some of the more prevalent forms of malignancy—namely cancers of the lung, prostate, breast, bladder, brain, colon, stomach, esophagus, liver, and pancreas. We'll also review some of the key evidence for using PDT for cancers that have responded poorly to conventional treatment alone, and we'll spotlight those areas in need of more rigorous clinical testing.

As you'll see, PDT has shown considerable promise against some rather dangerous diseases, such as inoperable cholangiocarcinoma, a rare cancer of the bile ducts inside the liver. For such conditions, as well as advanced cancers that have become resistant (refractory) to chemotherapy and other mainstream treatments, photodynamic treatment strategies represent a reasonable alternative that is increasingly supported by clinical evidence.

Throughout this chapter, we will emphasize that prevention is always the best medicine. If we can treat cancer in its earliest stages—and ideally that would mean intervening at the pre-cancerous stage, before it emerges as a serious threat—then we have a much better chance of turning the malignant tide and preventing a great deal of emotional distress, pain and suffering.

Lung Cancer

On a global scale, lung cancer is the most deadly of all cancers, responsible for at least three million deaths per year. Though the number of new cases has been declining among men, it continues to increase among women. In several western countries, lung cancer is the leading cause of cancer death in women—even surpassing breast cancer, ovarian cancer and uterine cancers combined. Based on recent statistics, about six out of ten people with lung cancer are projected to die within one year of being diagnosed with the disease, and approximately eight out of ten people will die within two years.

Lung cancer was one of the first indications for which PDT was tried back in the early 1980s. Initially, only patients with advanced inoperable cancer and major obstruction of the airways (bronchial passages) were given the light-based treatment, the primary goal being the relief of airway obstruction and easing of symptoms. In the past few decades, however, the scope of treatment has broadened, and many oncologists have come to accept PDT as a viable option for the treatment of several types of lung cancer.[91]

When it comes to lung cancer, PDT is mainly effective against malignancy that arises in the broncho-pulmonary area or central airways. This is also classified as bronchogenic carcinoma or central lung cancer. The results have been highly favorable for early-stage squamous-cell lung cancers in this central part of the lungs. A 2009 study of these patients found a complete response rate of 94 percent for those receiving PDT.[92] In eight out of every ten patients in this study, the disease had not progressed after five years. Another recent PDT study found exactly the same complete response rate for lung cancer lesions measuring 1.0 cm or less in diameter (94 percent), along with a 90 percent response rate for lesions measuring greater than 1.0 cm in diameter.[93]

So, when used on a stand-alone basis, PDT for central lung cancer may be most effective when treating early, superficial lesions—those involving the lining of the bronchi. Large tumors can also be treated, but only if they have been surgically "debulked" or reduced in mass prior to the PDT treatment.[94] Again, the reason for this is that the light can only penetrate so far into a bulky tumor.

Before going further, you may be wondering: How is light delivered during PDT for central lung cancer? Your thoracic surgeon will use a rigid scope to visualize the lung lesion while you're under general anesthesia. Once this is visualized, the surgeon feeds a flexible bronchoscope through the biopsy channel; inside this scope is a PDT fiberoptic. (In contrast, a pulmonologist might use a flexible bronchoscope under conscious sedation to visualize and then treat the lesion.)

Once the fiberoptic is in position, various types of illumination diffusor—located at the end of the fiberoptic—are used to expose the tumor or lesion to the required light duration and intensity. By increasing the length of the diffusor, longer lung lesions can be treated. Bulky lesions need to be treated several times because the light may not penetrate more than one centimeter; or the fiber may need to be inserted directly within the lesion in order to deliver light to the target tissue.

It's important to understand that the actual treatment process is done under constant, direct visualization. That is, your physician uses the bronchoscope to actually *see* what he or she is treating because the tumor or lesion is glowing, thanks once again to the interaction between light and the photosensitizer. An appropriate laser light is then delivered through the bronchoscope, and the resulting light and chemical interaction results in the death of the tumor. This see-and-treat approach greatly increases the accuracy of bronchoscopic PDT.

PDT seems to work best when integrated into a comprehensive treatment regimen that includes surgery and possibly other conventional treatments such as chemotherapy, stenting and laserthermia. This will be up to the judgment of your oncologist, who would need to have a good working understanding of PDT principles and strategies.

Now, your oncologist may argue that surgery is a better option for most lung cancer cases—including early-stage central lung cancer patients. However, this argument is not entirely on track. To begin with, the long-term survival of patients who receive PDT is only slightly inferior to that achieved by surgery. Moreover, keep in mind that the vast majority of these lung cancer patients who are referred to PDT are not suitable for surgery. This is partly because they have multiple lung spots or lesions, not just a single lesion.[95] There are also more technical reasons related to the research itself, but the basic point is that comparing survival outcomes for surgery versus PDT is like comparing apples and oranges.†

So there's little doubt that bronchosopic PDT can play a major role in the treatment of these early-stage cases. And in the event that the patient is unable to undergo surgery, PDT's value could be even more pronounced. This is because, compared with the other standard treatment options (chemotherapy and radiotherapy), PDT is better able to target specific lung lesions and incurs far less damage to normal tissues. This results in fewer complications and a better overall quality of life. Also, PDT treatments can be given repeatedly without causing harm.

Finally, there does not appear to be any cross-resistance between PDT and chemotherapy.[96] The term *cross-resistance* refers to resistance to one cancer treatment that confers resistance to another treatment; this often happens between chemotherapy drugs, and can even happen between chemotherapy and radiotherapy.[97] In fact, PDT has been shown to increase the efficacy of chemotherapy against lung cancer and other cancers as well. In a study of lung cancer cells, researchers in Naples (Italy) compared the effects of either PDT or chemotherapy to a combination of the two treatments. They found that PDT enhanced the effectiveness of the chemotherapy drugs, cisplatin and gemcitabine (also known as Gemzar). In the case of cisplatin, the proper timing of PDT allowed a lower dose of cisplatin without diminishing the cancer-killing impact of the treatment.[98]

When PDT is compared to YAG laser therapy (laserthermia) for the treatment of non-small cell lung cancer, the two treatments show equal efficacy, but the remissions last longer with PDT.[99] As noted above, however, PDT can also be combined with laserthermia for a stronger effect.

In a clinical trial in Germany, patients with central lung cancer were treated using a combination of PDT and radiation (brachytherapy). Six weeks after PDT, the radiation treatment was given. After an average follow-up time of two years, 26 or the 32 patients were still free of residual tumor and local recurrence. The remaining six patients

† Another key research difference: Whereas in most surgical series, the survival results are matched to pathological staging, in bronchoscopic PDT the staging is entirely clinical. This should bias the results toward more favorable survival for surgical patients.

received a second treatment with PDT, YAG laser coagulation, or radiotherapy, and two of those patients developed metastases of the lung and lymph nodes. All 32 patients were still alive and well at the time of the report, and only four patients had evidence of lung cancer. None had developed any severe complications. The researchers concluded that the combination of PDT and brachytherapy for treating patients with lung cancer is safe and may have superb therapeutic efficacy.[100]

In general, PDT by itself is only effective for the treatment of smaller lung tumors—that is, smaller than 10 millimeters in diameter. When larger than this critical size, the treatment response rate for PDT falls from 98 percent to 43 percent. Underestimating the extent of the tumor burden (for example, if there is invasive cancer or spreading of the disease) and then under treating the disease have been identified as major reasons for the failure of PDT in lung cancer.

In our experience, the combination of PDT and radiotherapy is more effective against larger tumors. Both cell culture studies and animal studies have shown a possible synergistic effect of combining PDT with radiotherapy.[101] This combination does not raise the risk of complications. Also, a combination of PDT and radiotherapy results in the bronchus remaining open longer (not re-occluding) when compared to radiotherapy alone.[102] This means that PDT tends to make radiation treatments more bearable.

Other advantages of PDT in the context of lung cancer are as follows:

- The treatment has far fewer side effects when compared to more conventional treatments for lung cancer, e.g., surgery, external beam radiation therapy, or endobronchial brachytherapy.
- PDT is typically provided on an outpatient basis, which provides more scheduling flexibility and helps keep treatment costs down.
- Lung cancer patients can be retreated with PDT if they have an incomplete treatment response or a recurrence following treatment.
- PDT does not limit or compromise future therapeutic options in the event that additional treatments become necessary.
- Cancer mutations that result in resistance to chemotherapy or radiation treatment do not limit the efficacy of PDT. This is very important, because such treatment resistance is among the main reasons chemotherapy and radiotherapy tend to fail against advanced lung cancers.
- For early-stage lung cancer, PDT is used to treat the inside of the bronchial passages and to definitively treat occult tumors—those patches of cancer that are too small to be seen and thus need to be "illuminated" with the help of a photosensitizer.
- Individuals diagnosed with multiple primary lung tumors may be effectively treated with PDT; however, for advanced-stage or metastatic disease, PDT is typically used to ease symptoms in patients with lesions that are obstructing the airways.
- Those with advanced lung cancer may be treated with PDT in an attempt to boost the chances of successful surgery afterward, or to reduce the extent of surgery required.
- Finally, patients with pleural spread of non-small cell lung cancer may also be treated with PDT following surgical removal of the primary tumor or tumors.

Non-small cell lung cancer that has spread to the pleura is considered to be incurable using the standard trio of surgery, chemotherapy, and radiotherapy. Surgery alone has been unsuccessful and does not prolong survival beyond that obtained with standard chemotherapy. Studies at Tokyo Medical University in the late 1990s showed that giving PDT before surgery could significantly improve the outcome for advanced lung cancer patients with evidence of pleural disease.[103]

In a recent study, PDT given prior to surgery achieved the control of advanced and recurrent pleural disease at six months in 73 percent of patients, and the median overall survival for all patients was close to 22 months.[104] These findings are impressive, particularly given that patients with this form of advanced lung cancer have a median survival of only six to nine months after undergoing conventional treatment.

To summarize, using PDT as an adjunctive approach—that is, complementing surgery or other mainstream treatments—should be viewed as a very promising treatment strategy for lung cancer. In some cases it may even be used on a stand-alone basis, depending on the size and loca-

tion of the tumor. The use of PDT alone is suitable for smaller tumors, while larger or invasive tumors would require combination treatments.

In Chapter 7, we will introduce you to Bremachlorin®, a new second-generation photosensitizer derived from chlorophyll. This drug already has begun to show excellent results against central lung cancer. We have documented superb clinical responses with this drug used in PDT[105] and PIT[106] for central lung cancer. We've also observed exceptional treatment responses even with thick nodular lesions, up to about one centimeter in depth. This is very significant, since most other PDT drugs are ineffective against thick nodular lesions in the lungs.

PDT FOR LUNG CANCER:
Understanding the Risks

Conventional cancer treatments have a rather unsavory reputation due to the complications and side effects that often accompany these treatments. For example, surgery can result in pain, fatigue, infections and limited mobility. Radiotherapy can severely burn the skin, kill nerves, and weaken the body. Chemotherapy can do a number on your brain, heart, and digestive systems, to cite just a few examples of treatment-related morbidity. And all three types of treatment tend to weaken immunity.

In contrast, PDT bolsters the body's anticancer immune defenses and results in far fewer side effects when compared to the conventional treatment trio mentioned above. But this doesn't mean that PDT has no downside. If you receive an intravenous dose of the photosensitizer, you're likely to develop some degree of skin photosensitivity—that is, your skin becomes quite sensitive to light. If you go out in the sun after you've received the infusion, you're likely to contract a bothersome or even severe sunburn.

Most of these skin reactions are mild and easily tolerated. Your physician or PDT specialist will let you know how long you should avoid going out in the sun. This will vary from a few hours to a few months, depending on the photosensitizer and dosage. By simply not going out in the sun for the allotted time, you can avoid any uncomfortable skin reactions. But if you don't feel that you can respect the light restriction rule, then you shouldn't undergo PDT.

Although the PDT treatment itself is generally painless, you will be under some form of anesthesia in order to undergo the bronchoscopy. Having a tube inserted in your mouth and then passed down your throat can be extremely uncomfortable! Fortunately, the light treatment or illumination period for each central lung lesion is only about 10 to 20 minutes, which means that prolonged anesthesia is unnecessary.

Another point is that the intense treatment light used in PDT can damage your eyes, so care must be taken to avoid any direct exposure to those delicate light-receiving structures. During the treatment, you and your caregivers will be wearing appropriate shielding with specially designed goggles. This is a requirement for anyone who happens to be in the room during your PDT session.

When the PDT removes the lung lesions, it creates a wound that will heal. Usually, in this process, the tumor and surrounding normal tissue will slough off, and sometimes this can lead to a blockage in the bronchial tubes. Your physician should therefore repeat the bronchoscopy two to four days after PDT to ensure that the passages are clear.

After the treatment, removal of dead (necrotic) tissue is essential and can be helped by further stimulating the immune system, in particular those immune cells known as the macrophages. This is a natural effect of both PDT and PIT. A follow-up PDT treatment may be indicated in some cases if some evidence of lung lesions remains.

Mesothelioma

Asbestos is an industrial mineral that became increasingly popular among builders in the late 19th century mainly because of its low cost and impressive resistance to fire, heat, and chemical damage. Unfortunately, prolonged inhalation of asbestos fibers can cause cancer and other serious illnesses, and thus asbestos usage has been banned in most developed countries. The European Union has banned all use of asbestos, while the United States has only banned certain asbestos-con-

taining products. In many developing countries, asbestos use continues at a steady clip, and many countries are now experiencing an epidemic of asbestos-related diseases. China is the world's top asbestos consumer, followed by India. Millions of people may be occupationally exposed throughout the year in both countries.

The two most feared risks of asbestos exposure are the malignant conditions, mesothelioma and lung cancer. Mesothelioma develops in the lung and is mainly caused by exposure to asbestos particles. It develops from mutated cells originating within the mesothelium, the protective lining that covers many of the internal organs of the body. The most common site for the development of mesothelioma is the pleura, a thin double-layered membrane structure that covers the surface of the lung. Between the two pleural layers is a thin space known as the pleural cavity. Most cases of mesothelioma arise from the mesothelial surfaces of the pleural cavity and are therefore known as *malignant pleural mesothelioma* (MPM).

MPM has a very grim prognosis, similar to the advanced forms of lung cancer we alluded to earlier. If you choose to go without treatment after a diagnosis of MPM, your oncologist may inform you that the median survival is six to nine months, and your chances of surviving up to five years is less than five percent. Of course, statistics are not predictions etched in stone, but rather abstract probabilities; the actual survival outcome will depend on individual factors such as the cancer's stage at the time of diagnosis, the cell's histology or extent of "mutatedness", your body's ability to respond to the disease, and of course, how effective your particular treatment regimen will be.

Because MPM is considered "incurable" from the conventional standpoint, there is an obvious need to explore reasonable alternatives and to develop innovative treatment strategies. We believe PDT is just such an alternative. PDT using the photosensitizer, Photofrin, has been tested as a treatment that is used during surgery in several countries. Clinical research suggests that this approach offers a good survival advantage for early-stage MPM (stage I or II).[107] Though PDT is less effective for patients with stage III or IV disease, it still appears to be superior to using surgery alone.[108]

Moreover, PDT outcomes in these patients could be further improved with the help of an increased oxygen supply, since hyperoxygenation has been shown to enhance the cancer-killing effects of PDT.[109] Therefore, for advanced-stage patients in particular, PDT should be given during hyperbaric oxygen treatment (breathing in oxygen under high atmospheric pressure) to help amplify the therapeutic effects.[110] For patients with locally advanced MPM, the best hope may be to first undergo surgery—or more technically speaking, lung-sparing surgical debulking—and then use PDT during hyperbaric therapy.[111]

Brain Cancer (Glioma, Glioblastoma)

Brain cancer is another potentially lethal form of cancer, though it is not very common. Worldwide, about 238,000 new cases of brain and other central nervous system (CNS) tumors were diagnosed in the year 2008, resulting in an estimated 175,000 deaths. The incidence of primary brain tumors is higher in whites compared to blacks. Brain tumors that occur in childhood behave much less aggressively than from those that happen in adulthood. Death rates from brain cancer are higher in men than in women, and older people in general are more likely to get the disease.

Malignant brain tumors, or gliomas, include high-grade glioblastoma multiforme (GBM) and anaplastic gliomas. These tumors usually come with a lethal prognosis. When treating primary GBM, the conventional treatment trio of surgery, chemotherapy and radiotherapy results in a median survival of 15 months, whereas for recurrent or high-grade GBM (WHO grade IV), the median survival is only three months. Fewer than one in four patients will survive two years, and the five-year survival rate is a mere 1 percent. With such dismal odds, it's no wonder that many patients are looking for reasonable alternatives to the conventional approach.

Now, from the conventional standpoint, surgery is considered to be the most critical step for effectively treating malignant gliomas. However, full surgical removal of the tumor is technically impossible due to the tumor's spread into normal brain tissue. Also, 95 percent of recurrences occur locally or very close to the initial site of the original tumor.

For these reasons, PDT would seem to hold some obvious appeal. This approach has undergone a great deal of investigation as an option for patients with aggressive brain tumors. The research has clearly demonstrated two key points. First, photosensitizers will accumulate to a much higher extent in the cancerous brain tissue than in normal brain tissue (glowing red upon exposure to light); and second, PDT causes selective destruction of the malignant tumor while sparing the normal brain tissues.

Neurosurgeons have begun to rely on photodynamic technology as a way to help guide their treatment decisions and to see how much cancer is actually present. This approach is used during surgery to allow a "real-time" assessment of the brain's condition, so that the surgeon can actually tell normal from malignant tissues. This is technically referred to as intraoperative photodynamic diagnosis. Once the cancerous tissue is illuminated, the surgeon can then perform either partial surgery or PDT, or both.

The concurrent use of PDT during the photodynamic diagnosis offers a logical and efficient way to completely eliminate the cancerous tissue from the brain. In other words, it simply makes sense to carry out PDT once the brain tissues have been illuminated, hence the slogan favored by many photodynamic medical experts, "to see and to treat". If the tumor is very large, then partial surgery can also be done at that time, allowing PDT to get rid of any remaining malignant tissue.

A number of clinical trials—mostly uncontrolled or non-randomized studies—have focused on using PDT in patients with the advanced high-grade brain tumor known as glioblastoma multiforme (GBM).† This extremely aggressive brain tumor has a very poor prognosis, mainly due to its strong propensity for recurrence or relapse. In fact, the recurrence of GBM is thought to be both inevitable and fatal. Surgery is rarely curative, and radiotherapy has had little if any impact on survival. Overall, the five-year survival rate is less than 10 percent, with an ultimate mortality rate of nearly 100 percent.

† Using criteria established by the World Health Organization, glioblastoma multiforme is a WHO Grade IV tumor that represents 15 to 20 percent of all primary intracranial tumors.

Several randomized clinical trials have sought to test the possibility that fluorescence-guided surgery (i.e., using a photosensitizer to help reveal the cancerous tissue during surgery) and repetitive PDT treatments could be an effective strategy for advanced, recurrent GBM cases. Two earlier randomized clinical trials showed that the approach slowed the progression of malignant disease in these patients but did not significantly improve survival.† In one of these earlier studies, 18 clinics in Germany enrolled patients with advanced, recurrent GBM, including those cases considered to be inoperable.[112] This study compared patients who received the fluorescence-guided surgery and repeated PDT to patients receiving only white light treatment (the control group). After six months, 41 percent of the PDT group was still free of relapse, compared to only 21 percent of the control group.

A 2008 randomized clinical trial of advanced, recurrent GBM patients again focused on the innovative PDT approach described above.[113] This clinical trial demonstrated a statistically significant survival advantage in patients receiving PDT compared to surgery alone. The average survival for the intervention group was more than double the control group—that is, 53 weeks survival for PDT-treated patients compared to about 25 weeks in the group receiving conventional surgery. In addition, the PDT group had a superior quality of life, based on the Karnofsky performance assessment. This study provides some intriguing evidence of a considerable survival advantage for people diagnosed with this very deadly form of brain cancer. Nevertheless, a large multi-center clinical trial is now needed to more comprehensively test the efficacy of this approach.

One way to evaluate the evidence from the clinical trial research completed to date is to pool the various studies' findings together in an approach known as meta-analysis. According to a recent meta-analysis, the median survival after PDT for primary GBM was 22 months versus 15 months for conventional treatment.[114] The same meta-analysis found that the median survival after PDT for recurrent GBM was 9 months versus only 3 months for standard conventional treatment. Fluorescence-guided surgery in these cases also led to a significantly greater reduction of tumor burden and fewer relapses.

† The researchers attributed the lack of a survival effect to variability in the management of recurrent tumors and significant residual tumor cells left over after fluorescence-guided surgery in about one-third of the patients, who then had a relapse.

A combination of PDT and fluorescence-guided surgery may be regarded as the neurosurgeon's best option for treating infiltrating high-grade gliomas—those aggressive brain tumors that have begun to move more deeply into the brain.[115] Pituitary tumors, skull base tumors, cystic lesions at the skull base, spinal tumors and metastatic lesions (for example, metastasis of the vertebrae) are also good indications for using PDT, at least as a second-line therapy. The use of this treatment for brain metastases offers a compelling choice for patients with malignant melanoma, colon cancer, breast cancer and other malignancies that may spread to the brain.[116] Compared to surgery, there is a considerable delay in relapse for brain cancer patients who undergo PDT, and the need for invasive or toxic interventions is greatly reduced.[117]

In summary, at least two well-designed clinical trials indicate a benefit for the GBM patients treated with PDT. According to a report in the 1 October 2012 *Journal of the National Comprehensive Cancer Network*, however, PDT offers a promising treatment option, and clearly more studies are warranted.[118] With no clear standard of care for advanced, high-grade brain tumors, there is reason to believe that the innovative PDT strategy described in this section could emerge as the treatment of choice in the years ahead. The combined use of PDT with fluorescence-guided surgery allows your physician to treat exactly what they see during the operation—and to see much more than ever before. This versatile approach increases the probability of a complete remission, reduced risk of relapse, and better overall survival and quality of life for patients with both newly diagnosed and recurrent brain tumors.

Head and Neck Tumors

Head and neck cancers mainly involve those that affect the mouth (oral) and throat (pharyns and larynx). These are primarily squamous cell carcinomas, which we discussed in a preceding section. Let's start with the mouth. We know that oral cancer is highly treatable with PDT. A recent clinical trial in London concluded that up to three rounds of PDT resulted in outcomes comparable to those of conventional treatment.[119] Although multiple rounds of the light-based treatment are needed, the side effects are much less than those observed with the three conventional treatments—surgery, radiotherapy, and chemotherapy.

Let's take a look at a few examples from published studies of head and neck cancers. In a clinical case series study of 133 patients with primary or recurrent laryngeal carcinomas (cancers of the larynx, or voicebox), a single PDT treatment led to a 90 percent cure rate after five years. The researchers also observed a second group of 138 patients who had undergone PDT for oral cancer; they reported that all these patients achieved complete clinical responses and were still clear of oral cancer after five years. For patients with more advanced-stage oral cancer, a single PDT treatment again led to complete remission, with a 100 percent cure rate after three years of observation.[120]

Throughout the world, hundreds of individuals with early-stage cancers of the larynx, pharynx, nasopharynx, and oral cavity have been treated with PDT—all with similarly impressive and well-documented results.[121] The chances of having a recurrence are extremely low. If a recurrence does happen, it can be successfully treated with either repeat PDT or surgery. Complications observed in these cases were typically related to sunburn and any pain associated with the therapy was easily controlled with the help of pain-killer medication.

When it comes to treating head and neck tumors, PDT shows some major advantages over conventional treatment—beginning with the ability to help preserve the normal tissue as well as the vital functions of speech and swallowing.[122] More direct treatment advantages are also coming to light. In one small clinical trial, patients with nasopharyngeal carcinoma were randomly assigned to receive either PDT or chemotherapy (5-FU and cisplatin, both very commonly used chemo drugs). The clinical response was significantly better with PDT than with chemotherapy, and PDT also resulted in better quality of life and physical functioning.[123]

Our experience and that of many doctors who use PDT is that the therapy represents an effective first-line treatment for patients with early head and neck tumors. For patients with more advanced-stage situations, it's a reasonable experimental treatment to consider. Let's look at the findings of a clinical trial in which 128 patients with advanced head and neck cancer had either not responded to conventional treatment or were unsuitable for such treatment. These patients underwent a single PDT session, with the light treatment delivered four days after admin-

istration of the photosensitizer, called temoporfin. In 43 percent of the lesions, PDT resulted in complete elimination of the tumor; the remaining lesions were reduced in size by at least 50 percent. At the same time, more than half the patients reported significant improvements in their quality of life.[124]

These findings are quite striking, given that the head-and-neck cancer patients who participated were labeled "incurable". Other studies might well have labeled these same patients "terminal" instead, the implication being that they would surely die from the disease, despite any treatments used. Because of the poor track record of conventional cancer treatments for patients with advanced cancers, it is understandable that patients would seek out reasonable alternatives such as PDT and other targeted light-based therapies. As research continues to accumulate, we expect these treatment options to continue garnering more and more attention from both the medical community and general public.

There is, however, an important caveat about the study just mentioned. For the study population as a whole, the complete response rate was only 13 percent (based on World Health Organization criteria). However, this figure jumped to 30 percent when the tumor was no deeper than 1 centimeter and when the total surface area of the tumor could be visibly "lit up" or illuminated by the laser. Other smaller studies of patients with advanced head and neck cancers have reported less impressive results.[125]

Many cases of head and neck cancer are actually classified as "second tumors", meaning that the tumors were found after an entirely different cancer had been treated. Other cases involve *multiple primaries*—that is tumors that are diagnosed for the first time, all located in the head and neck region. In general, the cure rate for PDT when treating second or multiple primary head and neck tumors is probably about twice as high for patients with early-stage disease (stage I or *in situ*) than for those with advanced-stage disease (stage II/III).[126]

The ideal approach to head and neck cancer may involve combining PDT with other innovative treatment strategies, as well as with nutritional and herbal approaches, including some of the strategies we discuss in Chapter 6.

Esophageal Cancer and Barrett's Esophagus

The esophagus is your gullet, the tube that carries food from your mouth to your stomach. Sometimes cells along the esophagus can mutate and develop into cancer. Esophageal cancer, technically known as *esophageal adenocarcinoma*, is a deadly disease that has attracted much attention in the past few decades because of the rapid increase in its incidence. Between 1976 and 1990, for example, the incidence of this cancer in the United States actually tripled. It continues to be among the fastest increasing cancer types in the U.S. and in several European countries, including the United Kingdom.[127] The incidence of this deadly cancer is still on the rise.

Esophageal cancer is partly caused by smoking and drinking alcohol. Nitrosamines in meats and certain nutrient deficiencies also are thought to play a role. There are basically two types: squamous cell and adenocarcinoma. Tumors that develop in the top part of the esophagus are mostly of the squamous cell type and account for about 60 percent of esophageal cancer cases. Those that occur in the lower part tend to be adenocarcinomas. In this section, we focus mainly on the latter, as well as on the conditions that seem to promote esophageal cancer.

Recent improvements in surgical techniques as well as in chemotherapy and radiation approaches have boosted the survival of patients with early-stage esophageal cancer. Despite this progress, however, patients with advanced forms of the disease still fare very poorly. In many cases, the cancer is detected too late and is considered "terminal" or incurable. Conventional treatment for this more advanced-stage disease is directed at reducing symptoms and perhaps slowing the spread of the disease.

Barrett's esophagus is a major risk factor for developing esophageal cancer. This is a condition in which the squamous cell lining of the esophagus is replaced by an intestinal-type lining with mucus-secreting cells. Barrett's esophagus is considered to be a precursor to cancer, which means that if you leave it untreated, you run a much higher chance of developing esophageal cancer down the road. Indeed, the evolution of esophageal cancer among patients with Barrett's esophagus seems to follow a well-studied pathway that goes first to low-grade dysplasia, then

to high-grade dysplasia, and finally to esophageal adenocarcinoma—the most dangerous manifestation.†

Once again, prevention may be the best medicine. We now know that gastro-esophageal reflux disease (GERD), more commonly known as "acid reflux", is the main risk factor for the development of Barrett's esophagus. You can take steps to stop or reverse a GERD situation by eating meals in smaller portion sizes, supporting healthier stomach acid production, and using dietary and herbal methods to improve overall digestion and stomach health. You can further lower your risk of esophageal cancer by avoiding alcohol, tobacco smoke, and cured meats that contain nitrosamines (e.g., bacon and sausages).

Two additional strategies would involve using PDT to directly eliminate Barrett's esophagus and to eliminate any dysplasia (pre-cancerous tissue) in the esophagus. Because the esophagus is a hollow structure, its lining can be readily accessed by light treatment. The PDT procedure is facilitated by an endoscope, a flexible scope that allows you to peer down the esophagus and take biopsies of anything that appears suspicious. This makes PDT a breeze, because the physician can actually see what it is he or she is treating.

At this time, Barrett's esophagus is among the best-studied PDT applications in the digestive tract. Let's take a look at how effective PDT has been in treating this condition as well as the precancerous disease (dysplasia) and esophageal cancer itself.

Historically, the standard treatment for Barrett's esophagus was surgical removal of the bottom part of the esophagus, a procedure surgeons refer to as *distal esophagectomy*. Nevertheless, the surgery carries a number of potential complications that can seriously detract from one's quality of life. For these reasons, PDT has become an attractive treatment option for patients with Barrett's esophagus—especially for those wishing to avoid surgery, those considered "high risk" or not well-suited for surgery, and those in whom other forms of treatment previously have failed.[128]

Conventional surgery for esophageal cancer has resulted in plenty of complications—including heart problems, postoperative bleeding, anastomotic leakage (leakage in the sutured area following the surgery),

† If you have dysplasia, your physician will want to determine whether it's a low-, intermediate-, or high-grade situation. If it's high grade, this means that the cells are more mutated and thus more likely to develop into esophageal cancer.

breathing complications, and even death in about one in twenty cases. Older age and receiving chemotherapy or radiotherapy prior to the surgery both tend to heighten the risk of surgery-related complications. It's important to recognize that these complications *per se* tend to worsen the prognosis following the operation.

In our clinical research, esophageal cancer was successfully treated by Dr. Victor Sokolov using a number of photosensitizers including Radachlorin®.[129] PDT was performed in 48 esophageal cancer patients (total 48 lesions) from 1992 to 2006. Complete regressions were observed in 77 percent of esophageal cancer lesions, and partial regressions in 23 percent. The follow-up period was up to 11 years. Median survival was 4.59 years.

Once again, the avoidance of such complications makes PDT an especially attractive option for patients with esophageal cancer. A number of randomized clinical trials have evaluated PDT in patients with Barrett's esophagus who also had either high-grade dysplasia or superficial esophageal cancer (cancer on the outer layers of esophageal tissue, readily accessible to light treatment). In another clinical trial involving 102 patients, complete removal of the dysplasia or carcinoma was accomplished after just one course of PDT in over half the patients (56 percent).[130]

Those patients not included in this complete response tally still had the option of surgery afterward. When PDT failed to remove the dysplasia or carcinoma, subsequent surgery was successful in three out of four cases. It seems quite plausible that the targeted light treatment helped set the stage for surgical success in these cases because it would have reduced the overall tumor burden, the bulk of the disease.

Despite these favorable results, some untoward effects of PDT also bear mentioning. In particular, a narrowing or constriction of the esophagus—which then required dilation or widening of the canal—occurred in about one in every five patients. This unfortunate event, known as a *stricture*, is the most serious complication of PDT in these cases.† In addition, as noted previously, patients may experience pro-

† It is not known why strictures can form after PDT. One theory is that the deep tissue injury achieved by PDT leads to an aggressive fibrotic response that leads to the stricture. Risk factors for developing strictures include having an endoscopic mucosal resection before PDT, more than one PDT application during a treatment session, and a history of previous esophageal stricture.

longed photosensitivity reactions when they go out in the sunlight. Nevertheless, the researchers concluded that PDT is a safe and highly effective first-line treatment for patients with Barrett's dysplasia and superficial esophageal cancer.

A long-term clinical trial involved 62 patients with esophageal cancer who were treated with PDT. The complete response rate after PDT alone was 37 percent, compared to 82 percent for PDT plus radiotherapy. As expected, the complete response rate for PDT alone was nearly twice as high in the small-lesion patients compared with the larger-lesion patients (44 versus 28 percent).[131] Of those who had a complete response, about half remained free of disease through the follow-up period, which was up to 7.5 years in some cases.

The median time it took for a recurrence of the esophageal cancer was just over four years for early-stage patients, compared to two and one-half years for later-stage patients, and just over a year for patients originally treated for recurrent tumors. Based on these findings, the investigators concluded that PDT was effective for early-stage esophageal cancer and that the addition of radiotherapy could be beneficial in patients who had not responded completely to PDT alone. The study also confirmed that PDT is less optimal against larger tumors, which of course require more light penetration.

One other PDT study is worth mentioning here: a randomized clinical trial conducted by the International Photodynamic Group for High-Grade Dysplasia in Barrett's Esophagus. The study enrolled 128 patients and compared the effects of drug treatment with omeprazole to omeprazole with PDT. After five years, the PDT group had half the high-grade dysplasia of the omeprazole alone group. Similarly, the likelihood of cancer occurring in the PDT group was about half that of the omeprazole group (15 versus 29 percent).[132] As you might expect, patients in the PDT group also had significantly less progression of their disease. Based on this research, the U.S. Food and Drug Administration approved PDT for patients with Barrett's esophagus and high-grade dysplasia who do not undergo surgery.

The main limitation of PDT for esophageal cancer is the depth of light penetration: Any progression of the cancer beyond the submucosa implies locally advanced disease and will likely require chemoradiation therapy followed by surgery. Also, certain genetic factors may determine those individuals will probably respond best to PDT, and research is ongoing to identify such factors.[133] Studies in Austria indicated that adding hyperbaric oxygen therapy to PDT could substantially improve the treatment outcome for patients with esophageal cancer.[134] This too is an area in need of further research.

In conclusion, the clinical trial research to date suggests that PDT for Barrett's esophagus and high-grade dysplasia is a safe and reliable treatment that prevents the development of invasive esophageal cancer. The successful removal of combined low-grade dysplasia or Barrett's esophagus can in occur in up to 100 percent of cases, while the successful removal of high-grade dysplasia or cancer occurs in about 85 percent of cases. Complete remissions can be achieved after just one or two treatments, and recurrences can be treated repeatedly without the toxicity concerns that come with chemotherapy and radiation treatments.

For early-stage and precancerous disease of the esophagus, PDT represents a cost-effective alternative to surgery and intense endoscopic monitoring.[135] Nevertheless, the treatment does carry with it a risk of skin phototoxicity, severe chest pain, nausea and stricture formation—all of which will depend on individual factors that your physician may be able to modify or take into account before you begin treatment. It is our belief that these risks will continue to diminish with the further development of new photosensitizers and more integrated PDT regimens, possibly including the addition of hyperbaric oxygen therapy.

Hilar Cholangiocarcinoma (Klatskin Tumor)

Some of the most compelling results with PDT have been achieved with inoperable hilar cholangiocarcinoma (HCC), a slow-growing yet deadly cancer of the bile ducts. This cancer is also known as Klatskin Tumor, named after Dr. Gerald Klatskin, an American physician working at Yale University. HCC comprises about two percent of all cancer diagnoses, with most cases occurring in men and women over the age of 65. Parasite infections of the bile ducts, exposures to nitrosamines and asbestos, and the use of the radiologic dye, Thorotrast (thorium dioxide), are all considered to be risk factors for this unusual cancer.

PHOTODIAGNOSIS:

Using Light to Detect Cancer and Pre-Cancer

Many tumors are first detected only *after* they've become bothersome or symptomatic. At that point, they've had ample time to mutate and evolve into a more entrenched or potentially aggressive disease. Had these malignant growths been detected much sooner, they could have been treated more effectively. This is where the approach known as *photodiagnosis* comes into play.

As you might have guessed, photodiagnosis involves the use of light and tissue fluorescence for diagnostic purposes.† The basic principle is that abnormal tissues—whether cancerous or precancerous—will glow or fluoresce upon exposure to specific wavelengths of light. This enables the physician to literally see where the abnormal tissue is. German scientists first recognized the value of this method for detecting abnormal growths back in the early 1900s. As a logical extension of PDT, the photodiagnostic approach uses photosensitizers that selectively concentrate in cancerous tissue and fluoresce or "light up" when exposed to light.

The reason light is so helpful in this photodynamic context is that it can detect small tumors as well as clusters of cancer cells that have not yet grown into a visible tumor. And as alluded to above, photodiagnosis can even pick up pre-cancerous or *dysplastic* growths. Again, catching cancer in its earliest phases of evolution, well before it has a chance to become malignant, can set the stage for curative treatment. PDT is often a great choice for these early-stage situations, and it works very logically as a complement to photodiagnosis.

Let's consider the example of gastrointestinal (GI) tumors or adenocarcinomas. You're more at risk of developing such a tumor if you have a history of Barrett's esophagus, adenomatous polyps, or long-standing ulcerative colitis. If you're judged to be in such a risk category, you may undergo annual or biannual endoscopies with multiple biopsies. But most dysplastic areas are not visibly obvious with these conventional methods, and tissue staining (chromoendoscopy) can yield very mixed results. Again, photodiagnosis could offer a meaningful and effective solution.

In its simplest form, photodiagnosis entails giving a suitable photosensitizer, illuminating the suspicious tissue with light, and then observing for areas of reddish fluorescence. Though the fluorescent signal is usually weak, detection can be enhanced with the help of image intensifiers and specially designed video cameras, as well as other types of sophisticated technology.

So far, the use of photodiagnosis has brought about some encouraging results. As far back as the 1960s, fluorescence was observed in 80 percent of patients with bronchial or esophageal carcinomas.[136] In another early study, photodiagnosis resulted in positive fluorescence in 77 percent of patients with various tumor types; it also picked up benign tumors in 22 percent of patients.[137] This approach can also help differentiate high-grade dysplasia or esophageal adenocarcinoma from normal tissue in the esophagus.[138]

The best photosensitizers for tumor detection show a high fluorescence yield, high selectivity for cancerous tissue during the first 24 hours after administration, and rapid elimination from the body (to minimize photosensitivity). Many so-called second-generation photosensitizers are beginning to show promise in this regard. These agents have a low risk of side effects, are easy to administer, and seem to be diagnostically useful because they accumulate so easily in tumor tissues. Following the description given above for the best diagnostic agent, Bremachlorin meets all of the requirements and has demonstrated clinical efficacy with many types of malignant tumors.[139]

By detecting precancerous growths in patients with Barrett's esophagus, ulcerative colitis or adenomatous polyps, photodiagnosis provides vital information for anyone hoping to avoid a malignancy.[140] This information can be used to help alert you, the patient, to the need to be more aggressively proactive in your efforts to ward off cancer, perhaps using a combination of nutritional, herbal and innovative medical strategies. As a novel method of tumor detection, photodiagnosis could very well play a central role in the medicine of the future—an approach grounded in the authentic, biologically guided practice of preventive medicine.

† Some experts also refer to photodiagnosis as *fluorescence diagnosis* or *photodynamic diagnosis.*

Even though it is not likely to metastasize, HCC tumors can impinge on vital structures of the liver and tend to grow into the sheath that surrounds certain nerve fibers in the lower torso (perineum), often with fatal consequences. Most patients are diagnosed at an advanced stage, and over half of all cases are inoperable at the time of diagnosis. The five-year survival rates all fall within the dismal range of 20 to 40 percent.

Because HCC is a relatively rare cancer, there are currently no large clinical trials of chemotherapy and radiation treatment for this disease. A few small clinical studies have failed to show any significant survival advantage with radiotherapy, which is considered to be a "palliative" option—that is, a treatment that can at least help to avoid or reduce suffering from the disease itself. Liver transplantation is also considered an option in some cases.

The discovery that PDT could be effective against HCC began with a single well-documented case published in 1991.[141] The patient was in considerable pain and discomfort. He could not be treated surgically and was offered PDT as a last resort. Repeated PDT sessions were given to illuminate the tumor and margin in combination with a bile drainage procedure called *stenting*. Despite having his grim prognosis, the patient was treated in this manner for many years, with a good quality of life. These days, the very same approach used for that patient is fast emerging as the standard of care for all patients facing a diagnosis of HCC.†

Complete surgical removal of the HCC tumor is widely considered to be the only treatment with a potential for cure. To be successful, however, the surgery is limited to removing small tumors that are confined to the bile duct wall.[142] This means that fewer than half of all HCCs can even be attempted with surgery, let alone cured. Completely clear margins (i.e., no cancer in the area surrounding the tumor) are only obtained in about one-third of these operations, and yet those fortunate patients may live about three times longer than patients who show unclear margins at the time of surgery (60 versus 22 months).[143] PDT was embraced early on as an alternative strategy for clearing those margins and thus increasing the chances of successful surgery.

† This case should also remind us that the survival data we see derived from existing clinical studies of conventional treatment can be misleading, especially when it comes to a slowly progressive tumors.

True to form, PDT seems to be able to treat the surgical margins as well as the tumor itself. At least two randomized clinical trials have demonstrated that patients with inoperable HCC who undergo photodynamic treatments have a significant survival advantage over the conventional practice of bilateral plastic stenting. In the first of these clinical trials, 70 patients were treated, including 20 who were randomized to PDT followed by stenting. Patients in the PDT group had a surprising median survival of 493 days, compared to only 98 days for the stenting-only group.[144] Those receiving PDT also had a better quality of life. The other randomized clinical trial showed similar results—a major survival advantage for patients receiving PDT plus stenting versus stenting alone.[145]

In these landmark clinical trials, the most common complication observed among HCC patients was cholangitis, or inflammation of the bile duct. This developed in about one out of every four patients who underwent PDT plus stenting. It should be noted that this rate is generally higher than those rates observed in patients treated with stenting alone. Also, the finding of cholangitis comes as no surprise, since part of the mechanism of PDT is to induce an acute inflammatory response.

Similarly, several other clinical studies of PDT have found a survival advantage for patients with HCC.[146] Because these studies were not randomized, however, they are not considered to be proof of efficacy. More recently, a large retrospective study confirmed these findings and concluded that survival was optimal in patients who received PDT earlier—the sooner, the better—and those patients who underwent multiple PDT treatments were more likely to have improved survival.[147] The size of the HCC tumors also makes a difference: patients with clearly visible masses based on scans generally do not respond well to PDT.[148]

Overall, these findings are highly consistent with our own clinical studies in Russia. Our PDT approach to HCC, using drug Bremachlorin®, has yielded dramatic therapeutic results against this challenging form of cancer, particularly when surgery was not an option for these patients. It is important to note that the typical prognosis for HCC is quite poor, with 80 to 90 percent of cases being considered inoperable. If the cancer cannot be surgically removed, the disease is usually deadly within three to six months from the time of diagnosis.

We have observed exceptional survival in other studies as well. In our study, for example, 25 patients with inoperable HCC underwent photodynamic treatment, with each patient receiving up to 10 sessions.[149] Patients were treated over different periods of time, ranging from two to 44 months. The median survival time was 13.8 months following the first PDT treatment and 27.5 months from the time of diagnosis—at least a fourfold improvement in expected survival. Using palliative PDT, the following results were achieved:

- 87 percent of patients lived more than one year.
- 60 percent lived more than two years.
- 40 percent lived more than three years.
- 20 percent lived more than four years.
- 11 percent lived more than five years.

All patients in this study reported a considerably improved quality of life.

Liver Cancer

Liver cancer (hepatocellular carcinoma) is the sixth most common cancer worldwide. It is most common in Africa, China and Southeast Asia. At the same time, however, its incidence in Australia, Canada, and the United States is rising steadily. Liver cancer mainly develops from various types of liver damage, most often due to infections (chronic hepatitis-B viral infection being the most common cause) or alcohol or both.

Most cases have already spread through the liver by the time of diagnosis. If the liver tumor cannot be removed, the main goal of treatment is usually to control the symptoms for as long as possible, using the approach known as palliative care.

The use of PDT for advanced liver cancer is still regarded as experimental. In cell culture studies, PDT treatment of liver cancer cells triggered apoptosis (programmed cell death) and reduced the viability of the cells.[150] Animal studies have shown that PDT can shrink liver tumors.[151] Finally, there is growing excitement about the possibility that PDT-generated vaccines may greatly boost the antitumor immune response and have the potential to be used as an adjuvant therapy for liver cancer.[152]

These experimental studies are interesting and certainly point to some promising therapeutic directions for the future medicine of light. At this time, such research provides only preliminary evidence that PDT may be effective against liver cancer. As always, controlled clinical trials are needed before physicians can embrace the routine use of PDT as a treatment tool for liver cancer. Certainly, given its wide margin of safety, PDT could be used on an experimental, adjunctive basis—that is, in tandem with conventional treatments already in use.

Cancers of the Lower GI Tract (Colon, Rectum, and Anus)

Cancer of the bowel refers to malignant disease in the colon and rectum. These tumors are fairly common and tend to develop very gradually, over the course of several decades. Colon cancer refers to tumors found in the large intestine (colon), while rectal cancer occurs in the last eight to ten inches of the colon. Often referred to together as *colorectal cancer*, these tumors typically start growing on the inner lining of the bowel wall. At this point they are considered to be highly curable with surgery. The procedure may be performed through a large incision in the abdomen (open surgery) or through small incisions (laparoscopic surgery) in the abdomen.

The disease is considered to be more aggressive if the tumor grows deeper into the wall, eventually spreading through the wall. At this point the cancer can spread to the lymph nodes in the abdomen. If it also spreads to the liver, the cancer is considered incurable. Colorectal cancer is a leading cause of cancer-related death in most Western countries. Over 90 percent of cases occur after age 50.

Within the bowel lining, the exaggerated growth of cells may lead to the growth of precancerous polyps (also called adenomas or adenomatous polyps). Polyps start out as benign growths, and there are many types. Over a period of time, some polyps may become cancerous. Large polyps are more likely to indicate a developing or imminent cancer.† If polyps in the bowel could be removed as soon as they developed, the risk of bowel cancer would be greatly reduced.

† By the same token, however, some colorectal cancers probably develop without any previous benign changes such as polyps. Thus, polyps are just one way in which bowel cancer may develop.

This is a tall order, however, as polyps themselves may spring up without producing any outward symptoms—at least until they grow quite large. There is currently no reliable way to screen the general population for polyps. Until such screening methods are available, we must rely more on family history, genetic screening, and dietary history. With regard to diet, for example, we know that eating too little fiber, along with too much fat and sugar, can predispose people to bowel cancer. Other risk factors include smoking, alcohol, obesity, lack of exercise, and being constipated on a regular basis.

Numerous reports have explored the use of PDT as a way to remove colon polyps as well as to reduce bulky colon and rectal cancers.[153] Nevertheless, most of the reports on PDT and PIT to date have come from experimental studies that took place in the laboratory experiments in which the photodynamic methods either killed colon cancer cells in the test tube or blocked the growth of colon tumors in animals.[154] A recent lab study found that PIT was able to destroy liver tumors in mouse models for colorectal cancer.[155]

Surprisingly, there have been very few clinical studies of PDT for colorectal tumors and polyps. This may be due to the assumption that surgery will produce good outcomes with early-stage bowel cancer (and of course polyps), and that laser therapy and stents alone can be effective.

This is not necessarily the case, however. Unlike laser treatment, healing from PDT occurs with less scarring, and because collagen is preserved, there is no reduction in the mechanical strength of the colon. According to early studies done in the 1980s and 1990s, PDT produced favorable response rates and good symptomatic relief and recovery. One scientific review concluded that approximately 35 percent of rectal cancer patients showed a complete response, 44 percent a partial response, and 21 percent no response to PDT.[156]

One of these early studies involved a small group of patients with colorectal cancer who were not suitable or eligible for surgery and thus turned to PDT.[157] The researchers inserted a fiber optic into the colon tumor during colonoscopy. They then observed that destruction of the tumor (necrosis) occurred up to a depth of six millimeters, as measured by endoscopic ultrasound. Two of the ten patients were found to be tumor free approximately two years after the treatment.

The same study found that PDT helped relieve bleeding and constipation in seven of the ten patients. Other scientists have reported that PDT is an effective method for relieving bowel cancer-related pain and anal malfunction (tenesmus), as well as controlling hemorrhage linked with radiation proctitis.[158]

PDT in the colon and rectum may work best for the treatment of adenomas and small tumors. This is because various complications—notably bleeding and strictures—may tend to occur after the photodynamic treatment of large tumors. In this regard, PDT has been used to treat adenomatous polyps thought to be unsuitable for surgery.[159] In a small pilot study, one out of six patients with colonic polyps showed a complete response to treatment, and no complications were reported.

PDT performed during surgery could be an effective strategy for treating colorectal cancer, even in the case of advanced disease or recurrent tumors. An early study involved 11 patients undergoing laparotomy for recurrent colorectal cancer (adenocarcinoma) in the pelvic area.[160] Six patients with inoperable disease underwent PDT alone, the other five after partial surgery (tumor debulking). Though there was no obvious improvement in survival, five patients did experience marked pain relief and tumor shrinkage based on CT scans. The pain relief has been confirmed in other studies of recurrent colorectal cancer in patients who underwent debulking surgery.[161]

There is some evidence that PDT can be helpful in advanced cases of anal cancer as well. In one study, chemo-radiation at the primary tumor site had failed, and some patients had refused chemo-radiation or additional surgery for early-stage anal cancer.[162] Every patient in the study showed a tumor response to the PDT treatment, while normal surrounding tissue was not affected. Although no major tumor reduction occurred, the tumor bed appeared to be dark-colored and unlikely to support the tumor itself. The actual PDT session was pain free, though all patients reported moderate discomfort in the anal area six to 12 hours later. This was easily treated with pain medications.

The investigators concluded that PDT appears to be an effective treatment for recurrent or persistent squamous cell cancers of the anal canal. Notably, all patients in the study maintained sphincter function throughout follow up. Although two patients did develop metastatic

disease, after 18 months of observation there was still no evidence of disease in the other patients with early invasive cancer.

So where do we stand with the use of PDT for bowel cancer? As we alluded to earlier, today's oncologists consider surgery to be the treatment of choice for colorectal cancer. So-called *radical bowel resection* (cutting out a major portion of the colon or large intestine) is used to treat 80 to 90 percent of colorectal cancer patients.† If the cancer has spread, the lymph nodes also will be removed in a procedure known as lymphadenectomy.

One's ability to recover from radical bowel resection will depend on factors such as age, overall health, and the extent of the surgery itself, or how much tissue needs to be removed. The operation often results in considerable fatigue, weakness, pain, and loss of appetite. Substantial dietary changes may be needed until the bowel has had time to heal. Possible complications from the surgery—aside from an allergic reaction to the anesthesia—could include formation of an intestinal blockage, blood clots, bleeding, wound infection, and leakage at the site where the colon was reconnected. None of these complications are an issue with PDT.

For these and other reasons, PDT could be viewed as a solid treatment option for colorectal patients who are either ineligible or not suited for radical bowel resection. This could include many older patients who are too weak to withstand such a major operation, perhaps due to having too many previous procedures and being in poor overall health to begin with. Because PDT leaves the colon intact and functioning well within a very short time, it results in a much better quality of life.

On the other hand, for those patients with more advanced-stage cancers of the lower GI tract, PIT may be the preferred treatment. To further boost the effectiveness of PIT, hyperthermia and hyperbaric oxygen treatment could be used as adjunctive therapies—that is, combined with the PIT approach to further enhance its efficacy. In the case of hyperthermia, for example, significant improvements in clinical outcomes have been demonstrated for rectal tumors, among others.[163]

As we noted in the preceding chapter, raising the body's core temperature with hyperthermia could help activate the anti-cancer immune defenses—thus potentially bolstering the efficacy of PIT.[164] Since the early 1990s, many scientists have explored linkages between anti-cancer immunity, hyperthermia, heat shock proteins and fever.[165] This exciting body of research has helped inform some attempts to combine laserthermia with PDT in cancer patients. (To read more about the possibilities for this combination, see the Chapter 2 sidebar, "In Situ Photoimmunotherapy: Blending Light and Heat to Cure Melanoma.")

† This is also called partial colectomy and hemicolectomy.

Pancreatic Cancer

Worldwide, pancreatic cancer ranks among the top ten most deadly cancers. Its lethal nature is due in part to the fact that the cancer is usually diagnosed at a late stage. Pancreatic cancer often spreads to other areas of the body, making it impossible for a surgeon to remove the cancer entirely. Even if diagnosed at a stage where surgery is feasible—as is the case in less than one in every five cases—the outlook is often bleak. The median survival after such surgery is only 12 to 18 months, and fewer than 30 percent of these patients will go on to survive five years after the operation.

At this time, there is no satisfactory treatment for pancreatic cancer. Inoperable pancreatic cancer is the norm and has an extremely aggressive character, almost always resisting mainstream chemotherapy and radiotherapy. The 12-month survival rate is about 18 or 19 percent for patients treated with Gemzar, compared to only two percent for those treated with 5-FU (which was the dominant chemo drug treatment for this cancer before Gemzar came along). Against this backdrop, we clearly need to be willing to embrace more innovative treatment strategies.

Since very few cases of this cancer actually lend themselves to surgery, you may be wondering: What good could PDT possibly do in this situation? Several possibilities have been highlighted by recent laboratory studies:

- PDT seems to synergistically enhance the effectiveness of Gemzar against pancreatic cancer.[166] Synergy means that the tumor-killing power of the drug was greatly increased by PDT.
- In animal studies, PDT had a substantial tumor-killing effect when combined with small doses of Gemzar—this effect was much greater than when either PDT or Gemzar was used alone.[167]

- PDT was shown to reverse the resistance that some pancreatic cancer cell lines showed toward Gemzar, and this too could bolster the treatment outcome.[168]
- PDT's effects against pancreatic tumors were strongest for fast-growing tumors. These tumors died by necrosis, which is the best response for harnessing the anti-cancer immune defenses.[169]

Of course, the real question is whether these laboratory findings will translate into the real-life clinical results. The initial evidence suggests that PDT can prolong survival of patients with advanced, inoperable pancreatic cancer.[170] This study, involving a small group of only 16 patients, was conducted by Dr. Stephen Bown and colleagues at the National Medical Laser Centre in London. The researchers were able to document that the tumor was indeed destroyed by PDT.[171] Over half the group (56 percent) was alive one year from the time of their diagnosis. Seven out of the 16 patients (44 percent) were alive one year following the PDT treatment, and two were still alive two years after completing PDT. The median survival of 9.5 months compared quite well with other survival statistics for these patients. The main difference is that PDT-treated patients experience much lower morbidity and thus a much better quality of life.

This was the first published report on PDT for pancreatic cancer. The researchers did also note that the tumor regrew around the edges of the PDT-treated area, and they proposed that future studies should extend the treated area beyond the tumor margins identified on the pretreatment scans. The researchers propose that the technique may be effective against localized tumors in patients who are poor candidates for surgery or in whom the location of the tumor makes surgery inappropriate. "These promising early results justify larger trials to assess PDT either as a single therapy or in combination with chemotherapy and/or radiotherapy," Dr. Bown's team concluded.

At this time, a great deal of laboratory research has documented the potential benefits of PDT on pancreatic cancer.[172] Some studies involved different pancreatic cell lines and showed that PDT killed those cells fairly effectively; others involved animals with implanted pancreatic tumors, all of which showed substantial shrinkage or destruction of the tumor. The possibility that PDT could destroy the tumor while also eliminating micrometastases (via an effect on the anti-cancer immune mechanisms, as explained in Chapter 3) seems very compelling and worth exploring in future clinical trials.

In conclusion, at least one pilot clinical study has suggested that PDT could be effective in locally advanced pancreatic cancer patients. PDT offers represents a novel treatment possibility for the approximately 80 percent of pancreatic cancer cases that are not amenable to surgery. PDT produces localized tumor destruction (necrosis) with light, most conveniently from a low-power, red laser, after prior administration of a photosensitizer. Also, given the potential synergy with Gemzar, PDT could be considered as part of a total treatment approach that includes Gemzar chemotherapy. Whenever there's a disease that's so hard to treat, one should remain open to trying options that are relatively safe and fairly easy to incorporate into a treatment regimen. This is certainly the case with PDT and Gemzar, but it will be up to your oncologist to consider trying the combination.

Gastric Cancer (Stomach and Duodenal Cancers)

Stomach cancer is the fourth most common cancer worldwide. Although an uncommon cancer in the West, stomach cancer is fairly common in the East. Japan and Korea have very high rates of stomach cancer, with most cases being attributed to lack of refrigeration, use of nitrate fertilizers, and excessive consumption of salted, preserved (sodium nitrite) or pickled foods. The cancer begins in the lining of the stomach and usually causes no symptoms, with the exception of occasional, vague belly pains or other kinds of discomfort. Often it may be mistaken for an ulcer. As a result, stomach cancer is typically diagnosed when it has already reached an advanced stage. On the other hand, if the cancer is detected early or at a stage when it can be removed surgically, there's a good chance of cure.

PDT is technically more difficult to use in the case of stomach cancer due to the stomach's rather unique anatomy and physiology, which is beyond the scope of this book. On the other hand, although PDT is limited in its ability to treat deep lesions, it can be quite effective in treating the smaller and more superficial stomach lesions that are charac-

teristic of early gastric cancer.[173] The approach could be especially useful in elderly individuals and those with compromised immune systems.

In several clinical studies of early gastric cancer patients in Japan and Korea, PDT produced a complete remission rate of about 60 to 100 percent.[174] The size of these groups of patients showed substantial variation, however, with most groups being small and mixed. For example, some patients were inoperable due to either severe health problems or refusal to undergo surgical procedures; others had incomplete surgery or signs of invasive disease around the surgical site. Such mixed characteristics make it difficult to draw meaningful conclusions about the true efficacy of PDT for these patients and helps explain the varying remission rates. The PDT protocols used in these studies also varied considerably.

Nevertheless, the existing evidence does suggest overall that PDT is a promising treatment option for anyone facing a diagnosis of gastric cancer. In particular, when PDT is provided along with surgery, the outcomes are more consistently favorable than with PDT alone. As new photosensitizers and better light delivery systems are developed, it is likely that an even stronger role of PDT will emerge in the near future. For the present, its use in cases of stomach and duodenal cancers must be considered fairly experimental.

In a pilot clinical trial, we studied 65 patients with mainly early stomach cancer (average age, 70 years old) who were treated using the photosensitizer Bremachlorin®.[175] Of this group, 50 patients were at a high risk of post-surgical complications, five patients had rejected surgery, and ten patients were in palliative care due to the advanced nature of their disease. A total of 264 photodynamic treatment sessions were performed, and each patient received from one to 23 sessions, with treatments taking place over a five-year period. During this time, a biopsy was done twice a year, then once a year for the next five years.

The most effective PDT treatment schedule was found to be three sessions in the first year and two sessions in each of the subsequent years. Two patients with the most severe forms of gastric cancer received 23 treatments each and have stayed alive for eight years at the time of this writing. Every patient responded in some way to the treatment, and the overall treatment benefit during the first five years for every patient can be summarized as follows:

- 35 percent had a complete response
- 49 percent had a partial response
- 15 percent showed disease stabilization
- 1 percent showed disease progression

Thirty percent of the patients had recurrences of their tumors and were treated repeatedly, without any serious side effects. Some patients complained of symptoms related to the rapid breakdown of the tumor tissues. These symptoms included pain in the upper central region of the abdomen (epigastrium), as well as nausea and toxic effects that were managed using standard medications and techniques.

There are many possible research directions for assessing PDT's usefulness as a treatment for stomach cancer. One is to see how combinations of anti-cancer drugs could perhaps improve PDT outcomes. In this regard, it was recently shown that Taxol pre-treatment of stomach cancer cells (gastric cancer cell line, NCI-N87) bolstered PDT's ability to kill those cells.[176] Taxol is a common chemotherapy drug, and giving it prior to PDT could be a worthwhile strategy to assess in clinical trials. The combination of PDT with immunotherapy is another important angle that warrants research attention, as confirmed by initial studies of elderly gastric cancer patients in Japan.[177]

It is very likely that the best treatment solution for most stomach cancer cases will involve blending PDT with different treatment approaches such as those described above. Various innovative combinations may be considered on an experimental basis to treat the more aggressive forms of this disease, particularly when the standard treatment options have been exhausted.

Prostate Cancer

The prostate, a gland found only in men, is located below the bladder and wraps around the urethra, the tube that transports urine from the bladder and out through the penis. The function of the prostate gland is to secrete a slightly acidic fluid, milky white in appearance, which usually constitutes just less than a third of the volume of the semen along with the sperm and seminal vesicle fluid.

The prostate gland has been a source of some distress and frustration for men around the world—especially those living in industrialized countries. Part of the reason is that the prostate tends to become enlarged as men get older, making urination more difficult. Another reason is prostate cancer, which afflicts hundreds of thousands of men worldwide every year. Indeed, this is a leading cause of cancer-related death for men living in the West, and the cancer is far more common as men get older. Some cancer researchers have estimated that if men lived to about 140, they would *all* develop prostate cancer by that age.

Many older men undergo annual screening for prostate cancer in order to detect the problem early. Screening is done by measuring the level of serum prostate-specific antigen (PSA) and conducting a digital rectal examination. The problem with such screening is that it often ends up detecting prostate tumors that are considered slow growing or inactive. Most men who are treated for such indolent tumors do not derive any real survival benefit from early detection and, as a consequence, are simply left to suffer the ravages of surgery and radiation treatments (we discuss these treatment effects below).[178]

When prostate cancer is very small, it is known as *microfocal prostate carcinoma*. If a biopsy is done and the cancer is also found to be of a low grade (i.e., not very mutated), then it is not considered a threat. Instead of surgery, in these cases men are encouraged to adhere to an anti-cancer diet and exercise regularly. This kind of "watchful waiting" or active surveillance approach is usually only chosen by a small percentage of men. The approach involves close monitoring, not only including the PSA and rectal exam, but also transrectal ultrasound-guided prostate biopsy in many cases. Most men prefer instead to have the surgery, which means removing most or all of the prostate (prostatectomy).

Prostatectomy is the standard treatment for early-stage prostate cancer, and it can result in a cure in most cases. Even if prostate cancer spreads or metastasizes to other parts of the body, it can be controlled with hormonal treatment for long periods of time. Radiation treatments may also be considered for more aggressive cases or for high-grade localized prostate tumors.

Our interest here is with early-stage prostate cancer, which is the situation for the majority of men. Men who undergo prostate surgery are often faced with some very specific complications. Surgery can damage the nerves and circulation around the penis, as well as the bladder and rectum. Depending on the amount of the prostate gland removed and the method used to remove it, the following complications may be fairly common: bleeding, difficulty urinating, impotence, erectile dysfunction, urethral stricture, and urinary incontinence soon after the operation.

Radiation treatments for prostate cancer include brachytherapy or external beam radiation. Surgery is carried out after the radiation treatments, the main complications of which include impotence, incontinence, and rectal injury. In addition, radiation treatments can increase the chances of cross-resistance with chemotherapy, which might be tried later if the disease advances to a metastatic form.

Many men diagnosed with early-stage, low-risk prostate cancer are extremely reluctant to have to deal with the complications we've just mentioned. And yet, they may be unwilling to accept the anxiety and uncertainty that is often associated with a "watchful waiting" approach (see sidebar, "PDT, Prostate Cancer, and the Art of Proactive Waiting").

In many ways, the prostate is perfectly suited for PDT. To begin with, the prostate gland does not typically serve a vital function in most men who have prostate cancer. For this reason, it is not absolutely critical that the photosensitizer is highly selective for cancer cells—there would be no major consequences associated with destroying normal prostate tissue. Nevertheless, it now appears that PDT does indeed have the ability to target the cancer while sparing the surrounding normal tissues of the prostate gland.

This has been demonstrated by studies in Egypt showing that the photosensitizer selectively builds up in the malignant cells within the man's prostate gland.[179] Thus, compared to surgery, the treatment is likely to have a far more focused effect and thus is referred to as an example of "focal therapy".[180] Once again, choosing PDT means that you avoid possible overtreatment and also avoid the onerous complications linked with surgery that we mentioned above—that is, no erectile dysfunction, no change in urination, and so forth.

PDT, PROSTATE CANCER, AND THE ART OF PROACTIVE WAITING

Watchful waiting, or active surveillance, refers to a more gradual and moderate way of managing low-risk prostate cancer. The approach is especially appropriate for men over age 50 who may be more at risk of complications from conventional treatment. "Low risk" means that the tumor is small, contained within the prostate, and expected to grow slowly (based on a low grade or Gleason score). With this approach, the condition is closely monitored, but treatment is postponed until either symptoms appear or some measurable increase in the PSA or digital rectal exam occurs. At that point, a more aggressive strategy may be considered, such as surgery and radiation treatment.

Watchful waiting is a good option for some men with low-risk prostate tumors because it is not known whether treating the cancer with surgery or radiation will actually increase longevity. Moreover, the treatments have well-defined risks and side effects that may eclipse the potential benefits for some men. On the other hand, some men are uncomfortable with watchful waiting; these men would rather hit the cancer right away and accept the possible complications linked with surgery and radiation.

What if you have a low-risk situation, don't want to deal with the complications of surgery or radiation, but also don't want the anxiety and uncertainty associated with watchful waiting? What if you have a small prostate tumor and want to get rid of it slowly but surely? Or what if you have a small prostate tumor, but it shows a strong potential for rapid growth?

For all three situations, PDT offers an attractive middle-ground option, particularly given the choice between watchful waiting and aggressive local treatment (radiation or surgery). Remember that PDT can readily eliminate the smaller prostate tumors—regardless of whether they are low grade or high grade, minimally aggressive or possibly very aggressive. If the PDT does not succeed in eliminating the tumor, surgery and radiation can always serve as a back-up strategy in those cases.

Another strategy would be to do the watchful waiting, and then immediately start treatment with PDT if the cancer seems to be growing or getting worse, based on a rising PSA level or a change in the rectal exam, ultrasound or biopsy results. That option should be seriously considered, given the evidence for PDT's ability to remove small tumors in general without harming the rest of the prostate.[181] If subsequent biopsies show an increase in the Gleason score or extent of tumor (based on the number of biopsy samples containing tumor), then treatment with either surgery or radiation therapy could be tried at that point.

A possible downside to doing watchful waiting before choosing PDT (again, pending the appearance of symptoms, PSA increase, etc.) is that there's a chance the cancer could spread in the interim. This could limit your treatment options, and could possibly affect the chance to cure the cancer. However, several studies have shown that men who embrace the watchful waiting approach and later go on to be treated tend to do just as well as those who start surgery or other conventional treatment right away. This may indirectly support the idea that choosing PDT as an interim strategy is at least a safe bet, if not a highly effective way to greatly lower your chances of having to deal with a more aggressive prostate cancer later on.

To further safeguard you against a more serious disease situation down the road, we feel strongly that men should not just sit back passively during the watchful waiting period. They should instead adopt a strong anti-cancer diet and physically active lifestyle that is specifically geared toward preventing and controlling prostate cancer.[182] In a recent study, for example, simply eating more broccoli and other cruciferous vegetables—to the tune of three or more servings per week, compared to less than one serving per week— resulted in a statistically significant 41 percent decrease in prostate cancer risk.[183]

Though debate continues as to how often testing should be done during watchful waiting, and when might be the best time to start treatment if things change, this still seems to be the best overall strategy—particularly if you consider PDT as a first option

for low-risk prostate tumor situations. Perhaps we should use the term "proactive waiting" instead, to help drive home the idea that this is not a passive, do-nothing approach. Your health and longevity are always, ultimately, your own responsibility. We feel strongly that our proposed PDT-based holistic approach to watchful waiting is a superb middle-ground option for men who are don't want to sit idly by yet also would rather not have to suffer the consequences of invasive and potentially unnecessary treatment.

How exactly does PDT "light up" the prostate cancer? In the PDT approach, light can be used to treat either the entire gland or small tumors within the gland. With the whole gland approach, light can be effectively delivered under ultrasound guidance to the entire prostate gland using special optical fibers.† The fibers are inserted into the prostate using a standard brachytherapy grid. Alternatively, using modern imaging technology, these small light-delivering probes can be positioned in the prostate to deliver PDT to specific portions of the gland.

The therapeutic target can also include the vascular bed that directly supports the prostate. A photosensitizing agent is injected intravenously and is distributed throughout the body. The PDT's light reaction selectively destroys the vascular supply to prostate tumors, causing them to shrink and die. This latter approach is referred to as vascular-targeted PDT.

PDT also offers substantial advantages over radiation treatments, another very common conventional strategy. Unlike radiotherapy, PDT's mechanism for tumor destruction is not dependent on DNA damage. This decreases the chances of treatment resistance (as well as cross-resistance with chemotherapy) and also eliminates the chances of delayed adverse effects such as developing a second cancer. These considerations make prostate cancer a very attractive target for PDT treatment.

This brings us to the bottom line: Does it really work? The answer is a definite yes. In clinical studies, various photosensitizers have been successfully used for treating prostate cancer via PDT. The first documented cases of successful PDT for prostate cancer were reported in 1990.[184]

† Specifically, these are interstitial, cylindrically diffusing fiber optics.

Since that time, most of the research has focused on PDT's use as a "salvage therapy", which means that the conventional treatments had failed, and the disease had then either recurred or progressed. In multi-center clinical studies of men facing this situation, 60 percent of patients showed a complete response to PDT as confirmed by an MRI and negative biopsy after six months. There was no reduction in urinary or erectile function. All these men had received the maximal dose of light energy during their PDT sessions.[185]

Another clinical trial focused on locally recurrent prostate cancer after radiation therapy. Treatment options for this group of patients are very limited, and the disease tends to be fairly aggressive. PDT is an attractive treatment option modality it offers the possibility of repeated treatments in the case of disease progression, all of which can happen with minimal side effects or complications.

In this study, 16 patients with this more aggressive form of prostate cancer were treated with PDT, and then the patients' PSA levels were monitored at regular intervals up to 11 months after treatment. Patients who received high-dose PDT showed much higher PSA increase compared to patients treated at the low PDT dose. This indicated that more tumor tissue damage was achieved with the higher dose. (Note: The initial rise in PSA correlates with the invasiveness of procedure, and the success of treatment is typically measured through the subsequent drop in PSA levels.) After the initial rapid surge in PSA, the levels steadily decreased and returned to the original baseline level within six months. At this point, however, the disease began to progress again, and PSA levels rose accordingly.[186]

The ultimate role of PDT as a treatment for prostate cancer will depend on whether the disease can be reliably eliminated. It is likely that men with low-risk tumors (low-grade, non-aggressive) will benefit most from PDT. At this time, only about 10 percent of men diagnosed with low-risk prostate cancer choose watchful waiting as their initial treatment; the rest choose treatment. Also, about half of men diagnosed with low-risk prostate cancer who elect to undergo radical prostatectomy or radiation therapy actually have very minimal disease. These men are unwittingly exposing themselves to invasive and harmful treatments without any real benefit to their survival.

EAST-WEST INSIGHTS INTO PROSTATE CANCER PREVENTION

Broadly speaking, there are two types of prostate cancer: latent and clinically significant. The incidence of clinically significant prostate cancer varies greatly on a global scale while the incidence of latent prostate cancer is relatively uniform in its geographic distribution—occurring in large but equal rates among men, regardless of whether they live in the East or the West. This latent form affects about one in every three men in their fifties, and three out of every four men after age 70.[187] Most cases do not require surgery but instead warrant an approach that has been called "watchful waiting" or expectant management.

On the other hand, the rate of clinically significant prostate cancer is much higher in men living in the United States and various European countries compared to those living in Southeast Asia.[188] A few decades ago, death from prostate cancer was ten times lower in Japan than in the U.S.; however, when Japanese men moved to the U.S, after just one generation their prostate cancer rates come to resemble those of other American men.[189] Some researchers believe that it is the traditional Japanese diet that accounts for the apparent protective effect, as suggested by findings from a number of observational studies.[190]

While the overall disease burden in Japan, China and other Southeast Asian countries remains lower than in Europe and the U.S., mortality rates for prostate cancer patients in those countries have risen dramatically over the past 40 years.[191] According to T. Colin Campbell, author of the best-selling 2004 book, *The China Study*, prostate cancer rates have increased primarily in urban areas in China that have rapidly adopted western lifestyles and modern technology.†

† Dr. T. Colin Campbell's book focuses on the knowledge gained from the China Study, a 20-year partnership of Cornell University, Oxford University and the Chinese Academy of Preventive Medicine that showed high intakes of animal products were associated with more chronic disease, while those who consumed a plant-based diet were the healthiest.

> This strongly suggests that dietary and other lifestyle factors could play a major role in promoting and fueling the more aggressive forms of prostate cancer. For example, men living in the United States typically consume plenty of refined carbohydrates (e.g., sugar and white flour products) and saturated fats from meats and dairy products, while eating very few vegetables and omega-3 fatty acids. This kind of dietary pattern has been linked with more aggressive prostate cancers.[192]

The true therapeutic potential of PDT using second-generation photosensitizers for treating prostate cancer is an area of active study. Many men are currently struggling with the decision regarding surgery because of the psychological burden posed by not taking action. We believe that PDT offers a very promising option for men with early-stage prostate cancer. Future clinical studies will determine whether this option, along with what we call "proactive waiting", can help men forego surgery and preserve the prostate gland in the face of such uncertainty. Again, please be sure to read the sidebar, "PDT, Prostate Cancer, and the Art of Proactive Waiting".

Bladder Cancer

The bladder is a hollow organ responsible for collecting urine excreted by the kidneys. The urine is then eliminated through the process of urination. Given its hollow structure, it should come as no surprise that scientists interested in targeted light-based therapies would want to explore the potential for using PDT to treat conditions such as bladder cancer. The interior of the bladder is readily accessible with the help of endoscopy (a scope that is passed through the urethra), and most bladder tumors are superficial, occurring on the mucosa or submucosa of the bladder wall.

Bladder cancer (also called urinary bladder carcinoma) is the ninth most common cancer in the world, with more than 12 million new cases occurring annually. It is the most common malignancy of the urinary and genital organs, affecting both men and women equally. The incidence of this cancer varies over the world with the highest rates in developed nations. The incidence is highest in Egypt, followed by

Europe and North America. At any point in time, nearly three million people on the planet have a history of bladder cancer.[193]

In about three-quarters of all cases, bladder cancer occurs as a non-muscle invasive papillary tumor and shows very high rates of recurrence. The recurrence rate at one year is between 15 and 61 percent, and by five years it may be as high as 78 percent.[194] At the same time, this cancer has a very low mortality rate, and thus patients often need lifelong monitoring. This is especially true for the type of bladder cancer oncologists refer to as *superficial bladder transitional cell carcinomas*.

The very high recurrence rate and need for ongoing monitoring have given bladder cancer the dubious distinction of being the most expensive cancer to manage on a per-patient basis.[195] Based on recent estimates, the world market for treating bladder cancer is projected to reach $544.4 million by the year 2015. The heavy price tag is due not only to the high recurrence rate, but also to the fact that our elderly population continues to expand.

Bladder cancer is most often treated with surgery, and this usually means transurethral resections that require hospitalization. Surgery itself has paved the way for using photodynamic diagnosis, or *photodiagnosis*, which was first reported over 40 years ago but has been in vogue ever since the 1990s. The technique relies on the rapid accumulation of the natural photosensitizer, Pp-IX, inside cancer cells (we highlighted this wonderful compound in Chapter 1).

The Pp-IX accumulates up to ten times more in tumor cells than in normal tissues. Oncologists can get the Pp-IX to become concentrated in bladder tumors by administering a drug called 5-aminolevulinic acid, or 5-ALA. Within two hours of giving the 5-ALA, the Pp-IX has accumulated sufficiently and can be exposed to light. Upon exposure, spots of cancer will appear red when viewed under blue-violet light. Areas of cancer can either be removed surgically or treated "on the spot" with focused light, thus bridging photodiagnosis with PDT.

Using this "see and treat" technique, oncologists can readily identify bladder tumors during the surgery, especially the highly aggressive bladder carcinoma in situ. Photodiagnosis is considered an easier and more complete method of diagnosis compared with conventional approach known as white-light cystoscopy.

Why would this combination of photodiagnosis and PDT be so valuable in the case of bladder cancer? We believe that there are several reasons bladder cancer recurs with such a high frequency. One is that the surgery itself is incomplete. With photodiagnosis, one can actually "see" where the cancer is, and thus treat it more effectively, using either surgery or PDT, or both. Photodiagnosis may therefore translate into more complete and effective overall treatment, thus reducing the risk of subsequent recurrences and possibly curbing future progression of the disease.[196]

As you might expect, there are other reasons bladder cancer manages to recur with such vigor. First, without photodiagnosis, it is very easy for microscopic tumors to be missed during surgery; those tiny masses will then form into new tumors later on. Second, if you remove a tumor, there is always a chance that some cells will be shed into the circulation. This opens the door for the possibility of one of these cells re-implanting itself into the bladder wall after the surgery.

Given this last possibility, it is helpful to use an approach that not only targets the cancer, but also harnesses the anti-cancer immune defenses. As we explained in Chapter 3, this is precisely what both PDT and PIT can accomplish, and it's yet another reason we favor these therapies for the treatment of bladder cancer.

Most of the research to date has focused on using PDT for patients with recurrent bladder tumors after they had initially undergone conventional treatment. There may be a special role for PDT in patients with diffuse non-muscle invasive bladder carcinomas for which standard treatments had clearly failed (as indicated by rapid recurrence or progression of the disease); in these cases, the PDT would be used prior to surgery, in order to minimize cancer in the bladder and allow the surgeon to take care of the rest. This approach could be particularly helpful in patients who are considered to be at high risk of complications following the surgery.[197]

A number of clinical studies have attempted to determine whether PDT could accomplish the same outcome of surgery while also lowering the recurrence rate. In general, the more lasting or durable responses to PDT—that is, going at least one to two years without a recurrence—have been observed in up to 60 percent of bladder cancer

patients treated with PDT.[198] Also, a recent study pooled the data from prospective studies on 1345 patients with known or suspected non-muscle-invasive bladder cancer. This meta-analysis concluded that the use of photodynamic methods (hexaminolevulinate cystoscopy) significantly improved the detection of bladder tumors and moreover resulted in a significant drop in recurrences within 9 to 12 months of follow-up observation.[199]

We should point out, however, that most of the patients included in these studies had recurrent disease that developed after standard therapies such as bacillus Calmette-Guérin (BCG), a powerful immune-stimulating agent. This kind of disease could be harder to treat. Urgently needed are studies that use PDT as a first-line treatment for bladder cancer, perhaps in combination with BCG and follow-up surgery.

How about comparing BCG and PDT for bladder cancer treatment, or possibly combining the two? Although most of the patients treated with PDT had previously not responded to BCG, one randomized controlled study did compare PDT with multiple BCG treatments and found that these therapies were equivalent in terms of producing a durable treatment response.[200] Also, studies combining BCG with PDT showed that this unique type of immunotherapy may significantly enhance the bladder tumor's response to PDT. Similarly, chemotherapy such as mitomycin C also enhances PDT's effectiveness against bladder cancer.[201]

For both superficial bladder transitional cell and the more aggressive form, refractory bladder carcinoma in situ, the short-term response rate may be about 74 percent. However, 78 percent of patients with the more aggressive form may experience a recurrence after two years, at least based on one study.[202] Clearly there is still much work to be done to figure out the best way to keep bladder cancer from recurring. Some research suggests, for example, that high-dose antioxidants could reduce the risk of bladder tumor recurrences.[203] Such a strategy might be considered after PDT treatment has been completed, as we discuss in Chapter 6.

Treatment of superficial bladder cancer using PDT is fairly well tolerated, though there are some potential side effects, such as problems with urination and skin photosensitivity. In addition, rigidifying of the bladder wall (fibrosis) and reduced bladder capacity continue to be a problem for some patients undergoing PDT. It is hoped that, as the dosing and timing of PDT regimens are improved, there will be fewer side effects in the future.

In addition, the specific choice of photosensitizer will prove to be critical. For example, studies of locally applied (intravesical) ALA have found durable complete response rates of 52 to 60 percent at two to three years. These response rates were achieved for patients with bladder cancer in situ for whom conventional treatment had previously failed. The ALA-guided PDT did not produce any of the prolonged skin photosensitivity that has been experienced with another popular photosensitizer, systemic porfimer sodium.[204]

Along similar lines, there is some evidence that chlorin-based photosensitizers may be the most effective choice for bladder cancer.[205] This is why we favor Fotonaflor, the chlorin-based PDT agent we'll be introducing you to in Chapter 7.

The initial research on PDT for bladder cancer has been promising. If photodiagnosis is used to detect bladder cancer, it makes sense that PDT could be implemented right away, since the tissue is already glowing and therefore would lend itself to prompt photodynamic treatment. This is a logical coupling that should be exploited in future attempts to treat this very persistent and cost-intensive form of cancer. PDT for bladder cancer is currently approved in Canada and in some EU nations but has not yet been approved by the U.S. Food and Drug Administration.

Breast Cancer

Breast cancer is the most common type of cancer in women worldwide, with well over a million new cases diagnosed each year. In 2008, according to the International Agency for Research on Cancer, breast cancer caused nearly half a million deaths, accounting for at least one in every ten deaths from cancer in women around the world.[206] The overall incidence of this disease is still on the rise. The incidence is quite low for women in their twenties, but then gradually increases and reaches a plateau at the age of 45. After age 50 (in particular, after menopause), the incidence shows a dramatic increase.

Breast cancer probably begins when some cells in the breast mutate and begin dividing more rapidly than healthy cells. The abnormal cells may spread through the breast tissue to the lymph nodes or other parts of the body, such as the liver or lungs. The most common form of breast cancer starts in the milk-producing ducts, but the malignant growth may also take root in the lobules or other breast tissues. Older men, too, can get the disease, though it is extremely rare, occurring in fewer than one out of every 100 cases of breast cancer.

Breast cancer actually manifests as a number of different diseases depending on the woman's age and on the different cell types within the breast tumor. Some breast tumor cells are fast growing and more likely to invade other tissues; others grow more slowly and are considered low invasive or even non-invasive. Some breast cancer cells are stimulated by the female hormone, estrogen, as well as by other growth factors, while other cells get their impetus from an out-of-control oncogene or cancer gene (e.g., BRCA1 or BRCA2). The choice of treatment is almost always based on specific characteristics of the breast cancer.

There are several ways in which photodynamic principles could improve the treatment of breast cancer (please also refer to our lengthy discussion of the clinical aspects of PDT for breast cancer in Chapter 7). Perhaps the most obvious benefit would be as a photodiagnosis technique to complement and enhance surgery. A clinical study of breast cancer patients in Switzerland used the photodynamic approach to see whether breast tumors could be distinguished from normal tissues.[207] After giving patients the photosensitizer, the primary breast tumor tissues glowed much brighter (had significantly higher fluorescence intensity) than the surrounding normal tissue of the breast. Thus the researchers were able to reliably distinguish breast tumors from normal breast tissue in all the patients.

The Swiss scientists suggested that the "glow" or fluorescence produced by the light-activated photosensitizer could be used to help guide the surgical process. With this method, known as flourescence-guided surgery, the surgeon can actually see areas of cancer more clearly, as well as the tumor margins around the surgical site. However, their study also suggested that the method would *not* be helpful for detecting lymph node metastases of breast tumors.

A major challenge for the use of PDT for breast cancer is ensuring that light can actually reach the tumor. In some patients, the breast cancer spreads to the skin, producing what are known as cutaneous metastases. In an earlier study of nine breast cancer patients with cutaneous metastases, PDT using argon laser resulted in the outcomes listed below.[208] The first of these results is obviously the most important:

- Total obliteration of the tumor in three of the nine patients;
- Reducing the tumor size by more than half in two patients;
- Reducing the tumor size by less than half in two patients;
- No regression in the remaining two patients.

The PDT used an extremely low light dose and was well tolerated, with no photosensitivity of the skin. The lack of side effects is of course a sharp contrast with conventional radiation treatment, which tends to burn the skin, suppress immunity, and trigger mutations.

The findings from this small clinical study are consistent with a series of laboratory experiments in which various types of PDT easily destroyed tumors in mouse models for breast cancer.[209] PDT also seems to greatly enhance the breast tumor-killing impact of the chemotherapy drug, doxorubicin (Adriamycin), and seems to help overcome the resistance that some breast cancer cells develop toward this and other chemotherapy drugs.[210] This is extremely important, since treatment resistance is among the main reasons for the failure of chemotherapy in metastatic breast cancer.

Part of the mechanism for overcoming treatment resistance may have to do with blocking the process of angiogenesis, the formation of new blood vessels that allow new tumors to spring forth. Researchers at Yale University School of Medicine have been developing a special form of PDT that inhibits this process in animal models for breast cancer, resulting in reduced breast tumor growth and spread.[211] The PDT targets something called *tissue factor*, a substance found on the vascular endothelial cells that support the development of new tumors.

PDT could also play a valuable role in women whose breast cancer has spread to the spine. This all too common problem is linked with accelerated breakdown of the vertebrae, resulting in spinal compression

and other "bony" problems. Chemotherapy and radiation can help in this situation but tend to have serious side effects, and treatment resistance can occur as well.

How might PDT offer a solution to this vexing problem? In numerous animal studies, PDT selectively knocked out the spinal metastases while at the same time improving the vertebral bone's integrity.[212] If clinical studies confirm these findings, then PDT could prove to be a superb alternative to the use of drugs called *bisphosphonates*. These drugs are now widely used for this situation, but they don't always work and often exact a heavy toll on one's quality of life due to numerous, serious side effects.

One of the primary treatments for breast cancer in the past century was mastectomy, the surgical removal of one or both breasts, either partially or completely. These days, the decision to carry out mastectomy is based on various medical considerations, such as the number of breast cancer lesions, aggressive character of the disease, genetic factors, breast size, and the patient's reluctance to accept the higher rates of tumor recurrences that come with the main alternative—the breast-conserving surgery known as lumpectomy, which is followed by radiation treatment.

When mastectomy is compared to lumpectomy plus radiotherapy, however, it is clear that radical mastectomy surgery does not always preclude the possibility of "distant" metastases happening later on. This could be due to the likelihood that micrometastases existed in those other parts of the body before the diagnosis and operation. As we explained in Chapter 3, this would set the stage for a recurrence happening possibly many years later, unless the woman managed to eliminate those micrometastases in the interim. (We mentioned that PDT and PIT are possible ways to make this happen; however, there are certainly other methods that could markedly enhance her anti-cancer immune defenses and help eliminate those micrometastases.)

One of the recurrences that can take place after mastectomy is a return of breast cancer in the chest wall. This affects only between five and eight percent of all cases, but it is much more common in the poor or underserved populations. It's also highly dependent on the stage of the original diagnosis, with incidence as high as 60 percent in some breast cancer patient groups. Many of these patients are facing a very aggressive, metastatic disease situation that cannot be adequately controlled with conventional treatment. When the traditional methods of surgery, radiotherapy and chemo-hormonal therapy have failed, there are few other options available.

PDT has emerged as possibly the best alternative treatment for patients in this situation. The basic approach uses a photosensitizer along with laser light to trigger the selective destruction of the metastases in the chest wall (via necrosis). Favorable findings from a number of small clinical studies attest to this claim. Here's a quick summary of the findings from two of these studies.

In the first study, 14 patients diagnosed with more than 500 chest wall metastases were treated with PDT. All received the photosensitizer Photofrin on an off-label basis, as part of a low-dose PDT regimen using a diode laser. The follow-up period was up to two years. All the patients showed evidence of tumor destruction (necrosis) during PDT. Nine out of 14 patients had complete responses, even in lesions that were greater than two centimeters. The researchers concluded that this low-dose approach to PDT "offers patients with chest wall progression a treatment option with an excellent clinical response. To date, the response is prolonged and offers good local control."[213]

The second study included nine breast cancer patients with multiple metastases to the chest wall. A total of 102 chest wall sites were treated with PDT after failure of intensive conventional treatments. All patients received PDT and were observed for at least six months. Despite all patients having received previous surgery, full-dose radiation and intensive chemohormonal therapy, chest wall lesions healed with no scarring. Only one large lesion (9 centimeters) took longer than three months to heal fully following PDT. Total elimination of the lesion (complete response) was noted in 89 percent of the lesions; however, regrowth of most lesions occurred. Only three percent of the lesions did not respond to PDT.[214]

Three other small clinical studies showed very similar results to those reported above. Rather than list all their findings, we will just include a few quotes from the conclusions of each study:

- "PDT is an effective treatment for chest wall recurrence in patients with breast cancer in whom other treatments have failed. PDT is also well tolerated, especially when compared with traditional therapies." [215]
- "PDT offers an excellent local control rate of chest wall recurrence with minimal morbidity after multimodality treatment failure. The treatment is given in a single session and on an outpatient basis. In patients who may register a partial response or have recurrence or the incidence of further chest wall nodules after photodynamic therapy, the treatment is repeatable." [216]
- "PDT offers a minimal-invasive, outpatient treatment modality for recurrent breast cancer on the chest wall with few side effects, high patient satisfaction, and with possible repetitive application." [217]

As more studies accumulate, we feel confident that there will be a positive shift in the oncology community's views toward PDT and PIT when it comes to treating breast cancer and in particular managing the more advanced, metastatic manifestations of this disease. What seems particularly attractive about these light-based therapies is that they can be used in a highly cost-effective way compared to conventional treatments, and that they're associated with very few side effects and complications.

Aside from surgery, PDT is really the only other effective treatment for chest wall progression in breast cancer. While conventional PDT has been in clinical use for over three decades, it has yet to gain the breast cancer community's respect and serious attention for a number of reasons:

- Many oncologists are attached to the standard treatment trio of surgery, radiation and chemotherapy—the main focus of their rigorous training—and are just not interested in having to learn about an entirely new and different way to treat the disease.
- There are concerns about patients getting sunburn after they receive the photosensitizer, even though this side effect can be avoided with proper patient education (and even though the side effects of conventional treatment can be far more drastic than a sunburn!).
- There may be concerns that the photosensitizer is not specific enough for breast tumors—an outdated belief, but nonetheless one often expressed by skeptics and critics of PDT.
- The treatment is so different from the existing standard treatment that some oncologists may feel concerned about having to learn an entirely new modality.

Research is now under way to determine which light delivery devices and light dosage regimens may be optimal for use in the treatment of chest wall progression of breast cancer. If larger clinical trials are performed and PDT continues to prove itself effective as a treatment for chest wall progression in breast cancer patients, these approaches should open a new therapeutic paradigm that can be applied to other breast cancer situations.

Before closing this chapter, we wish to emphasize the need for combining PDT (as well as PIT) with other innovative strategies that could perhaps create a potent synergy and thus greatly enhance the treatment outcome. Perhaps the best example of this is hyperbaric oxygen therapy, or delivering oxygen under higher atmospheric pressure by having the patient sit in a pressurized chamber. This approach can improve the treatment of many solid tumors using either radiotherapy or chemotherapy.†

Hyperbaric oxygen therapy is a relatively benign treatment with very few contraindications, even for patients with active cancers. Given that the actual effectiveness of PDT depends in part on the availability of oxygen, the use of hyperbaric oxygen would be a very logical way to make the light-based treatment more effective, and to perhaps improve the chances of overcoming even some of the most deadly cancers we face today.

In summary, the use of PDT and other photodynamic technologies is still a work in progress, and it will take some amount of patience and courage for the medical community to more fully embrace this power-

† Hyperbaric oxygen therapy has also been used for reducing the following in patients receiving radiotherapy: radiation injuries for soft tissue and bony injuries; laryngeal radionecrosis; radiation reactions of the urinary bladder and the bowel; radiation-induced optic neuropathy; radiation-induced proctitis; and radiation-induced necrosis of the brain.

ful technology. We believe there is a strong possibility that combining PDT with hyperbaric oxygen, hyperthermia, and various nutritional-herbal strategies (such as those we describe in the last chapter) will prove to be an even more effective way to treat and manage many types of cancer. This more integrative, targeted light-based approach to cancer medicine is surely the wave of the future. (Again, please refer to our detailed discussion on breast cancer in Chapter 7 and learn how PDT can be integrated into a more comprehensive treatment approach.)

CHAPTER 5

Lighting Up Other Health Problems

Some four thousand years ago, the ancient Egyptian, Indian and Chinese civilizations used sunlight, either alone or in combination with herbal salves, to treat psoriasis, rickets, vitiligo and other diseases. No doubt the Native Americans and other cultures realized the healing powers of sunlight—they just didn't bother to leave us written records to document the knowledge. Over the last century, targeted light-based treatments in the form of photodynamic therapy (PDT) and photoimmunotherapy (PIT) have exploited this same principle—albeit with a greater degree of sophistication than was ever realized by ancient civilizations—to address an even wider range of health problems.

In the preceding chapter, we presented a wealth of research-based insight on the use of PDT, photodiagnosis and other light-based methods used for the diagnosis and treatment of common cancers. In this chapter, we will apply photodynamic principles to other diseases or conditions. For example, PDT has well-established therapeutic applications for acne, psoriasis, atherosclerosis, and age-related macular degeneration, the leading cause of visual impairment and blindness among older Europeans and Americans. We will begin with heart disease, the number one killer disease in developed countries.

Atherosclerosis and Coronary Heart Disease

Coronary heart disease (CHD), also known as coronary artery disease, is now the leading cause of death worldwide, according to the World

Health Organization. Back in 1969, the WHO referred to it as "mankind's greatest epidemic" because it had already reached enormous proportions and was striking people at younger and younger ages. Since the 1960s, death rates from CHD have dropped steadily in Europe, Australia, the United States and other parts of the developed world. In recent years, however, the CHD mortality rates have reached a plateau in people under age 55, and have even increased in some countries for the first time in over two decades.[218]

Atherosclerosis refers to a slowly progressive process that begins at an early age and drives the development of CHD. This process involves an imbalanced metabolism of body fats (lipids) along with chronic inflammation within the walls of the arteries, blood vessels that carry blood to the heart.[219] In atherosclerosis, cholesterol-laden plaque builds up inside the arteries, gradually thickening the artery walls. The narrowing of those blood vessels makes it easier for clots to form; blood clots forming around the plaque may cause the artery to narrow even faster.

The overall effect is to limit and eventually block blood flow to the region of the heart supplied by the artery. Chest pain, or *angina,* can result when lack of blood flow "starves" some of the heart muscle. Heart attack, or myocardial infarction, occurs when the blood flow is completely blocked, usually due a blood clot forming over a plaque that has ruptured. Insufficient blood flow to the heart is responsible for about seven million deaths from heart disease per year around the world, according to the WHO.

Despite the considerable progress that has been made toward preventing and treating CHD, there are still many obstacles to long-term cure for anyone who has developed the condition and then undergone surgery. A major problem is the tendency for the arteries to become blocked once again, a process known as *restenosis*. The use of light-based therapy, or PDT, may have strong potential as a tool to complement vascular surgery and is now being evaluated in clinical trials for cardiovascular disease and CHD.[220]

But first, how does restenosis come about? Various procedures that are typically used to treat the vascular damage from atherosclerosis include cardiac surgery, angioplasty, and vascular surgery. When an artery is cleared or opened up, it can subsequently become narrowed again, and this is thought to involve an inflammatory immune response to damaged tissue. Indeed, up to 50 percent of all heart disease patients experience this phenomenon within six months of their procedure, most commonly stenting and angioplasty.[221]

Before going further, let's be clear about our terms. *Stenting* is used in about eight out of every ten coronary procedures. This refers to inserting a slender tube inside the blood vessel to provide support during and after the surgery. *Angioplasty* refers to a procedure used to widen vessels narrowed by atherosclerosis and subsequent blockages or occlusions. When a stent is used and restenosis occurs, this is known as *in-stent restenosis*. If the event takes place after balloon angioplasty, it is called *post-angioplasty restenosis*.

So to summarize: Restenosis appears to be the result of a complex inflammatory process in the arterial wall in response to either stent insertion or balloon angioplasty. As you might imagine, given how common the problem is (and the immense cost to modern health care systems), solving the problem of restenosis is a top priority for medical researchers working in the field of cardiology.

Only a few clinical studies have examined the possibility that PDT could be an effective way to prevent in-stent restenosis following surgery. However, the findings do indicate that it's both safe and effective.[222] The photosensitizer is administered through a local delivery catheter to coronary-stent implanted lesions; this is then followed by treatment with a pulsed laser to those same lesions. Given that this is a painless, quick-and-easy procedure, it would seem to be a very logical way to ensure more long-lasting results after cardiac surgery. (And of course, if you're going to submit to open-heart surgery and have your entire chest opened up, you may as well make it count!)

Furthermore, PDT can be used as a way to treat vascular disease directly—by stabilizing atherosclerotic plaques and inhibiting their progression. It accomplishes this by targeting the inflammatory macrophages that tend to gather in lesions in the arteries. In a recent animal study, for example, the area of the plaque occupied by inflammatory macrophages was reduced by 98 percent within one week of treatment![223] PDT destroyed both the macrophages and smooth muscle cells without damaging the structural integrity of the blood vessels—after

one month, the tissue was intact, and repopulation with smooth muscle cells was well under way.

Other recent laboratory studies have confirmed that PDT can substantially shrink the size of the plaque area in blood vessels and also greatly reduces the macrophage content of the plaque itself.[224] These and other favorable findings suggest that PDT represents a potential clinical strategy that may substantially lower the incidence of heart attacks or other CHD events.[225] It is likely that the light-based therapy will begin to receive serious consideration as a clinical treatment option for slowing and stopping the development of fatty plaques. This has led to the development of a novel approach called *photoangioplasty*, which entails light activation of a photosensitizer that is injected into plaque-laden artery walls. Once activated, the agent has the potential to open up large segments of narrowed blood vessels.[226]

Though heart disease is a grave public health problem, it's also highly preventable. The practical key is to implement prudent lifestyle changes, including a mostly vegetarian, whole foods diet (with small amounts of coldwater fish, wild game, or grassfed beef. This amounts to what some are calling an "anti-inflammatory diet".[227] In addition, we highly recommend that you engage in regular exercise, good stress management skills, and avoidance of smoking. It is the combination of these lifestyle habits that adds up to a reduced risk of CHD. Research is needed to see how these "heart-friendly" connections might influence the effectiveness of PDT against cardiovascular disease.

In summary, we now have exciting evidence that PDT can reduce the chances of restenosis that plagues many heart disease patients after they undergo a procedure. Moreover, there is now suggestive yet compelling evidence that PDT may offer a promising way to stop atherosclerotic plaques from developing further.

Age-Related Macular Degeneration and Other Eye Disorders

Many elderly people are all too familiar with a vision problem known as age-related macular degeneration, or ARMD. This familiarity stems from the fact that ARMD is the number one cause of blindness in people over age 60 living in Europe and North America. These days, ARMD is the third leading cause of blindness (after cataract and glaucoma), causing nearly one in every ten cases of "legal blindness" around the world.

So, what exactly is this vision-stealing condition? Scientists have come to conclude that ARMD involves degeneration of the retinal pigment cells making up the macula. This results in the loss of rods and cones that largely determine our visual acuity or ability to see fine detail. Although ARMD does not lead to total blindness, it's often extremely disturbing because it can make reading and fine-detail work all but impossible. The macula also enables our straight-ahead vision, which is why the famous artist Georgia O'Keefe described her experience of the condition later in life as only being able to see "around the edges" of her eye.

PDT's primary role is to help eliminate the early signs of ARMD. The treatment is performed with red laser light after intravenous injection of the photosensitizer (such as a porphyrin), which leads to accumulation of the porphyrin in cells involved in the progression of ARMD.† In a study of 20 patients with ARMD, the retina was observed to swell following PDT during the first 24 hours after treatment. In the days that followed, however, the patients' retinas contracted, and a normal retinal shape and function was observed within one week of completing the PDT treatments.[228]

PDT was introduced in the late 1990s as a novel treatment for neovascular forms of ARMD and choroidal neovascularization (CNV), secondary to pathologic myopia (nearsightedness). The term neovascularization refers to proliferation of blood vessels in tissues not normally containing them, such as the eyes. Abnormal or excessive formation of blood vessels in the eye can result in vision problems such as ARMD.

The specific mechanism in this case is as follows: The neovascularization process can be stopped with the photosensitizer, verteporfin, which accumulates in the choroidal vessels of the eye and is activated by blue laser light. Upon light exposure, this agent generates reactive

† These cells are the endothelial cells of choroidal neo-vessels. This is important, since choroidal neovascularization is among the symptoms of age-related macular degeneration. In these studies, a technique known as Optical Coherence Tomography is used to visualize the retinal structure in patients with ARMD in the weeks following PDT.

oxygen molecules that trigger a series of mechanisms leading to the blocking of blood vessels and breakdown of the neovascularization process. Note that even though these blood vessels do not grow back, other vessels will still be formed due to continued expression of the growth factor, VEGF.

The latest drug treatments are aimed at inhibiting this process by blocking the underlying mechanism, which is known as angiogenesis. VEGF, which we just mentioned above, is a key angiogenesis factor. Anti-VEGF therapy is becoming increasingly popular for early-stage and progressive ARMD; however, PDT itself can have similar effects by inhibiting the same mechanism.

In 2000, the U.S. Food and Drug Administration approved PDT as a first-line treatment for ARMD. In Europe, PDT is approved for the treatment of subfoveal lesions composed of predominantly classic CNV, and for hidden (occult) lesions with no classic CNV but evidence of recent disease progression. At this time, millions of treatments have been administered with good results throughout Europe and North America. Many of the current treatment recommendations for PDT are based on the results of two large clinical trials, the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy and Verteporfin in Photodynamic Therapy Studies.[229] For this research, thousands of patients were treated worldwide over the course of several years.

Nevertheless, the recent introduction of anti-VEGF therapy (which blocks angiogenesis, as we noted above) is rapidly outshining PDT—even though the latter still represents a good first-line treatment option for people facing this condition. Findings from several clinical trials suggest that PDT works best when combined with anti-VEGF therapy.[230] In contrast, it appears that anti-VEGF therapy can be used on a stand-alone basis to treat a wider range of neovascular disorders that affect the eyes.[231]

PDT seems to provide some remarkable benefits when used for other eye-related disorders as well. These include the following: CNV secondary to choroiditis and retinochoroiditis, central serous chorioretinopathy, retinal angiomatous proliferation, angioid streaks, parafoveal telangiectasia or CNV associated with macular dystrophy and idiopathic CNV. It also includes diseases without CNV, such as choroidal hemangioma, retinal hamartoma, choroidal melanoma, chronic central serous chorioretinopathy, angiomatous lesions secondary to systemic diseases, rubeosis iridis and neovascular glaucoma.[232]

One complication that may occur after glaucoma surgery symptoms is known as a *thin-walled cystic filtering bleb*. A *bleb* refers to the elevated area in the conjunctiva, the tissue that lines the inside of the eyelids and covers the white part of the eye (sclera). The trouble with having a bleb is that it filters or leaks the fluid (aqueous humor) out of the eye after glaucoma surgery and often gets infected and inflamed, so that the afflicted individual may lose vision. This complication is not uncommon for some types of glaucoma surgery.

In one of our earlier studies, a total of 60 glaucoma patients with this particular surgery complication were treated with Radachlorin® along with argon laser treatment.[233] This involved a month-long course of both anti-inflammatory and antioxidant therapy, along with continuation of blood pressure medications.† The results of this light-based therapy can be summarized as follows:

- A stabilizing of the fluid pressure inside the eye (intraocular pressure).
- A decrease in filtration in seven days on average, with this benefit being most pronounced two to three weeks from the time of PDT.
- A decrease in inflammation of the conjuctiva (conjunctival hyperemia grade) within four weeks of PDT.
- Radachlorin® showed excellent tolerance and high efficacy. Because of these findings, the drug has been recommended by healthcare authorities in Russia for treatment of patients with this complication of glaucoma surgery.

† The procedure specifically involved administering the Radachlorin® subconjunctivally and singly nearby the filtration cushions with following putting laser overlays onto the conjunctiva at the site, within 1 session. The irradiation was made using an argon laser unit performing at 514.5 nm (green beam). The beam power was set to 0.5W, and its exposure time amounted to 0.2 seconds; the beam provided a light spot with the diameter of 50 μm and 100 μm, and the overlays number was 40 to 60. Patients received anti-inflammatory therapy (garason, 1 drop 3 times a day) and antioxidant therapy (emoxipin 1 percent, 1 drop 3 times a day).

Our elderly populations in Europe, the USA, and other industrialized countries are constantly expanding, and thus blindness due to ARMD is likely to increase steadily in the coming years. Until we have reliable treatments for ARMD, prevention will be critical for reducing this condition's impact on our growing elderly population.

Macular degeneration has been linked with a number of lifestyle factors, such as cigarette smoking, alcohol, chemicals, excessive sunlight, and consumption of high-fat, low-vegetable diets. People with a history of cardiovascular disease also are more at risk. It is thought that older individuals may be able to prevent ARMD by sticking to a plant-based diet (in particular, plenty of dark, leafy vegetables), avoiding smoke and chemicals, and consuming moderate amounts of wine.

In addition, certain nutritional supplements may further improve the treatment of early-stage ARMD.[234] This could include supplementing with zinc and the carotenoids, zeaxanthin and lutein is also thought to be helpful. Carotenoids are pigments naturally abundant in many fruits and vegetables; however, there are well over 600 different carotenoids. Among these, zeaxanthin and lutein appear to have unique effects in terms of curbing the degeneration of the macula.

Given that ARMD represents the leading cause of blindness amongst the elderly in all the big industrialized nations, we expect PDT to serve a key role in helping people fend off this common eye problem. A recent review of European guidelines for the treatment of ARMD—and you may want to consult with your opthalmologist to clarify each of these specific situations—recommended that PDT be used for the following situations: (1) juxtafoveal classic CNV that is close to the fovea, making it risky to use thermal laser photocoagulation; (2) for predominantly or minimally classic juxtafoveal lesions with evidence of occult CNV; (3) for occult with no classic juxtafoveal CNV; and (4) small minimally classic lesions; and (5) for eyes with small subfoveal occult with no classic CNV and presumed recent disease progression, or with visual acuity at a lower level (worse than 20/50).[235] Combining the PDT approach with nutritional changes and other strategies to inhibit angiogenesis may be the best hope for reversing this very bothersome visual problem.

Acne (Acne vulgaris)

Acne is a common skin condition that shows up most often in young people, though older people can also be affected. It is estimated that at least four out of five people between the ages of 12 and 24 will get acne at least once in their life. This is most common in young men during puberty and is understood to be a normal response to abnormal levels of the male hormone, testosterone. Nonetheless, women too may experience mild to moderate acne as a result of hormonal changes associated with puberty, menstrual cycles, birth control pills and other feminine health issues.

Physiologically speaking, acne is an inflammatory condition in which the skin's sebaceous glands are producing too much oil, resulting in an eruption of pimples or pustules. These unsightly outbreaks usually crop up around the face, but can also affect the neck, back, chest and shoulders. Bacterial infections also may be involved, due to increased oil secretions that result in accumulations of bacteria in the pores. This allows the bacteria and yeast to proliferate, producing an inflammatory reaction. The main organism that has been identified in these skin infections is called *Propionibacterium acnes*.

Other factors that may increase the risk of having an outbreak of acne, especially in younger people, may include the following: chronic physical pressure on the skin, such as that caused by tight collars, backpacks, bicycle helmets, hats, hair bands, and cell phones; skin irritation and scratching, which in turn triggers inflammation; various medications, such as anabolic steroids, anti-seizure medications, and lithium and iodine-containing medications; and chronic exposure to chlorinated industrial chemicals, which can cause severe, long-lasting acne (a condition known as *chloracne*); emotional distress; and regular consumption of dairy products, which has been linked with acne in several studies.[236]

On the protective side, simply getting out in the sun can have a beneficial effect on acne, often helping to shrink and eliminate those bothersome pimples. This fact is not lost on many sunbathing teens or their observant parents. Of course, too much sun can be harmful, so we're not advocating this as a therapeutic strategy. Rather, sunbathing or casual encounters with the sun during the summer months should be

viewed more primarily as a preventive strategy that seems to work quite well for teens—especially if the other risk factors (mentioned above) are addressed as well.

Probably owing to its various causes, acne continues to be a major challenge to dermatologists and primary care physicians alike, accounting for millions of visits to physicians each year. For many years now, the mainstream treatments have been antibiotics and retinoids (vitamin A compounds), which are available in topical and oral formulations. However, there is a growing openness in the modern medical community toward new treatments such as PDT, laser therapy, comedo extraction, and chemical peels.[237]

PDT in particular is fast emerging as a useful off-label treatment for acne vulgaris. Among the key mechanisms of action for this treatment is the light-triggered destruction of the main infectious agent we mentioned earlier— *Propionibacterium acnes*—as well as a reduction in the size of the sebaceous glands and a decrease in overall sebum production.

One of the notable advantages is that the PDT will kill the organism regardless of any antibiotic resistance.[238] This is a salient point, given that antibiotic resistance has emerged as a medical and environmental crisis of global proportions. Many doctors are scrambling to figure what to do for their patients when antibiotics seem to be ineffective. PDT could very well be the answer, along with diet and other lifestyle-related risk factors we listed previously in this section.

In the typical clinical situation, the photosensitizer is either taken orally or applied topically. Then the acne outbreak areas are exposed to either blue light or red light, with the light treatment delivered up to several hours after administration of the sensitizing agent. In some cases, the use of intense pulsed light may also be effective for the treatment of acne.[239] In this vein, the photosensitizer "MORION®" gel has been undergoing development by a Japanese company as an antiacne and skin photorejuvenation technique.†

It is interesting to note that blue light alone can help clear up mild cases of acne due to its antiinflammatory effects; however, it is thought that the photosensitizer tends to provide an extra therapeutic punch for more advanced cases. Also, more serious cases of acne may require high doses of red light-based PDT in order to shut down the sebaceous glands and produce more substantial improvements.[240]

Findings from many clinical studies have shown that the PDT approach is quite effective as a treatment for acne, regardless of the severity of the condition.[241] The incubation time of the specific photosensitizer will vary depending on the agent, usually ranging from fifteen minutes to three hours. In addition to killing bacteria, it is clear that PDT can result in substantial phototoxicity to the sebaceous follicles, along with prolonged suppression of sebaceous function—a drop-off in the skin's oil production (which of course accounts for this condition's nasty-sounding name, *Acne vulgaris*).

The recent surge in the dermatology and infectious disease communities' interest in PDT seems to have been largely driven by the inexorable increase in antibiotic resistance to many different types of organisms—including those associated with acne and other skin infections. As mentioned above, PDT has the obvious advantage of circumventing the antibiotic resistance issue, and at the same time there does not appear to be any induction of resistance to the PDT. On the flip side, the disadvantages of PDT may include the fact that the microbe-killing effect stops when the light is turned off, and the photosensitizer's selectivity for the bacterial cells (versus the normal body cells) may not be perfect.

Nevertheless, for mild to moderate cases of acne, the research to date points to PDT as an excellent treatment option. Particularly as concerns are increasingly voiced by scientific and governmental agencies regarding the global problem of antibiotic resistance, we can expect more and more attention to be given to PDT and other sensible alternatives to antibiotics.

Ear, Nose, and Throat Conditions: Tonsillitis and Sinusitis

Tonsils are soft tissue masses located on both sides of the back of the throat, and they are considered part of the lymphatic system—the system that's constantly filtering the blood of toxins and carrying various immune cells throughout the body. As an extension of the immune system, tonsils help your body fight infection by producing antibodies to

† Morion has a chlorin composition with a central coordinated atom of zinc, and is optimally used with a blue light exposure (420 nm).

eliminate bacteria that enter through the mouth and nose. Most people never think about their tonsils until they become repeatedly infected and thus inflamed—the condition known as chronic tonsillitis.

Despite some progress in the use of the novel antibiotics, chronic tonsillitis continues to pose a challenge to modern medicine. PDT is among the therapeutic angles that merit serious attention. In one study, 32 patients were included in a PDT study, all of whom had chronic tonsillitis of various degrees of severity (see Table 1).[242]

Grade of the Pathology (Patients Number)	Number of PDT Sessions		
	1 Session	2 Sessions	3 Sessions
Slight (19)	19	0	0
Toxic and Allergic I (9)	7	2	0
Toxic and Allergic II (4)	1	2	1
Total (32)	27	4	1

Table 1. *PDT in Patients with Chronic Tonsillitis*

In this study, the effects of PDT were evaluated in terms of the clinical manifestation of each case of tonsillitis, as well as bacterial samples and immune system changes. Radachlorin® was mixed with a 2% lidocaine gel was, and this was applied directly to the tonsil gaps, then followed by up to 15 minutes of light treatment using a laser beam.

The efficacy of this light-based treatment was assessed one month after the treatment, and the patients were then observed for up to six months. In nearly nine out of every ten cases, the bacteria found in these patients appeared to be sensitive to the various antibiotics. PDT was highly effective for treating chronic tonsillitis, particularly in the milder cases (lower grade). The researchers concluded that this approach, using Radachlorin® as the photosensitizer, can be recommended to patients with chronic tonsillitis who cannot tolerate antibiotics or even as a painless, non-invasive alternative to tonsillectomy.

Another common ENT challenge is the problem of purulent sinusitis. Sinusitis is an inflammation of the sinuses, small cavities in our skull that are filled with air and help to keep bothersome bacteria out of our body. The inflammation usually results from an infection, allergy, or autoimmune issues. When acute purulent sinusitis occurs, the lining of the sinuses becomes inflamed and air is trapped inside the cavities, resulting in infection, pus, pressure and headaches. Acute purulent sinusitis can last for several weeks; it can also be a chronic illness that occurs several times during the year.

Despite some achievements in the use of novel antibiotics and surgical treatments, chronic recurrent sinusitis continues to be a major health problem, and this is mainly due to the reality of antibiotic resistance. This is one of the most common chronic conditions in North America and Europe. A significant number of individuals with chronic sinusitis remain resistant to a cure despite aggressive treatment that may include surgery, allergy therapy, and prolonged antibiotic therapy. The main reason for treatment failure is thought to be the breakdown of the natural sinus defense system followed by the development of antibiotic-resistant bacteria and biofilms (protective coatings that shield the bacteria from antibiotics and from attack by the immune system) in the sinuses.

Thankfully, PDT offers a broad-spectrum antimicrobial treatment that can eradicate antibiotic-resistant bacteria and biofilms. In fact, cell culture studies conducted by Advanced Photodynamic Technologies, Inc., in Minneapolis, Minnesota (USA), have demonstrated the effectiveness of PDT against the biofilms and bacteria that have been linked with chronic recurrent sinusitis. The researchers observed that PDT reduced the antibiotic-resistant bacterial biofilm by greater than 99.9 percent after a single treatment.[243]

Going further, we have conducted pilot clinical studies to address this issue. In one study of 40 patients, all had chronic sinusitis in the form of purulent inflammation of their maxillary sinus that had lasted from one to eight years.[244] All had undergone a careful examination prior to receiving PDT treatment, including the following: studies of the bacteria in their sinuses, CT scans of their paranasal sinuses, inspections by oral surgeon using X-ray examinations, and endoscopic

examinations of their maxillary sinuses in vague cases.

The PDT treatment again used the photosensitizer, Radachlorin®, which was injected directly into the sinuses, and laser treatment was provided 2.5 to 3 hours later. The clinical and bacterial examinations revealed that the PDT was highly effective in treating chronic sinusitis, comparable to the results achieved with antibiotics. Thus, for chronic sinusitis patients who cannot tolerate antibiotics or for whom surgery may be contraindicated, PDT may be an excellent option. None of the 40 patients experienced a worsening of their general health status, nor did they show any adverse changes in various physiological outcomes or a progression of allergies or toxic reactions.

Psoriasis

Psoriasis is a common, irritating, non-contagious skin disease that affects 2 to 3 percent of the world's population. Over 125 million people living in Europe, Japan and the United States have psoriasis, which can occur at any age, affecting men and women alike. Though the condition occurs worldwide, the incidence is lower in warmer, sunnier climates. Whether this is partly due to sun exposure is not known, but it seems plausible, at least given the sun's effects on immune system functioning and the fact that psoriasis does have a strong immune system component.

Psoriasis is a chronic condition that can come and go. It usually appears as a buildup of dry, rough, dead skin cells, often with raised, reddish-pink areas and an abundance of white or silvery scales. Patches of psoriasis can either manifest in a few small areas or they can span large areas of the body—though often showing up on the scalp, elbows, knees, and lower back. Though the majority of cases are not painful, some of the more severe ones can be, particularly in the case of psoriatic arthritis, which entails painful and swollen joints.

The cause of psoriasis is unknown. We do know that there's a positive family history in about one out of every three patients, and your chances of getting it are higher if you have a close relative with the condition. Emotional distress also plays a role, as does obesity, smoking, alcohol abuse, cold or dry air, skin injuries (including sunburn), and streptococcal throat infection. All of these factors could possibly trigger or exacerbate the condition. For example, if you have psoriasis and you're exposed to alcohol or certain dietary factors (e.g., gluten), you're more likely to have flare-ups of the disease.

As we noted above, psoriasis entails an abnormality in immune system functioning. This mainly involves overactivation of the T-cells, which can in turn affect many immune functions. This awareness has led to therapies aimed at blocking or modulating T cell activation. To date, however, T-cell-targeted therapies for psoriasis have only been effective in a small percentage of patients and moreover carry the risk of severely suppressing the immune system.[245] Most psoriasis sufferers require lifelong treatment; however, many of the current therapies are complicated by major toxicities or by inconvenience since they have to be provided over the long term.

Phototherapy, the use of different types of ultraviolet light without a photosensitizer, remains a very strong treatment option for psoriasis. In particular, the use of ultraviolet-B (UVB) continues to be one of the most reliable therapies for mild to moderate psoriasis, despite concerns about an increased risk of skin cancer. For many years, UVB phototherapy was provided as a broadband source, 290 to 320 nm. At this time, however, a more promising phototherapy approach is known as narrow-band Ultraviolet-B therapy (NBUVB). Narrow-band refers to a specific wavelength of UV radiation, 311 to 312 nm.

It now seems clear that the NBUVB lamps are superior to conventional broadband UVB in clearing the more moderate forms of psoriasis. During treatment, which may take place a few times a week, the patient is placed in a specially designed cabinet containing fluorescent light tubes. He or she stands in the center of the cabinet, undressed except for underwear and protective goggles. Typically, the whole body is exposed to the UVB for seconds to minutes, depending on factors such as the individual's skin type, age, skin condition, etc. The amount of UVB is carefully controlled during treatment. The skin may remain pale or turn slightly pink after each treatment, and patches of psoriasis may start to clear up after five to ten sessions. Most cases of psoriasis require 15 to 25 treatments to clear completely.

Another approach, photochemotherapy with ultraviolet-A light (PUVA), is considered to be the best option for severe, extensive forms of psoriasis. There has been a trend towards providing a whole-body

PUVA bath for individuals in this situation.[246] During the PUVA bath, you stand in a booth that contains light tubes that give off UV light. Goggles are worn to protect your eyes during treatment, and men need to shield their genitals to avoid an increased risk of genital cancer. After the treatment, your skin should be checked frequently—at least once or twice a year—for signs of damage or skin cancer.

PDT has been used to treat psoriasis, but there is some debate as to its usefulness and which specific treatment regimens are optimal.[247] In a randomized clinical study of 150 patients with psoriasis, scientists in India sought to evaluate the effects of oral psoralen, a plant-derived photosensitizer whose use in this context dates back to ancient Egypt. The researchers used natural sunlight as a light source and referred to their approach as "photochemotherapy using natural sunlight", or PUVASOL. The study compared PUVASOL alone to PUVASOL along with a topical (photosensitizer) therapy.[248]

The combined photodynamic treatment involved 75 patients (group I) and included 30 minutes sunlight exposure, which was done every other day. There was a complete clearing of lesions in about 91 percent of patients, and lesions began clearing within 18 days on average. The skin lesions cleared more quickly, even with fewer treatments compared to the PUVASOL alone group.

Ninety percent of 51 patients who used topical therapy on their scalp managed to clear their psoriasis in this area. In contrast, only about 4 percent of patients with scalp involvement showed a clearing of their condition with PUVASOL alone. Lastly, all seven patients with psoriatic arthritis showed a clearing of their psoriasis; however, none of those patients noted any symptomatic change in the severity of their arthritis during the course of treatment in both the groups.

A 2008 review of the scientific evidence regarding PDT for psoriasis offered this conclusion: "After a thorough review of the literature, PDT remains a potential treatment for psoriasis. Clinical improvement has been observed in most studies. The major limiting factor seen in many of the studies was the side effect of pain and burning sensations associated with PDT."[249]

We agree with that assessment. Nevertheless, it seems likely that phototherapy using NBUVB will remain the favorite among light-based treatment approaches for mild to moderate psoriasis in the years ahead. Compared to the psoralen-based PDT approach, NBUVB has equal therapeutic potential but also a lower carcinogenic risk, therefore probably safer in the long term than the psoralen-based approach.[250]

It's important to recognize, however, that NBUVB is not without potential risks. It can result in burning, just as can occur with sunlight and broadband UVB. Frequent use of topical emollients (agents that sooth and soften the skin) should be applied to burned skin. Emollients are fats and oils such as lanolin, aloe vera, and liquid parafin. They work mainly by moisturizing the skin and protecting it from drying. In some cases, topical steroids may be advised. Long-term exposure to UV radiation ultimately leads to premature skin aging and a heightened risk of skin cancer. Although the risk from NBUVB is unknown, it appears to be no more risky than broadband UVB and less risky than PUVA.

As with other conditions we've addressed in this chapter, several dietary and lifestyle factors may come into play. High-fat or high-sugar diets, along with consuming too many gluten-containing foods (mainly wheat), have been linked with more severe psoriasis. Vegetarian diets, intermittent fasting, and diets rich in omega-3 fatty acids from fish oil may help reduce psoriasis symptoms.[251] In randomized clinical trials, a low-calorie, gluten-free diet proved to be effective in the treatment of psoriasis.[252] When you combine these dietary habits with stress reduction, weight control, and avoiding alcohol and smoking, you stand a much better chance of keeping psoriasis from advancing and possibly even reversing the condition.

CHAPTER 6

Eat, Live, Heal

You are far more in control of your health and healing than you may realize. Whether you're facing a serious illness or just wanting to feel better throughout the day, there's a profound benefit to paying attention to your daily living habits and their impact on your wellness. More specifically, the way you choose to eat, move, rest and relax in daily life can play a major role in helping you get healthy and stay healthy. And the best healing outcomes after a diagnosis of cancer or other serious disease may come from choosing foods and activities that will strengthen your body's immune system and other inner healing resources.

Our society's typical reaction to illness is not unlike that of a driver whose automobile has just broken down. In most cases, the driver's only recourse is to hire a mechanic, then stand by and await the outcome. The driver assumes the mechanic will understand the problem and know how to correct it. We relate to our bodies in much the same mechanical fashion—that is, by finding a doctor to "fix" our health problems, without having much power in the process. If we don't take the time to reflect on how we may have contributed to the disease, we may do nothing to change the causes or internal conditions that helped bring about the problem in the first place.

Yes, your physician and medical team can certainly help guide and facilitate your recovery, and they can provide essential tools for turning around even the most aggressive diseases. But your ability to stay healthy, your long-term health, is ultimately up to you, and you can do a great deal to improve your chances of overcoming an existing disease.

You yourself are the ultimate weapon against illness and degeneration, because the true source of healing lies within you, not outside of you. Your body has a remarkable ability to both nurture and heal itself, because your organs, glands and bodily functions are all designed to last a lifetime!

Throughout the day, you make choices that can affect your personal health and wellness. Every time you choose a food to eat, an exercise to perform, or even a way of thinking about or responding to a situation, you're influencing the dynamic condition called health—sometimes even allowing yourself to be driven closer to the precipice of illness. If you're already ill, then such behaviors may tend to undermine the benefits of medical treatments, and in some cases can nullify those benefits altogether.

For example, at end of the preceding chapter, we briefly alluded to some of the dietary and lifestyle factors that affect the onset and progression of psoriasis. Whether PDT would be more effective in the context of an "anti-psoriasis" diet and lifestyle is not yet known. It stands to reason, however, that the benefits of PDT would be more readily achieved and perhaps more lasting if the individual's daily living habits were aimed at discouraging rather than promoting the condition.

As another example, consider how your diet could affect the outcome of surgery, a well-studied medical situation. If you eat and live in ways that weaken or stress your immune system, your chances of avoiding an infection and having a smooth recovery after the operation are greatly diminished. Habitual intake of various meats, corn oil, safflower oil, hydrogenated fats, sugar and refined grain products (e.g., white bread and pastries) will promote *chronic* inflammation in the body, one that interferes with healing and can even promote cancer and heart disease.[253] In fact, excessive inflammation around the time of surgery has been linked with poorer survival for a number of different cancers.[254]

In addition to the dietary factors just mentioned, the body's inflammatory pathways are activated by tobacco, stress, obesity, alcohol, infectious agents, irradiation, and environmental pollutants, which collectively account for as much as 95 percent of all cancers.[255] There is little doubt that exposure to smoking, alcohol and other aspects of a "pro-inflammatory lifestyle" tends to worsen your recovery from sur-

gery and other conventional treatments. (This is why seasoned surgeons will routinely ask their patients not to smoke or drink after a major operation.) Though only time will tell whether these same lifestyle factors will affect the efficacy of PDT and other photodynamic modalities, the basic rationale is sound.

On the positive side, there is also reason to believe that specific nutritional, herbal and lifestyle strategies can improve your internal chemistry in such a way as to bolster the outcome of PDT and other photodynamic modalities. Such a dietary pattern would allow your body to mount an acute or healthy inflammatory response—one that does not linger long after the treatment and therefore will not encourage cancer, diabetes, arthritis, heart disease and other chronic diseases that have been strongly linked with chronic inflammation. Various herbal and nutritional supplements (also known as nutraceuticals) can further bolster the anti-inflammatory effects.[256]

In this chapter, we will lay the groundwork for a practical and effective approach to your health and healing, an approach rooted in an understanding of the effects of nutrition and lifestyle habits on the chemistry of healing. The strategies outlined here should nicely complement or perhaps even reinforce the use of PDT. Although most of these ideas are theoretical, we believe that they're safe and effective in their own right, and that their application should could help render PDT more effective and, in the long run, curative. We encourage you to incorporate these dietary tips into your overall treatment plan and to consider the long-term suggestions as well.

Diet for Health, Healing, and PDT Support

It has often been said that a whole-foods, plant-based diet is the foundation for the prevention and treatment of cancer and many other diseases. At least four decades of research have lent support to the role of dietary factors in the development of various disease states. Everything we eat changes the chemistry of our blood, affecting us not only physically, but also emotionally, psychologically, and socially.

So, just what type of diet is best for promoting health and healing in the context of PDT? And could this same diet help stave off cancer and other chronic diseases?

In our experience, there are two different types of diet to be considered here: one supporting PDT, and another helping to prevent cancer after finishing PDT. For both preventing and overcoming cancer, the expert consensus is to embrace a plant-based dietary regimen, one centered around green leafy vegetables, root vegetables, legumes, whole grains, nuts, seeds and fruits. These plant foods all contain an abundance of anti-cancer compounds, though with fruits, nuts and whole grains, one must be more selective.

The addition of small amounts of animal products could provide additional nutritional benefits. In the so-called Paleolithic-type diet or "Stone Age diet", people are encouraged to consume more lean meats (primarily fish, bison and wild game), nuts, seeds, fruits and vegetables, including wild or uncultivated plant foods. Some scientists contend that, when considering the needs of the entire human population, this type of diet may be more effective than strict vegetarianism because it's more in line with the body's evolutionary wisdom as determined by the human genome.[257] There is increasing evidence that such a diet could help lower the rates of cancer, obesity, hypertension, diabetes, and cardiovascular disease.[258]

For supporting PDT, we believe that further dietary modifications may be in order. These would apply only on the days on which you're actually undergoing PDT. Rather than eating an abundance of vegetables and antioxidant-rich fruits on those days, we would encourage you to eat very few of those foods, and to instead eat mostly grains, legumes, and fish. Though some fruit is acceptable, our advice is that you avoid eating berries, cherries, and grapes on the PDT days.

As you may have guessed, our reason for making this suggestion is that bright-colored and deep-colored vegetables, as well as berries, cherries, and grapes, all tend to be quite high in antioxidants. Though grains, nuts, seeds and legumes contain antioxidants as well, they are not nearly as well endowed as the other plant foods just mentioned. In principle, consuming a plethora of antioxidants from berries, cherries and other antioxidant-rich "power foods" could diminish some of the effectiveness of PDT, and so we'd suggest tempering your intake of those foods while you're going through the light-based treatments.

Other foods that are encouraged during or around the time of the PDT sessions include soy products and fatty fish such as salmon or tuna. The reason for this is that the omega-3 fatty acids in these fatty fish help generate a stronger oxidizing "punch" that seems to reinforce PDT effects.[259] PDT itself generates active oxygen radicals that steal electrons from biological molecules—including those that help keep tumors alive. Omega-3 fatty acids become concentrated in the tumor tissues, and this results in a more rapid destruction of the tumor.[260] (See sidebar for suggestions on supplements that can also help accomplish this effect.)

Once you complete your PDT treatments, we'd like you to think about incorporating plenty of those "power foods" back into your daily diet. In addition to the berries and other fruits mentioned above, these "power foods" include cruciferous vegetables such as collards, kale, Brussel sprouts, bok choy and broccoli. They also include bright-colored vegetables like squashes, peppers and tomatoes. Other great power foods, though somewhat less popular, include sea vegetables (kelp, alaria, dulse, and other varieties of seaweed) and traditional soy products (tofu, tempeh, miso, and soy milk).

A few caveats are in order before going further. First, if you have cancer, you should be careful about the type and quantity of fats and proteins you consume. In general, the scientific research has demonstrated that animal fats and proteins are more cancer promoting than the fats and proteins from plant foods. In particular, most sources of omega-6 fats (e.g., safflower oil, peanut oil and corn oil) should be avoided or minimized because of their cancer-promoting effects. We'll elaborate a bit more on these points later in this chapter.

Diet and Lifestyle for Long-Term Cancer Prevention and Control

As we noted, for long-term cancer control and prevention, we would suggest that you follow a mainly plant-based diet in between your PDT treatments, or after you finish the PDT. In this section, we'll give you a little more of an explanation as to the "why" of a plant-based diet.

To begin with, vegetarians are among the healthiest populations on Earth. All the nutrients your body needs (but which it cannot produce itself) can be obtained from the plant world—that is, from vegetables, fruits, algae, whole cereal grains, beans, nuts, and seeds. These nutrients include proteins, fats, carbohydrates, vitamins and minerals, as well as a vast array of plant-specific nutrients or "phytonutrients" (from the Latin *phyto* meaning plant). Truth be told, if the nutrients circulating in your blood can't be procured from plant sources, your body probably doesn't need them.

Through most of human evolution, wild plants were the primary source of food. Collecting plants for food represented a sensible adaptive strategy because plants didn't run away or try to attack you. Compared to animals, plants were far more ubiquitous in most temperate areas, and relatively little energy was needed to gather them (at least compared to hunting animals). Even today, most hunter-gatherer societies subsist mainly on wild plants, nuts and seeds, with relatively small amounts of animal food on the side.

The fact that most human societies from our ancient past evolved on a plant-based diet is reflected in the long length of the human intestinal tract—approximately seven to eight meters (25 feet) long in adults! This long tube appears to be designed for slow digestion of plant foods. In sharp contrast, true carnivores like lions, tigers and wolves have short intestinal tracts, allowing for the rapid breakdown and absorption of high-protein fare.

Our ancestors also ate what was made available in their regions through in-season local harvests. Those foods were fresh, unaltered, and mainly seasonal, and they provided the necessary nutrients at the right time. This pattern predominated until the refrigerator and other technological developments made it possible to choose our foods from almost any region in the world. Nevertheless, this is the type of diet that we should consider following today—that is, choosing foods that have been harvested locally and in season, as much as this is possible and affordable. Organically grown foods would be preferable as well.

Vegetables are among the only foods you can eat to your heart's content without gaining weight and promoting illness. That is, on a per-calorie basis, vegetables concentrate all the nutrients needed for good health. For instance, a half cup of broccoli provides a generous 70 milligrams of vitamin C, which the body needs to neutralize harmful free radicals and keep cancer cells from turning into deadly tumors.

SUPPLEMENTS THAT MAY SUPPORT PDT/PIT/SYLT

A number of supplements have been shown to kill cancer cells through pro-oxidant effects rather than antioxidant effects. This means that the supplement changes conditions inside the cancer cell such that there are too many free radicals floating around inside the cell. Free radicals are highly unstable and reactive molecules that constantly steal electrons from molecules and tissues, causing their destruction. We now know that the following supplements tend to kill cancer cells, in part, through these pro-oxidant effects:

- Soy proteins, 20-25 grams per day
- Selenium, 200-400 micrograms per day
- Green Tea (EGCG), 1000-3000 milligrams per day
- Curcumin, 1000 to 6000 milligrams per day
- Fish oil or algae oil (including *Spirulina* oil, containing CLC, chlorophyll-lipoid complex), 1-3 grams per day

Dosages for compounds will vary depending on individual factors such as past diet and inflammation. In general, the dosage ranges listed above are safe, though we encourage you to consult with a health care professional who has sufficient clinical experience with these agents. In some cases, it may also be helpful to have testing done to help you determine the optimal dose.

Additionally, keep in mind that the form of the supplement can affect its absorption and therefore the correct dosage. For example, for curcumin (or turmeric, standardized according to curcumin content), please be sure that you're using a form of curcumin that either contains biopiperine (from pepper) or is in the form of a phytosome (phosphatidyl-choline complex). These forms will enable maximum absorption of the curcumin, and thus make it far more effective in the body.

The following foods, herbs and spices are also recommended:

- Cruciferous vegetables (especially, marinated or seasoned)
- Turmeric (as cooking spice)
- Chili pepper (as cooking spice)
- Beetroot (steamed, marinated)

Two months after completing PDT, you may freely add other anti-oxidant-rich supplements such as grapeseed extract and various berry extracts, as well as vitamins C and E.

A half cup of even the most starchy vegetables, such as potatoes and squash, provides no more than 100 calories. This is less than the calories in a tablespoon of butter or oil. Indeed, the butter or cream sauce you may have added to your meals in the past has many times the calories of vegetables—and very few valuable nutrients.

Various herbal teas may be considered for daily consumption and are a good substitute for coffee and alcoholic drinks. Hundreds of laboratory studies have indicated the anti-cancer benefits of green tea in terms of preventing a number of cancers, notably tumors of the breast, ovaries, prostate, bladder, skin, lung, colon, rectum, stomach, esophagus, and oral cavity.[261] Several human studies have suggested green tea's promise for the prevention of tumor recurrences or possibly as adjuncts to conventional treatment. For example, two clinical studies found that drinking more than three cups per day could lower the risk of breast cancer recurrence by about 27 percent.[262] In addition, green tea may enhance the effectiveness of many anti-cancer drugs.[263] Though black tea appears to help protect against some cancers, the effects of green tea appear to be far more consistent.

Regular consumption of coffee has very clear protective effects against endometrial and liver cancers, and recent studies also suggest increased protection against breast and prostate cancers as well.[264] However, too much coffee could promote bladder cancer—a good reason to favor herbal teas in general.

In our own recent studies of herbal teas, done in collaboration with Dr. D. Howard Miles of the University of Central Florida, we found the following herbal components to have significant anti-cancer effects in cell culture studies: nettle leaves, linden flowers (Tiliae Flos Tea), fennel fruit, and cowberry leaves. These herbs were shown to kill leukemia cells when used only in microgram quantities—by 77 to 100 percent after only two hours of incubation.[265]

Another good idea is to mix different combinations of the following herbs with olive oil and use this blend as a seasoning for salads: garlic, horsetail, great burnet (roots), marsh labrador tea (in very small amounts, as too much is toxic), St John's wort, eleuthero roots, common knotgrass, viola, shepherd's purse, and licorice root. An old traditional method is to leave the herbs immersed in the oil for as long as two months before using as a dressing. Be sure to keep any herbal remedies in a cool and dark place and consume within a year.

Lastly, if you must drink, then consider a glass of red wine, a rich source of various flavonoids known to have both anti-cancer and cardiovascular benefits. In general, hard alcohol is not recommended or should be consumed only in moderation. For example, you may consider drinking small amounts in the form of herbal balsams, which have been used in traditional herbal medicine in parts of Eastern Europe.†

How Dietary Fats Either Fuel or Fend Off Cancer

Fats and oils are the richest dietary source of calories, containing twice as much as either protein or carbohydrate. When you eat high-fat foods, you're exposing your body to a host of factors that could increase your risk of developing various cancers and other diseases. The average dietary fat intake for the U.S., Russian, and several European country populations is between 35 and 40 percent of total calories consumed daily. A large body of scientific evidence suggests that this level of fat intake can raise the risk of cancers of the breast, colon, and prostate.

Nutritional biochemist T. Colin Campbell of Cornell University, author of *The China Study*, notes that a fat level of 20 percent is more desirable for human health and cancer prevention. He contends that many public health agencies have refused to acknowledge this level because it would mean converting to a largely vegetarian diet—a diet free of red meat, poultry, eggs, and dairy products (white-meat fish does not raise the fat level appreciably). Many public health experts have regarded this kind of diet as unrealistic or unpalatable for modern society, so they've routinely raised the recommended fat guideline to at least 30 percent of total daily calories.

† For example, Riga Black Balsam is a traditional Latvian herbal liqueur that contains vodka; it has been used as a cold remedy and for treatment of digestive problems.

The experience of many integrative medicine experts in both Europe and the United States has shown that a dietary fat level of between 20 and 25 percent of total calories is optimal for recovery from life-threatening cancer, and in some cases getting down to even 15 percent may be best, depending on the disease risk situation. As you will see, this means removing virtually all animal products from your diet and primarily focusing your creative culinary energies on members of the vegetable kingdom, where there is plenty of variety to choose from.

In addition to the quantity of fat consumed, specific types of fat can impact the risk of cancer as well. Omega-3 fatty acids from fish oil, algae oil, and certain plants (flaxseed, soybeans, pumpkin seed, canola) tend to inhibit certain cancer-promoting substances—PGE2 and other "bad" eicosanoids—while most other fats tend to increase those same substances. The omega-3's exert a major favorable influence on key immune functions, including those involved in warding off both cancer and autoimmune diseases.

A number of studies suggest that omega-3s from either fish oil or algae oil could suppress the growth of a range of cancer cells and could be helpful in the control of breast cancer, prostate cancer, colon cancer and liver cancer. Also, raising your body's omega-3 levels (while also lowering your omega-6 levels) should translate into better responses to PDT and other cancer treatments, fewer recurrences, and better overall survival.[266] For example, several studies demonstrated that omega-3s inhibit breast tumor growth and metastasis, and may reduce the risk of recurrences by about 25 percent.[267]

The two most important omega-6 fatty acids are linoleic and linolenic acids. Linoleic acid can be metabolized to gamma-linolenic acid, which can be further converted by enzymes to dihommo-gamma-linolenic acid and arachidonic acid (which we discuss more below). Linoleic acid is the main omega-6 polyunsaturated fatty acid found in cold pressed vegetable oils, and a deficiency of this ingredient can lead to:

- Skin eruptions
- Loss of hair
- Liver degeneration
- Susceptibility to infections
- Poor wound healing

- Male sterility
- Arthritis
- Growth retardation
- Circulatory problems

Though a deficiency of linoleic acid certainly can cause these problems, an excess of this omega-6 is also undesirable. This is the more common situation in modern society, and it's mainly due to habitual consumption of corn oil and other vegetable oils, all of which can increase the risk of breast cancer, prostate cancer, and other cancers. Recent studies suggest that too much linoleic acid also makes breast cancer more aggressive.[268] Part of this effect may be due to the ability of linoleic acid to promote the formation of new blood vessels (angiogenesis), which tumors need to grow and metastasize.[269]

Arachidonic acid, another of the omega-6 fatty acids mentioned above, is the most abundant omega-6 fatty acid in the body. This fatty acid is very concentrated in butter, lard, egg yolks and fatty meats, and too much of this fatty acid is clearly harmful. Its overabundance in the diet may be linked with heart and blood vessel problems, strokes, immune suppression, and increased cancer rates.[270] On the other hand, a deficiency of arachidonic acid can lead to dermatitis, intestinal problems and central nervous system dysfunctions.

One other omega-6 fatty acid that bears mentioning is gamma-linolenic acid, or GLA. This is found in borage oil, evening primrose, black currant seed, and *Spirulina* oils. GLA is often combined with omega-3s in the form of a "complete fatty acid" dietary supplement, and actually has some unique anti-inflammatory benefits. In short, it is simplistic to say that all omega-6 fats are "bad fats". Research has shown that GLA has favorable effects on the immune system and also inhibits the process of tumor angiogenesis mentioned earlier.[271]

The Importance of Balancing Omega-3 and Omega-6 Fats

If you have a very low-fat diet, it is possible that you can become deficient in *both* omega-3 and omega-6 fats. In the preceding section, we explained that deficiencies of either of the omega-6 fatty acids, linoleic acid or arachidonic acid, can be detrimental. However, it is far more common to be lacking omega-3s and to have an excess of omega-6s.

HOW DIET AND LIFESTYLE CAN SUPPORT ANTI-CANCER IMMUNITY

As we've sought to emphasize in this chapter, the best overall dietary pattern for sustaining a high degree of health over the long term is primarily a well-rounded vegetarian diet.[272] The key is to think about integrating this plant-based eating pattern into a comprehensive lifestyle approach. It is very likely that any benefit of diet will be reinforced by attending to other aspects of a healthy lifestyle such as exercise and stress reduction. Here's an example of how such a diet and lifestyle might bolster your anti-cancer immunity, using the example of Natural Killer (NK) cell activity.

- Research indicates that vegetarianism and diets low in fat may result in increased NK activity.[273]
- Exercise, too, has been shown to enhance NK cell activity, even after immune-suppressive events such as cancer surgery.[274]
- Stress reduction through mindfulness relaxation practices has been shown to improve NK activity as well.[275]

Collectively, these lifestyle factors could have an important bearing on your survival after a diagnosis of cancer. The reason is that NK cells can halt the spreading of microscopic clusters of cancer cells, or what are called *micrometastases*. For people already diagnosed with cancer or even those technically in remission, lifestyle habits that bolster NK activity have the potential to help avert the development of metastases later on, thus perhaps contributing to better survival in the long term.

Studies that focus exclusively on the omega-3s but neglect to consider the adverse effects of excessive omega-6 fats may be missing the big picture. It is really the overall *balance* of these fats that makes the difference in terms of promoting health and healing. If you try increasing your omega-3 intake, but the omega-6 level is still too high, you may not be able to derive any benefit in terms of curbing chronic inflammation and lowering your risk of various diseases.

So what might be the ideal balance? The World Health Organization's recommendation is to have an omega-6: omega-3 that is between 5:1 and 10:1.[276] Other experts contend that the optimal ratio should be 2:1 or even closer to 1:1. There is evidence that human beings evolved on a diet with a ratio of omega-6 to omega-3 fatty acids that actually approximated the latter ratio.[277]

Practically speaking, this means that people need to cut back on the omega-6 sources and include additional omega-3 to their diet, as the ratio nowadays in most westernized countries is about 15:1 or possibly higher. Thus, the typical western diet found in the United States and some European countries has an omega-6 to omega-3 ratio that is many times higher than is deemed healthful!

Some individuals may benefit by obtaining their omega-3s in the form of alpha-linolenic acid from cold-pressed flaxseed oil.† The trouble here is that at least half of all adults lack the ability to produce the necessary enzymes to convert the omega-3s from flaxseed oil or other plant sources into the active anti-inflammatory forms, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

The good news is that EPA and DHA are readily provided by both fish oil and algae oil, or from coldwater fish, algae, or seaweed. These represent the best omega-3 sources and are also available in the form of a dietary supplement. Taking either fish oil or algae oil as a dietary supplement could be the best way to increase your body's omega-3 reserves.

Again, keep in mind that the *balance* between omega-3 and omega-6 fatty acids is crucial to your body's ability to maintain normal control over inflammation and to lower the risk of chronic inflammation, which can contribute to cancer and other serious disorders. Current research does indicate that improving the ratio of omega-3 to omega-6 can impact the risk of developing cancer and may also play an invaluable role in your body's ability to prevent, control and reverse cancer.[278]

A Brief Caution About Adopting Low-Fat Diets

Very often when people try to adopt a low-fat diet, they fail to pay attention to the other ways that they compensate for the lack of calories from fat. Remember that, of all the macronutrients (protein, carbohydrates and fat), it is dietary fat that provides the richest source of calories. Many people on low-fat diets will automatically consume more carbohydrates to compensate for the dropoff in calories, and the carbs they choose are often in a form that makes too much blood sugar available to cancer.

For this reason, low-fat diets tend to fail to achieve the benefits that would otherwise be provided with a healthier overall diet. Another reason for the failure is that people may ignore the types of fats, i.e., not including enough of the high-quality omega-3 sources, or perhaps even using some of the partially hydrogenated fats or "trans fats", which actually promote many different diseases. In some instances, they could even become deficient in essential omega-6 fats, such as linoleic acid.

So, aside from paying attention to the types of fats you consume, make sure that you're not compensating with the wrong type of carbohydrate when you adopt a low-fat diet. This means increasing your daily intake of complex carbohydrates from whole grains and beans. Thanks to their high-fiber content, these complex carbohydrate sources tend to encourage a more gradual rise in blood sugar and thus more favorable effects on immune system functioning and the prevention of tumor growth (fast-growing tumors tend to thrive on excess blood sugar).

Keep in mind, too, that excess blood sugar tends to reinforce the "bad fat" track in the body, the one that promotes inflammation. This involves an increased production of certain hormone-like substances, such as prostaglandin E2. A frequent spiking in the production of this prostaglandin may promote the development of cancer and heart disease, among other health problems.

Life After PDT: The Long-Term Anti-Cancer Diet & Lifestyle

As we have emphasized, the foods you eat on a daily basis can play a role in stopping cancer that has begun to develop in your body, or preventing a recurrence of the disease. Here we will use breast cancer as an example of how specific nutritional strategies can be useful in cancer prevention. In the past few decades, a tremendous amount of research has focused on how nutrition can help curb the growth and progression of breast cancer. It is by far the best studied of all the cancers with regard to nutritional factors.

† Moreover, ground flaxseed provides beneficial compounds called lignans that have protective effects against breast cancer and possibly several other cancers.

Many studies are now in progress to help advance our understanding of the relationship between nutrition and cancer. In addition to warding off cancer, specific dietary changes can be used to shift body composition, improve insulin metabolism, bolster treatment tolerance and recovery, and enhance overall quality of life. These too are important outcomes.

So in terms of the long term (after you have completed PDT or other photodynamic treatments), the key insights gleaned from hundreds of studies to date can be summarized as follows:

- **Maintain a vegetable-rich plant-based diet.** Make sure that your daily diet includes plenty of vegetables, legumes, whole grains, and non-tropical fruits. Literally thousands of anti-cancer compounds or phytochemicals have been identified in vegetables and other plant foods. The most important anti-cancer vegetables are broccoli, kale, collards, cauliflower, cabbages, brussel sprouts and other cruciferous vegetables, as well as carrots, onions, radishes, turnips and garlic. For example, at least six studies have demonstrated that women who consume larger amounts of these and other vegetables (or who show blood marker levels that are indicative of frequent consumption) have significantly increased survival or lower recurrence rates after a diagnosis of breast cancer.[279] The most important anti-cancer fruits are berries, cherries, grapes, and apples. Blueberries and strawberries are excellent choices for regular consumption.
- **Emphasize a relatively low total fat intake.** Many studies suggest that a low-fat diet (15 to 22 percent of total calories) may lower the risk of developing cancer or having a recurrent cancer. Thus, your total dietary fat intake should be relatively low—which, alas, means avoiding cheese, butter, beef, bacon, and other fatty animal products. Also greatly curb your intake of fried and greasy foods. corn oil, sunflower oil and other sources of omega-6 fats, as well as partially hydrogenated fats or "trans fats".
- **Eat more of the healthy fats.** Omega-3 fatty acids are essential to our health and longevity, and the best sources are coldwater fish and algae. There appears to be a significant protective effect for omega-3 consumption against various cancer. The key is to balance low overall fat intake with a focus on getting more of the healthy fats from fish oil, algae oil, olive oil, walnuts, flaxseed, and avocado. Extra-virgin olive oil, canola oil, almonds, and avocados are all sources of omega-9 fatty acids. Reminder: Too much fat of any kind is unhealthy, so practice moderation. For example, do not eat more than 1/4 cup of nuts as a snack or with a meal.
- **Avoid refined carbohydrates.** Keep your consumption of processed sugar and refined grains to a minimum. For example, you should avoid refined carbohydrates such as white sugar, sweets, white bread, and other baked products made with white flour, as these tend to raise blood sugar levels easily. Many types of cancer seem to thrive on this kind of "high glycemic" diet. It is extremely important to avoid any "high carb" foods that will cause an increase in your glucose and insulin levels, as these may promote various cancers and worsen your chances of overcoming cancer. For example, studies of diet and breast cancer have shown an association between an excessive intake of refined carbohydrates and increased breast cancer risk.[280]
- **Protein in moderation, from healthy sources.** Plant proteins are best for regular consumption. On the other hand, your intake of animal protein should be limited to fish on a regular basis (3-4 times a week) and very small, occasional portions of poultry (1-2 times a week). Egg whites and whey protein are acceptable sources of animal protein. In general, however, red meats should be avoided altogether for optimal cancer control and prevention. Beans, legumes (including soy), nuts, seeds, hemp and *Spirulina* (algae) are among the healthier sources of protein and may be eaten daily.
- **Drink good, pure water daily.** Water is essential to cleansing and overall health and well-being. Most people do not drink enough water on a daily basis, and this has many adverse effects on your health and vitality. Therefore, stay well lubricated on the inside! Drink plenty of clean water throughout the day (6 to 8 glasses, depending on your activity level), especially spring water or filtered well water. Try to drink much more water on exercise days.

- **Regular, daily movement is key.** We consider exercise to be complementary to diet and other aspects of lifestyle. Exercise on a daily basis in order to help achieve and maintain a healthy body composition, as this is prognostically favorable for people with various types of cancer.
- **Find ways to relax and enjoy life.** Anxiety or other forms of emotional distress suppress the immune system and has other adverse effects that may pave the way for cancer's growth and progression. Therefore, we encourage you to engage in activities that help you relax and promote inner peace. Examples of these activities include meditation and prayer, taking a quiet walk in a park or other natural environment, a good novel or movie, some relaxing time on the beach or in the woods. Keeping your stress levels down may be critical for maintaining strong anti-cancer immunity.

Here are some practical points about gleaning the benefits of the anti-cancer diet we describe above:

- **Cleaning your non-organic produce.** Whether your produce is organic or conventional, it's important to eat fruits and vegetables on a daily basis. Ideally, we should attempt to consume seven to 10 to 12 servings of fruits and vegetables daily. Washing and peeling any conventionally grown fruits and vegetables may help to cut down on pesticide residues, though it will not eliminate them.
- **Estimating a serving size.** One serving of plant foods equates to the following: 1/2 cup steamed vegetable *or* 1 cup raw leafy greens *or* 1/2 cup steamed vegetable *or* 1/4 cup dried fruit or vegetable *or* 6 fl oz vegetable or fruit juice, e.g., blueberry or pomegranate juice. For protein, you can visualize a deck of playing cards or the palm of your hand as approximating the size of one serving of fish or poultry.
- **Getting your daily fiber.** By eating whole grains (not in flour form) and plenty of vegetables, you can easily get around 30-35 grams of fiber daily—a good minimum goal to meet. Whole grains include brown rice, barley, quinoa, amaranth, millet, oats, spelt, rye, and bulgur. Choose whole-grain breads (or sprouted grain breads) and whole-grain pastas that offer three or more grams of fiber per slice. Also include whole beans and legumes regularly in the diet.
- **Shun the refined/processed food items.** Avoid all sugars or refined sweeteners, and greatly limit your intake of any refined grains (e.g., white rice) or refined flour product such as white breads, pastries, and white pastas), alcohol, and desserts such as candy, cookies, cakes, and pies. People with advanced-stage cancer should take special care to avoid these food items.
- **Favor algae and sea vegetables.** Sea vegetables or seaweeds such as dulse, kelp, wakame and alaria are chock full of with anti-cancer compounds that have been shown to inhibit tumor invasion, as reported in the August 2002 issue of *Anticancer Research*. Dulse is quite soft and easy to digest, and cooks very quickly, whereas other seaweeds such as alaria and kelp require about 25-30 minutes of boiling.
- **Use superfoods.** The term *superfood* typically refers to any plant food that has a very high phytonutrient content—foods such as blueberries, olives, and broccoli. Certain food-based supplements or "functional food" products can provide a very practical way for you to obtain the specific cruciferous vegetable compounds that have indicated efficacy in preliminary studies. These are available as easily digested green powders or *green superfoods* that are easily absorbed when consumed as a superfood shake that can be consumed every morning before breakfast. These nutritious shakes are especially helpful for people who are very ill and have trouble eating, or for those who are suffering from nausea and poor appetite in the aftermath of intensive cancer treatments.

CHAPTER 7

Photodynamic Healing and Cancer Treatment:

A Dialogue Between the Authors

Introduction

Dr. Andrei Reshetnickov obtained his doctoral degree in bioorganic chemistry, a rapidly growing scientific discipline that combines organic chemistry and biochemistry, from M. V. Lomonosov Institute of Fine Chemical Technology in Moscow, Russia in 1999. His primary area of specialization was biotechnology before devoting most of his research expertise to the chemistry of physiologically active and natural compounds.

In the past decade, Dr. Reshetnickov has synthesized and studied the structure and properties of well over a hundred new photosensitizers. Some of these have become medicines while others are currently undergoing testing as candidates for future medicines. He has published a number of scientific reports about these agents in peer-reviewed journals and received 31 patents related to PDT and innovative ways to use this and other light treatment modalities to enhance health and healing. His participation in clinical trials and ongoing communications with scientists and physicians in the field have helped him stay on the cutting edge of developments in the burgeoning field of photomedicine.

Dr. Reshetnickov is the discoverer of several leading-edge photosensitizers, optical imaging probes, and tumor-selective MRI contrast agents. Among these discoveries are Radachlorin® (called Bremachlorin® in some countries), Fotonaflor®, Magnetaflor®, Thermochlorin®, Oscirad®, Sonorad® and FloraDynamica®. In addition, he serves as a reviewer for *Photodiagnosis and Photodynamic Therapy*, one of the leading international journals for sharing scientific knowledge and clinical developments of light-based medical applications.

Mark N. Mead, MSc, is a biologist, science educator, and nutrition research consultant who has written extensively on innovative approaches to cancer and other diseases. After receiving his Master of Science degree from the UNC Gillings School of Global Public Health, Mr. Mead went on to coauthor numerous papers published in scientific journals, including *Integrative Cancer Therapies, Cancer Treatment Reviews, International Journal of Cancer, Environmental Health Perspectives,* and the *Journal of the National Cancer Institute*. In addition, Mr. Mead served for many years as a contributing editor to *Natural Health* magazine and has coauthored a number of health-related books.

What follows is a transcript of two conversations that took place between the authors in August 2012 and April 2013 at the Natural Health Foundation headquarters in the Netherlands. Some of the content of this dialogue is fairly technical, so we encourage readers to share the information with their physician and other health care professionals.

On The Effects of Photosensitizers and Different Types of Light

MNM: Let's first briefly review the importance of photosensitizers and their role in cancer therapy.

AVR: As we've explained to our readers, PDT involves the use of a substance that absorbs light and then transfers the light's energy to oxygen molecules, which then ultimately kill or suppress the tumor. The destructive effects on the tumor can also happen without oxygen, but in either case the photosensitizer is essential for the success of PDT. Some of these substances have been derived from chlorophyll, and this makes sense because chlorophyll is among the best-known examples of

a light-sensitizing substance in plants that captures the sun's energy and converts it to other forms.

In our company's laboratory (Arev Pharm LLC), we've been able to create new photosensitizers from chlorophyll and bacteriochlorophyll. These light-sensitive compounds accumulate inside tumors more readily than in normal, healthy tissues. They would generally accumulate within a few hours. So, over the course of a day after giving the photosensitizer to a cancer patient, the PDT specialist provides light treatment to bring about the therapeutic effect.

MNM: The photosensitizer can be administered to the body in at least three ways—topically, orally, and intravenously. Also as I understand it, there is both a drug form and a dietary supplement form. Could you briefly mention the other modes of administration and also address the differences between the drug and the dietary supplement?

AVR: Yes, in addition to the modes of administration you just mentioned, the photosensitizer can be injected directly into the tumor. Other methods include inhalation, intravaginal suppositories (as well as gels and sprays), and injection through the peritoneum, for example. As you noted, when given orally, the photosensitizer is available as both a drug and dietary supplement. The drug has a more intense mode of action and is excreted quickly from the body. It builds up quickly in the tumor area, and that high concentration leads to a more focused treatment effect once the light treatment is provided.

In contrast, the dietary supplement builds up in the body slowly over the course of several weeks. It therefore has more gradual effects, and the compounds are activated when the person steps out into the sunlight. So in general, one would want the drug for achieving the anti-cancer treatment effects, and the supplement for the purpose of prevention.

MNM: What kinds of light can be used with different photosensitizers, for example with Fotonaflor®? Also, what are the main advantages of using a laser or LED as opposed to other forms of light?

AVR: Laser light is very focused and more direct. Non-coherent light sources have much more scattering. This is what you see with headlights of a car at night. From a distance, the lights appear far apart, but as the car gets closer, the light becomes more focused. With a laser or LED, the light stays focused, emitting more coherent light, even at a great distance. If you give laser light to the body, cells and tissues will absorbed it, but a small portion of the irradiation will even pass through the body. So some will definitely reach the tumor, but then the question becomes what you want to achieve in the tumor. You only need a few microJoules of light energy to achieve an effect in mitochondria, and some more in macrophages.

MNM: Perhaps you could speak about the different lasers and their effects?

AVR: Infrared laser is either used for cutting tissue, as in surgery, or for heating tissue, as in laserthermia. UV lasers are pulsed and are used for "burning" out the tissue, one layer at a time—often used to treat nearsighted vision in ophthalmology by evaporating a part of the eye sclera tissue to form a lens. The tissue actually turns into a gas. So we have UV lasers, IR lasers and visible spectrum (VIS) lasers.

UV is very aggressive, and IR tends to be painful, and that's partly why we prefer to use VIS lasers for photodynamic treatment applications. The more critical reason for using VIS is that the photosensitizer absorbs light mainly from the visible part of the spectrum, so VIS lasers tend to be safe yet effective.

At this time, however, LEDs are becoming a more attractive option than lasers, as they are lighter, cheaper, and can even be disposable. Daylight and sun-spectrum artificial light exposure are increasingly useful options with diverse photodynamic applications. Note also that photosensitizers acting at *longer wavelengths* can achieve deeper tissue penetration. This should greatly expand the range of cancers or tumor types for which photodynamic treatments are useful.

On the Use of PDT with Surgery

MNM: In *The Medicine of Light*, we talk about the possibility of using PDT in place of surgery. Why would cancer patients want to do this?

AVR: Surgery by itself is often the most effective way to eliminate a tumor, which represents the most visible evidence of the cancer. In other

words, the local manifestation of cancer is only part of the body's total disease burden. There are always abnormal or mutated cells somewhere in the body. For one tumor about the size of a walnut—let's say 3 to 4 centimeters in diameter—the person might have about 100 to 200 grams of cancer cells elsewhere in the body. This is the reason doctors give chemotherapy before or after the surgery, often along with radiation treatment. Without some type of systemic treatment, surgery can be fairly ineffective or can only produce short-term effects, at least in the case of aggressive tumors. Remember that even with early-stage cancer, much of the disease is invisible or not detectable with scans.

So, even though surgery is effective in removing the tumor, there is still a substantial risk of recurrence in many cases. Our clinical research suggests that the ideal way to get rid of tumors is not with surgery, but with slow resorption of the tumor using repeated PDT sessions over time, for example. Some holistic physicians assert that the time for resorption should, at a minimum, equal the time it takes for the tumor to grow to a significant size. Typically, it takes about two to three years for a tumor to grow to where it can be seen or felt, before it starts to impact physiology and function. So we propose that it should take approximately that same amount time to cause complete regression of the tumor, using a light-based treatment approach.

MNM: What are the potential consequences of foregoing or *not* using this more gradual approach and not recognizing that cancer is a systemic disorder?

AVR: Very simply, if you just cut the tumor out without making those changes, you run a greater risk of a recurrence or progression. The tumor is just a symptom of the larger whole-body imbalance, and it takes time to reverse the imbalance, the disturbance in the tissue and in the immune system. The tumor may be understood as the body's attempt to encapsulate or wall off the disease, helping to keep the disease under control.

We could compare it with a pot that has a kind of fermentation process going on inside it, an enzymatic process that is relatively contained. Very often, when you remove the tumor using surgery, you are bringing the whole-body process even more out of the balance, so that one develops a more aggressive disease later on. PDT allows you to remove the tumor *and* greatly lower the risk of having a recurrence or relapse, especially if you use additional methods that further strengthen the immune system.

Finally, with PDT, you also avoid the sometimes mutilating or disfiguring effects of having surgery. We need more clinical trials to examine the possibility of using PDT in place of surgery. On the other hand, we also recognize that surgery plays an important role as well. For example, if the tumor is too deep in the body, then laparoscopy or endoscopy enable us to reach the tumor with light and then carry out the photodynamic treatments. In many cases, surgical debulking—that is, removing the bulk of the cancer, as represented by the visible tumor—helps improve or maintain normal organ functioning.

MNM: Are there situations where you would want to use both PDT and surgery together?

AVR: Yes, this combination can be very helpful in some cases of more aggressive cancer, as in advanced malignant melanoma. With smaller but again aggressive tumors, you do PDT followed by surgery. The idea is that you would want to use PDT first to kill the tumor, and then you remove the tumor with surgery, along with some of the tissue around the tumor. This is what is so amazingly and skillfully done by the Russian surgeon Evgeniy Volkov, who contributed our book's photos of skin melanoma patients before and after treatment. With larger tumors, you do surgery followed by PDT. Again, this is what they call *debulking*, removing as much of the tumor as possible.

MNM: Could you give a specific example of how PDT can be used as an adjunct to surgery, with surgery being followed by PDT?

AVR: If you remove a brain tumor, you can then do PDT directly in the area to eliminate residual cancer. Those areas with residual cancer will actually glow a greenish color thanks to the photosensitizer. This is the so-called fluorescence effect, and it has been very helpful for diagnosis and for helping the surgeon to see what would otherwise be invisible areas of cancer. The same areas that glow or fluoresce will be targeted and destroyed by the light during the photodynamic treatments.

MNM: Specifically, how is this done?

AVR: The basic procedure is as follows. Prior to the surgery, the photosensitizer is administered to the patient. The surgeon removes the bulk of the tumor using surgery. Light then causes the remaining pieces of the tumor at its saddle to fluoresce or "light up", and then PDT is provided only to those spots. If you don't have the fluorescence detection equipment, then you give light to the whole area of the "tumor saddle". From the time of the operation, the surgeon has between 5 and 15 minutes to fluoresce areas that may have some residual tumor and clean those specific areas up, or do PDT afterwards. This approach has become a very popular focus of research and is called *fluorescence-guided surgery* or *fluorescence image-guided surgery*.

MNM: Providing laser light only to those fluorescing areas to destroy the residual tumor tissue seems like a perfectly logical and efficient approach, combining diagnostic and therapeutic strategies in one fell swoop.

AVR: Yes, and I should add that before the actual surgery, you can observe the borders of the tumor and even possible metastatic spreading around the tumor area, all thanks to the fluorescence of the photosensitizer. Once the surgery is done, and as long as the photosensitizer is still present in all the spots that reveal residual cancer, it is simply a matter of focusing light on those spots because the photosensitizer is already in those spots. You can kill the residual fragments with PDT. This is denoted as PD/PDT, where the PD stands for photodiagnosis.

The Example of Breast Cancer Treatment: Different Light-Based Strategies

MNM: Breast cancer is the number one cancer among women, and so I know many women will be interested in the possibility of PDT for this treatment. Let's say you're talking to a woman with breast cancer and she tells you she would like to explore the possibility of getting treated photodynamically. How would the woman know whether PDT could be helpful in her situation?

AVR: The effectiveness of PDT and the particular strategies used will depend on the stage and aggressiveness of the cancer, and whether the light can reach the tumor itself. Certainly PDT can be quite effective against Stage I or Stage II breast cancer. In such cases, after administering a photosensitizer, they use several thin optical fibers—less than 0.2 millimeters in diameter. These fibers are passed through the skin and other tissues, then inserted directly into the tumor. Laser light is then passed through the fibers. Assuming the tumor is compact and small, or under about 2 centimeters, then conventional PDT can be quite helpful, causing complete destruction of the tumor—just as radiation treatment would accomplish. By the way, the same approach is used to treat prostate cancer in men.

The advantage of PDT is that it's far more selective than conventional treatment with either radiation or chemotherapy. With PDT, there is much less damage to the surrounding normal tissue. On the other hand, there will still be pain due to inflammation around the tumor area. Also, whereas high-intensity X-rays or other high-dose radiation treatments suppress the local immune system, with PDT, the local immune system is activated against anything released by the tumor, including cancer cells.

MNM: Of course, many breast tumors are invasive or larger than two centimeters at the time of diagnosis. Let's talk about that kind of situation.

AVR: Yes, this is a common situation, and for such cases, a combined technique of radiotherapy followed by PDT is recommended. This allows the PDT effect to go deeper than the usual 5 to 10 millimeters from the surface, and also provides for a better and more selective accumulation of the photosensitizer. The radiation dose is two to four times lower than the conventionally used radiation dose, and the PDT dose is only about half the standard PDT dose. With these lower doses, the combined treatments will not trigger the form of cell death known as necrosis, but instead only create an inflammatory response as well as suppressed proliferation of the cancer cells. Basically, the cancer cells are multiplying much more slowly following this combined treatment, and they result in tumor stabilization, which means no additional tumor growth.

Now, by itself, tumor stabilization is a good and clinically significant result. Very often the woman whose body harbors such a tumor can go on living for many years; the tumor will not interfere with her life or cause any pain or discomfort. Many women view this option as preferable to mastectomy. They would rather keep their breast even if it means still having a tumor, as long as the tumor is stable or relatively dormant, either not growing any larger or growing only very slowly. On the other hand, to ensure long-term success, the combined PDT-radiation treatments must be done twice a year for many years, possibly for ten years or more.

MNM: Are there any logistical issues that the radiologist and the PDT specialist must consider when planning and coordinating these treatments?

AVR: First of all, it is not uncommon for radiologists to become PDT specialists, so a radiologist trained in the use of PDT can manage both treatments quite well. The key logistical concern is the specific time interval between the radiotherapy and PDT sessions—that can be tricky to determine and requires great expertise. If you perform the PDT treatment too soon or make a mistake in the dosing, the tissue will dissipate, creating a hole and resulting in an infection and discharge (exudate) in its place. Conversely, if you do it too late, there will be some stabilization, but the effect is only partial, so there will still be some tumor growth, albeit delayed. In some cases, there may even be tumor stimulation. So the trick lies in knowing the correct dosing and timing—knowing when exactly to deliver the PDT following radiotherapy. This is as much about the art of medicine as the science.

MNM: You mentioned the immune system being activated by PDT. Can this be helpful in the case of metastatic breast cancer? Let's take the case of Stage IV breast cancer—that is, with distant metastases, such as to the liver or lungs.

AVR: With conventional PDT, the anti-cancer immune response is activated but it is generally too weak to have a substantial effect on metastases. For this reason, you also need to use immune-modulating substances, which specialists refer to as *immune adjuvants*, to help the immune system actually recognize and act against the cancer. So in most cases, it's as if the cancer cells are carrying a passport, but the holder of the passport is not recognized as a potential threat to national security. If his face is changed, however, which is essentially what PDT does, then the cancer cells are recognized as a potential threat.

So these immune adjuvants are used together with either PIT or low-dose PDT in order to create a mild, short-term reaction in the tumor and simultaneously strengthen the anti-cancer immune response against the cancer. This is yet another area in need of research, but we believe that it has great promise in the case of metastatic cancers. Keep in mind, however, that the PDT must be administered at a low dose, and that the immune adjuvants need to be used as well. So in the case of advanced cancer, PDT plays a synergistic or additive role with the immune-modulating strategies.

MNM: How did you learn that PDT has therapeutic effects that extend beyond the primary tumor?

AVR: We originally discovered that PDT could affect other tumors beyond the primary tumor in our studies of bile duct tumors. Bile flows through the ducts from the liver. With Klatskin's disease, when tumors exist in the large ducts, there are always some tumors in the small ducts as well. However, we are only able to get the probes to deliver light into the large ducts. When we use PDT to treat the tumors in those large ducts, we also see structural changes in the tumors in the smaller ducts and also reaction in the regional lymph nodes, and those tumors basically stop growing. The tumors in those other areas don't disappear, but they no longer continue to grow. Eventually, the tumor tissue is replaced by scar tissue, and thus the cancer is effectively in remission.

MNM: Perhaps you could talk about Photoimmunotherapy, or PIT, as a novel treatment option for women with advanced breast cancer.

AVR: PIT is a more specific way of harnessing the immune system, and it is indeed a possibility for advanced cancer situations. In this case, you don't cut out the tumor; it stays in the body. The photosensitizer is still able to accumulate selectively in the tumor, but the photosensitizer is now in an oxidized form—that is, it's created in the presence of oxygen

and light—and yet it's also stable. So this oxidized photosensitizer is injected into the body, where it then changes the presentation of the tumor antigens. The immune system can recognize that cancer is there and thus needs to be eliminated.

A related approach involves binding the photosensitizer to an antibody, which in turn enables more selective delivery of the drug to the tumor tissue, and then the tumor is exposed to light. Ideally, the antibody is designed to bind so as to reach the most vulnerable parts of the cell, such as the lysosomes, which contain digestive enzyme. Destruction of the lysosomes causes the cancer cell to digest itself due to the release of the enzymes. This results in a greatly reduced dose of photosensitizer and much less light as well, because you're getting a more selective, focused treatment effect. Drs. Tayyaba Hasan and Allan Oseroff are some of the pioneers of this antibody-based approach to PIT.

Yet another immune-related strategy is the PDT-generated cancer vaccine or simply PDT vaccine. This is more of a whole-body approach and it's a major achievement in the field of PDT. With this strategy, they homogenize the tumor tissue and add a photosensitizer, which is then activated by light. Mladlen Korbelik's research in British Columbia (Canada) has confirmed that the tumor tissue surgically removed from the patient can be readily used for preparing without delay the PDT vaccine material, which can be directly tailored for the individual patient and is acting against tumor antigens for that specific tumor.

A related vaccine strategy is done via intra-tumoral administration of the drug—that is, injecting the photosensitizer directly into the tumor. The tumor is then exposed to light, surgically removed, and then homogenized. One is able to create a PDT vaccine from this material, after sterilizing the preparation. This kind of PDT vaccination is now an area of very active research. With this experimental approach, we believe that you can potentially control metastatic cancer, though of course clinical trials are needed to fully test this hypothesis.

MNM: The PDT vaccine seems to be a promising approach given that animal studies have shown significant tumor-killing effects even with cancers that typically do not respond to immune mechanisms. Dr. Korbelik claims these vaccine protocols can enhance the capacity of PDT to induce a strong immune response against the tumor and also may enable the immune system to mount a sustained and prolonged attack against the tumor.

AVR: One more approach is worth mentioning here. This involves the use of a neutron beam and a boronated substance as a radiosensitizer. The boron absorbs the neutrons, and this results in an increase in local heat and free radicals within or in the vicinity of the tumor. (When this approach is combined with antibodies, it becomes possible to make the effect even more localized.) This is done in tandem with PDT to achieve the optimal effect, but again, it's an experimental treatment and in need of further clinical research. The neutron beam requires expensive facilities. Nevertheless, this may be especially helpful in cases of inoperable, deep or hard-to-reach tumors.

MNM: What happens if you use PDT alone, without the addition of radiation or immune adjuvants?

AVR: If you use PDT alone, you can still achieve therapeutic effects against breast cancer but the light dose is absolutely critical. The optimal doses for light and for the photosensitizer are now being established by clinical trials. If you do not provide a sufficient dose for each of these factors, there is the risk of actually stimulating some tumor growth. PDT by itself is a tumor-destructive method, and obviously the goal is complete destruction or eradication of the tumor. If this is not achieved, then there will be some residual tumor growth. On the other hand, if you combine PDT with other methods, you can use the lower PDT dose and still achieve slower tumor growth, as well as tumor regression and stabilization.

Tumor size is a critical consideration here, as we discussed earlier. For small tumors, you can very effectively use PDT all by itself, and achieve total obliteration of the tumor. But for larger tumors, you need combinations—such as PDT plus surgery, PDT plus radiotherapy, PDT plus immune adjuvants, PDT plus chemotherapy, and PDT plus hyperthermia. Every combination allows you to lower the dose of both modalities, because there is synergy, and they involve different tumor-suppressing mechanisms. So in the case of chemotherapy, you're able to use a lower dose of the chemo drug and therefore toxic side effects are greatly reduced.

Also, it's important to understand that PDT does not suppress the immune system, whereas high-dose chemotherapy and radiotherapy tend to have immune-suppressive effects in most cases. When we're able to use lower doses of chemo and radiation, as in the combined PDT approach, we don't see the suppression of immunity and in fact we often see enhanced functioning of the anti-cancer immune mechanisms.

The specific treatment combinations we choose will depend on the patient's preferences as well. So for example, if a woman does not want to undergo surgery, but her tumor is too large to be treated by PDT alone, then we may use a combination of PDT and hyperthermia or PDT plus radiotherapy.

MNM: And if she also has metastases, then other combinations would be considered?

AVR: Yes, but it depends on whether the exact location of the metastases can be determined with the help of scans. Very often it's the case that there are multiple metastases present but only one or two can be located. In this case, you focus on the largest of the metastases, and treat that with a combination of PDT and immune adjuvants. On the other hand, if we know there has been metastatic spread of the disease, but we don't know where any of those tumors are, then the best strategy may be to use PDT with chemotherapy. We do not reduce the chemotherapeutic dose in this case. On the other hand, if we have one big tumor, then we lower the dose of chemotherapy and focus or concentrate all the power of PDT on that tumor.

MNM: So to summarize, we have discussed four possible approaches to immuno-PDT based on the research done to date: (1) you can cut out the tumor, homogenize it, add the photosensitizer, and then expose it to light to make a vaccine; (2) you administer the photosensitizer in the body, whereupon it accumulates in the tumor, or you inject it directly to the tumor, and then give light on the tumor to cause tumor cell death by necrosis, before cutting out the tumor and preparing the vaccine; (3) you use immune adjuvants together with PDT; and (4) you can activate a photosensitizer having an appropriate chemical structure outside the body with light in the presence of oxygen and administer it through inhalation, intravenously or intratumorally. These different approaches can be used in the case of breast cancer and for other solid tumors with metastases as well.

On the Three Main Approaches to Photodynamic Treatment

MNM: Please address the differences between PDT, Photoimmunotherapy (PIT), and Systemic Light Treatment, or SYLT.

AVR: First, let's address the difference between conventional PDT and SYLT. The current definition of PDT is using light together with a photosensitizer, causing cell death (necrosis) of the tumor or suppression of pathogenic microflora, while the light is given locally to the specific problem area. That's what most physicians or cancer researchers think of when they hear about photodynamic treatments.

In contrast, Systemic Light Treatment doesn't fall into this definition. The idea behind SYLT is to activate the photosensitizer circulating inside the bloodstream with whole-body light exposure, without producing a direct cytotoxic effect on the cells. So the photosensitizer shifts from its basic state into an oxidized state inside the body. The oxidized photosensitizer now accumulates in problem areas, such as sites of cancer or infections. When you perform SYLT, you give light to the patient with a laser or LED, luminescent tubes, light boxes, or even sunlight, and you then try to illuminate as much of the body as possible (see Figure 8).

Figure 8: *SYLT—activating a photosensitizer circulating inside the bloodstream.*

MNM: And what about PIT?

AVR: With our approach to PIT, the photosensitizer, oxygen and light are all brought together outside the body. We then take that oxidized photosensitizer and administer it to the body. This is not like either PDT or SYLT, because again the photosensitizer gets activated outside the body. Whereas PDT is mainly valued for its local effect, PIT is a systemic treatment, though it is much milder as a systemic or whole-body treatment compared to SYLT.

So with SYLT, you're activating the photosensitizer that's circulating in the bloodstream, not in the tumor directly. But with PIT, you give the oxidized photosensitizer without any light exposure to the body itself, so the light exposure is very brief and outside the body. You provide the inhalator—a device for inhaling an aerosol mist of the photosensitizer—along with the inlet for the laser fiber, and while the photosensitizer is being infused, it's also being irradiated (Figure 9).† Alternatively, you can provide it through an LED ring, and we've developed a device for this purpose.[281] (See Figure 10) So, the aerosol gets light activated followed by inhalation of the aerosol.

Figure 9: *PIT: Inhalation of the laser light-activated aerosol of photosensitizer. (Courtesy of Dr. Nikolay Vasiliev, Novosibirsk region tuberculosis dispensary, Russia)*

Figure 10: *PIT: Inhalation of the LED light-activated aerosol of photosensitizer using a special patented device. (Courtesy of Dr. Nikolay Vasiliev, Novosibirsk region tuberculosis dispensary, Russia).*

† The "inlet" is a valve (membrane) through which the optical fiber is drawn to illuminate and photoactivate the aerosol.

The presence of oxygen is crucial but there is always oxygen in the droppers because there is air in the tube itself. So you have a peroxide of the photosensitizer (the oxygen attaches to the photosensitizer), and thus the photosensitizer delivers the superoxide-anion directly to the tumor. This effectively oxidizes the tumor, taking out the negative charges or electrons from the mitochondria and shutting them down. In the process, the various glycoproteins on the cancer cells are also altered, and that's part of how PIT manages to improve the immune system's response to the tumor—by damaging or altering the surface of the cancer cell, thus improving recognition by the immune system.

In the context of cancer, PIT may be recommended when there's a diagnosis of infection or organ dysfunction, both of which invariably involve inflammation. Note that the presence of inflammation is critical to the success of PIT. Without some inflammation, there is no accumulation of the oxidized photosensitizer and thus no treatment effect. Because PIT is milder than SYLT, it may be more preferable in these particular situations.

MNM: Perhaps you could explain a bit more as to why you feel PIT and SYLT offer very promising forms of cancer treatment?

AVR: The primary benefit of both PIT and SYLT is that they strongly support the immune system without poisoning the body at the same time. With PIT, you don't need to expose the body to light, and not much local light is needed for SYLT. You can use moderate sunlight, and this will do the job for SYLT. Bright sunlight delivers about 5000 joules per square centimeter (J/cm^2), and five percent of that, or about 250 J/cm^2 per day, would be sufficient. So in one day of very moderate sunshine, meaning an overcast or cloudy day, one can theoretically get total eradication of actinic keratitis and even BCC just by topically applying the photosensitizer-containing cream.

Of course, we need a randomized clinical trial to confirm these observations. An example of one such study is described in Chapter 5. That study focused on psoriasis and used psoralen as the photosensitizer.[282] Sunlight is able to penetrate the skin and go deeper, actually reaching the organs with some photons. The question is whether the

light penetrates enough to activate the photosensitizer at life-critical sites of the cells and tissues deeper in the body.

Regardless of the answer to that question, the sun clearly is the best treatment for whole-body or systemic treatment. The red part of the light spectrum is what interacts with the FloraDynamica® to activate the immune system against cancer and eliminate the hidden infections. This could prove to be an ideal strategy for someone who has had conventional treatment such as surgery and now wants to prevent a recurrence.

Regarding Photodynamic Treatment Effects on the Immune System

MNM: Let's talk more about the immune system from the photodynamic point of view. For the general public, there seems to be an assumption that the immune system is designed to fight cancer, and that simply by making the system healthy or strong, it will help you overcome the disease. Let's first address this common misconception.

AVR: We start by noting that the immune system allowed a cluster of cancer cells to gain a foothold in the body, eventually evolving into a visible mass we call a tumor. One interesting point is that probably most cancers are coinciding with hidden infections and local inflammation. This connection between infection and cancer has been confirmed by the research of many scientists, including Dr. Olga Sergeeva in The Russian Oncological Scientific Center. Some cancers are linked to fungi such as *Candida*, as well as to various viral infections, such as Human Papilloma Virus or HPV. Other hidden pro-cancerous infectious agents include trichomonas and other protozoa.

Our research indicates that all cancer patients have chronic, latent, local infections, and we actually see confirmation of this fact by using Immuno-Fluourescence Assay (IFA) in the blood. These hidden infections are the spawning ground for new cancers. If you cure the *Candida* and HPV infections, the pre-cancerous condition of uterus cervix, for example, will often go away and a complete remission is achieved.

MNM: Let's talk about the role of the immune cell type called the *macrophage*. In people with cancer and various infectious diseases, we now know that macrophages are not working properly. In those situations, the macrophage is actually ingesting lymphocytes, suppressing the immune system, and promoting inflammation. So even though we think of macrophages as part of the immune system, in fact their activities can allow cancer to continue growing and spreading. Please comment a bit more about the role of these versatile immune cells.

AVR: Yes, when macrophages accumulate within the tumor they can actually become "trained" or programmed to support the growth of the tumor. These are what we call tumorigenic or tumor-generating macrophages. The specific cancer-promoting behavior of these immune cells seems to depend heavily on the biochemical environment, such as if there's a localized infection, or if there are certain nutritional and stress factors present. So the link between some cancers and infections is the inflammatory macrophages that are generating both low levels of ROS as well as growth factors. Professor Dolph Adams at Duke University proposed that excessive consumption of dietary fats, alcohol, tobacco, smoke and stress factors can all contribute to the tumor-promoting macrophage.[283]

Of course, what we really want is to generate a stronger anti-cancer immune response, which means cultivating the tumor-killing or *tumoricidal* macrophage. So in addition to attending to the lifestyle factors just mentioned, we want to use therapies that transform the tumor-promoting macrophage to the tumor-killing type. External light, together with a pre-activated photosensitizer, is quite enough to trigger this reaction, essentially transforming Mr. Jekyll into Mr. Hyde. Again, this is what we have referred to as Systemic Light Treatment, or SYLT. We are studying Fotonaflor® and other photosensitizers for this purpose. This approach can activate the tumor-killing macrophages, enabling us to attack metastatic disease.

MNM: Please talk about how the immune cells are affected by different intensities of light treatment, and how these effects are different in, for example, bacterial cells or in tumor tissues.

AVR: When we provide light below the 20 J/cm^2 dosage level, we do not see the killing of these cells. The cell death called apoptosis starts at a somewhat higher dosage in the range of 70 to 100 J/cm^2. Apoptosis starts much sooner than the other forms of cell death, necrosis and

autophagy, both of which may occur when you experience a burn or massive destruction of the tissue.†

Bacterial cells are much more sensitive to PDT, because they are more primitive and vulnerable than healthy normal cells. So an even lower light dose (about 50 J/cm^2) can trigger apoptosis in bacteria. Then, when you go down to the 20 J/cm^2 light-dosage level, you get some photochemical modification. This means that some reactions are occurring in the tissue, with ROS appearing at the stimulating concentrations. There are certain changes in the three-dimensional structure of the cell membrane as well as in the cell markers after that.

So we need to speak about two independent events or sets of processes due to the ROS action: (1) *rejuvenation*, a process that entails generating new cells and eliminating the old ones, and (2) improved *recognition* by the immune system. Both sets of processes are contrary to the organism's attempts to neutralize ROS or excessive oxidants. The paradox here is that, by removing or greatly lowering the oxidants, you prolong the life of existing cells but also may increase the chances of cancer or infections because the immune system kills those bad cells using ROS.

So, there are two ways to prolong longevity: (1) protecting and repairing existing cells, thus preventing the premature death of those cells, and (2) increasing the rate of production of new cells, by signaling the stem cells. Chlorophyll derivatives have been shown to increase the rate of production of new cells by 20 percent in hematology clinical studies with Bremachlorophyll®. In our 2006 patent called "Photoimmunotherapy treatment in a man by a photosensitizer activated with electromagnetic energy outside the body", my colleagues and I described the mechanisms underlying PIT and photochemical immunomodulation using oxidized porphyrins in the presence of light and atmospheric oxygen.[284] I will briefly explain the chemistry for our more scientific readers.

MNM: Okay, so this brings us to a much more technical part of the discussion about how light and photosensitizers interact with the immune system, and I'm sure readers with a good background in bioorganic chemistry will be intrigued by what you have to say about this. *[Editor's note: Readers who lack sufficient training in chemistry may elect to skip Dr. Reshetnickov's response to this question and jump ahead to the next section.]*

AVR: So from a chemist's perspective, the main point here is that many aromatic systems, including porphyrin macrocycles, are able to stabilize a metastable peroxide state of some peripheral functions—such as the vinyl, formyl, and carbonyl residues, which can be modified due to oxidation by addition of atmospheric molecular oxygen. That reaction is facilitated by light being a kind of electromagnetic energy, as it is after absorbing a quantum of energy that some aromatic (e.g. porphyrin) systems turn to an activated triplet state.

In this light-activated state, many unusual and impossible reactions may occur that would never start under normal conditions. There is some mystery about the porphyrin reactions, in that some moieties of porphyrins get easily oxidized to peroxides. What is really amazing is that those peroxides are incredibly long lived and stable. The peroxides include superoxide anions.

So, the increased immune recognition takes place due to chemical reaction of biomolecules with ROS. Oxygen, going from atmospheric O2 to O3, 1O2 and O, attaches to the biomolecules, creating polar moieties. There is then a spatial distortion of cell receptors or markers responsible for function of presentation to the immune system.

This is how it happens, starting in an acidic and reducing environment of the tumor with a known reaction of the superoxide-anion (oxygen attached to the porphyrin), previously formed from the porphyrin and oxygen under light. The reaction is called dismutation and results in singlet oxygen and hydrogen peroxide:

$$(\text{porphyrin}).O_2^- + (\text{porphyrin}).O_2^- + 2H^+ \rightarrow 2\text{porphyrin} + O_2O_2 + {}^1O_2 \quad (1).$$

Additionally, hydroxyl radical is formed as a result of reaction between the superoxide-anion and hydrogen peroxide from the above process:

$$(\text{porphyrin})\cdot O_2^- + H_2O_2 + H^+ \rightarrow \text{porphyrin} + O_2 + H_2O + OH\cdot \quad (2)$$

† Autophagy is a normal physiological process in which the cell destroys proteins and other substances in it cytoplasm, resulting in cell death under certain conditions.

Then, upon reacting with the superoxide-anion again, this makes one more molecule of singlet oxygen:

$$(\text{porphyrin}).O_2^- + OH. \rightarrow OH^- + {}^1O_2 \quad (3).$$

Hence, the final products in the tumor—again, in the absence of light—are oxygen, water hydroxide-anion (alkali) and *singlet oxygen*. The singlet oxygen is just a little weaker as an oxidizer than the hydroxyl radical.

Under certain conditions oxygen and singlet oxygen can further lead to ozone and a very reactive form of atomic oxygen:

$$O_2 + {}^1O_2 \rightarrow O_3 + O \quad (4).$$

Oxygen-containing radicals are byproducts of both the photosensitizer's reactive oxygen species (the ROS) and the oxidized substrates or biomolecules. Based on chemiluminescence measurements, we know that these ROS can persist from minutes to tens of hours. They can play an important role in PIT, adding to the oxidizing ability of the photosensitizer-peroxide itself that accumulated in the site of disease. So, the biomolecules sitting on outer membranes of cancer cells (or bacterial cells) get photochemically modified under the action of the peroxides and other ROS. Since many of the biomolecules play the role of signaling molecules and receptors, and many also have recognition-binding sites, the antigen-presenting function is changed. This leads to improved recognition by the immune system and thus to better disease control.

Additionally, ROS can easily attach to the polyunsaturated fatty acids (PUFAs) because of their double bonds. The ROS attach to the carbon, easily eliminating hydrogen or electro-positive moieties of the molecules. When it does so, it changes the spatial orientation of the molecule, and the resulting change in the configuration makes it more readily recognized by the immune system. So, in conclusion, antigen presentation on the tumor cells and bacterial cells is increased, and this makes these cells suddenly much more vulnerable to the immune system.

On Radiotherapy, Chemotherapy, and Other Approaches

MNM: How does this light-based approach to cancer treatment differ from, say, radiation treatment or radiotherapy?

AVR: Technically, there is no difference. Both radiation and PDT can affect different parts of the cancer cell, including the DNA and mitochondria, for example. However, the major difference is that the PDT is able to kill cancer cells more selectively and therefore has fewer side effects. Also, as we noted earlier, PDT tends to help or support the immune system instead of harming it, and this can be very important in the case of cancer.

MNM: When cancer patients' immunity is suppressed, they're more vulnerable to life-threatening infections and probably also more vulnerable to metastatic spreading of the disease. So in general, when would you want to combine PDT and radiation treatments?

AVR: The combination of PDT and radiotherapy is generally recommended for larger tumors, such as a breast or lung tumor that is larger than 2 centimeters. If used on the same tumor, the light dose and the radiation dose can both be reduced, and this results in fewer toxic side effects. In general, PDT by itself results in a far better quality of life compared to conventional treatments. Compared to weeks or months of either radiotherapy or chemotherapy, PDT has enabled patients to lead a more normal life throughout their recovery.

MNM: Speaking of chemotherapy, obviously it has its pros and cons. The toxic effects are a major concern for patients and oncologists alike, and then there is the problem of some of the tumor cells being resistant to the chemo drugs. What's your view of chemotherapy as a cancer treatment?

AVR: In April 2012, I attended a conference of chemotherapists of The Russian Oncological Scientific Center named by N. N. Blokhin. The focus of the conference was on recent research for many leading chemotherapy drugs. All of the clinical trials compared one chemo drug to another, but the success was extremely limited. Some studies showed a survival advantage of perhaps two or three months at most, but it was rather depressing to all the attendees.

At the very end of the conference, the chairman spoke about a single case in which an 80-year-old man, a prominent academic scientist, was diagnosed with stage IV lung cancer, confirmed by standard diag-

noses. He had multiple spots throughout the lungs by X-ray, along with very high cancer markers. Because of his age, now the chairman offered him the option of going without chemotherapy, in order to preserve the quality of life for the time he had remaining. Instead he went on a vegetable-based diet, herbs and a special treatment that included boiled tomatoes (without the peels) and a self-made extract of bee moth larvae (Galleria mellonella).

In one year, this elderly gentleman came back totally clear of cancer, according to the conference chairman. Everybody in the hall exhaled as the total mood got much less depressive. The conference was announced closed, and the participants went off to drink and celebrate. The point is that alternatives really can work, and chemotherapy experts know that these drugs do cause some harm to patients. It is difficult to say how much chemotherapy is really working because none of the clinical trials are comparing chemotherapy to no treatment. Instead they are only comparing one chemo drug to another.

MNM: The assumption is that no treatment, or treating metastatic disease without chemotherapy, is simply unethical. So are you concerned about cancer patients receiving PDT with Bremachlorin® who are taking or who have recently taken chemotherapy drugs that may have photosensitive properties?

AVR: With chemotherapy, Bremachlorin® will not be a problem because people are getting exposed to the normal or moderate amount of daylight. Some clinicians have expressed a desire to use PDT, PIT, and SYLT as an adjuvant to chemotherapy in their clinics. However, for patients being treated with 5-FU, Xeloda or other photosensitive drugs, they need to be careful about being exposed to any powerful or concentrated light sources. Those chemo drugs are not as selective for cancerous tissues as Bremachlorin® or Fotonaflor®, so they can result in more damage to normal tissues upon exposure to light. Future research will be able to demonstrate more convincingly how to use chemo together with these photodynamic modalities.

MNM: It seems that much research has focused on cancers for which chemotherapy and radiation treatment have been ineffective, cancers such as hilar cholangiocarcinoma or esophageal cancer. Both of these cancers tend to be highly resistant to chemotherapy, so it makes sense that people would be interested in PDT as an alternative to conventional chemotherapy. Which cancers do you think are most effectively treated with photodynamic strategies, or is it too difficult to answer this question?

AVR: My colleagues have seen superb results with hilar cholangiocarcinoma and central lung cancer (adenocarcinoma of the lung), and we can cite excellent research on this. BCC†, melanoma of skin, gastric cancer, and esophageal cancers also may have good responses. There are certain tumor types that respond very well, and others that don't respond well. So it is not necessarily a given that all superficial tumors are going to respond. With invasive breast cancer, for example, we have observed only partial responses, with tumor shrinkage or stabilization, but no complete responses. Still, it should be noted that the partial response can be achieved even after the tumor has become resistant to conventional treatment with chemotherapy and radiotherapy, and therefore it is quite possible that survival is being prolonged by PDT as a result of disease stabilization.

On the Different Photosensitizers Developed by Dr. Reshetnickov

MNM: Let us begin by talking about the basic differences between Radachlorin®, Bremachlorin®, Fotonaflor® and FloraDynamica®. Should any of these be considered "natural" photosensitizers, or are they more properly regarded as synthetic drugs?

AVR: When we speak of these different photosensitizers and their composition, there are three categories to consider: natural, artificial and synthetic. The term *natural* means that the drug is derived from plant or animal materials. There are about 130 such substances known at this time. Such drugs are the subject of pharmacognosy, a discipline that brings together ethnobotany and medicinal chemistry. Allantoin, ber-

† Nodular lesions are included, and these are not easily treated by ALA derivatives, which can only treat the erosive BCC but not the nodular lesions. Those lesions are quite thick, up to about 2 cm in depth; some of my colleagues have recorded an extremely high response rate with nodular lesions.

berine, betulinic acid, nicotine, caffeine, morphine, menthol, quinine, papain (from papaya), and rutin (from oranges) are common examples of natural drugs. In our book we mention some other common examples of natural drugs, namely hypericin from St. John's wort, glycyrrhizin from licorice, curcumin from turmeric, and the psoralen found in various vegetables.

On the other hand, the term *artificial* means the original substance has undergone some type of chemical modification. In contrast, synthetic agents are derived from simple precursors or building blocks. Although they may be labeled as artificial, their chemical structure can be identical to naturally occurring agents. Many fragrances fall into this category, for example. Synthetic agents are often designed to have more potent effects than the natural compounds or agents to which they may bear some very strong similarities.

MNM: Which of the photosensitizers that you developed has the greatest potency or effectiveness in terms of PDT applications?

AVR: As a photosensitizer, Fotonaflor® can enter and kill cancer cells more readily than Radachlorin® and Bremachlorin®, so of course it would be considered superior to those two. Thermochlorin® could be included here as well, though we will need to investigate this further in the future. In the science of pharmacology, we would say that Fotonaflor® has a much stronger lipophilicity—a property that reflects its ability to pass through the lipids or fats that make up cell membranes. This "lipid-loving" property is *ten times higher* in Fotonaflor® than Radachlorin®, and yet at the same time Fotonaflor® is also water-soluble. These characteristics mean that the agent has a higher degree of *bioavailability* or availability to the target tissue, which in this case is cancer! So the drug can pass from the aqueous blood (where its water-soluble part plays the major role) to the lipid-rich cellular membrane (the lipid-soluble part of the photosensitizer, which helps it dissolve) and get inside the cancer cell.

The most effective drugs have a good balance between oil and water solubility. Low water solubility means a slow absorption and action, but if water solubility is too high, then fat solubility will be lower, so that the photosensitizer cannot penetrate inside the cancer cell and reach the important cell organelles like mitochondria and lysosomes. As a result, Fotonaflor®'s efficacy in the context of PDT, as determined using the MTT test on rat pheochromocytoma cancer cells (PC12) was *150 times* higher than that of Radachlorin®. In other words, it was able to kill those cancer cells far more effectively compared to the other photosensitizer drugs. This experiment involved 670 nm laser light at a dose of 20 J/cm^2.

MNM: Let's summarize for our readers the criteria that help determine the superiority of a photosensitizer. I assume that Fotonaflor® meets all of those criteria.

AVR: Yes, Fotonaflor® is an ideal photosensitizer because it meets all of the following criteria: (1) a commercially available, chemically pure drug, one that is composed of a single substance, not a mixture; (2) preferential uptake by the tumor or cancerous cells, meaning that the drug is highly selective for those target cells as opposed to the normal, healthy cells; (3) low dark toxicity but exceptionally strong photocytotoxicity (cancer cell killing ability upon light illumination) —again, this being 150 times higher than that one of Radachlorin®; (4) excellent clearance or rapid removal from the body; (5) quick accumulation (from 15 minutes to five hours) and rapid elimination; (6) a strong absorption peak at light wavelengths greater than 630 nm (that is, absorbing the longer wavelengths); (7) good singlet oxygen quantum yield, meaning that a large amount of reactive oxygen species are produced to help kill the cancer cell; (8) good water solubility, and (9) ease of administration though various routes.

MNM: How did you achieve that?

AVR: By changing the character and spatial orientation of chlorin e_6's functions. Chlorin e_6 is a photosensitizer derived from the chlorophyll *a* found in *Spirulina*, and it's characterized by a strong light-sensitizing ability, good water solubility and still some solubility in fat and rapid elimination from the body. Many other scientists are interested in chlorin e_6 for these reasons. So, it has served as a very good precursor.

MNM: Perhaps you could talk a little more specifically about how it behaves in the body after being transformed into Fotonaflor®.

AVR: If you were to have a Fotonaflor® injection, then the level of the drug would start to drop off very quickly in the body. Every 15 minutes, Fotonaflor® is reduced by 80 percent. So after three hours, almost nothing is left of the drug. Most of what is taken up by the tumor in the first 15 minutes is what kills the tumor, and the body easily eliminates the rest.

MNM: Did you try to make an oral formulation of Fotonaflor®?

AVR: Not yet. Instead, I developed FloraDynamica®, which is basically an oral supplement containing pure chlorin e_6, and so much simpler chemically than Fotonaflor®. I am so far very happy with FloraDynamica® because this substance is quite well tolerated based on our many years of observing and monitoring its usage in humans. Making it readily available for the organism, stable during storage and easy to use was not simple, but it has been a success. Now it has a unique formula and a patented manufacturing process.

MNM: Are Bremachlorin® and Fotonaflor® the only photosensitizers derived from *Spirulina*? Are there other photosensitizers derived from algae or plants, and are they chlorins as well?

AVR: There are actually several that come from *Spirulina* or other types of algae. At this time, Tookad® (from Novartis) is another drug that also comes from algae. It quickly clears from the body, in only about 15 minutes. So you can treat some bladder cancers or various eye problems, such as macular degeneration. There are some other plant-derived photosensitizers that have come from Germany (BLC, for Biolitec Chlorin, and the same chlorin e_6 by Life Medics GMBH), Belarus (Fotolon, declared by its manufacturer to be a pure salt of chlorin e_6, and PVP-chlorin p_6), Russia (Fotoditazin, declared by its manufacturer to be a pure formulation of chlorin e_6), China (chlorin p_6, chlorin e_6), and the United States (MACE, a chemically modified chlorin e_6 by Light Sciences Oncology, Inc. and hypericin).

Again, however, chlorin e_6 has very rapid accumulation and fast elimination, so the range of potential treatments is limited. Moreover, chlorin e_6 accumulates mainly in normal blood vessel walls. As for chlorin p_6, it is poorly soluble in water, and the overall bioavailability of chlorin p_6 is inferior.

MNM: I understand that Bremachlorin® is already being used as a photosensitizer for PDT in clinics and that studies are ongoing. Please talk about its composition and how the different components exert their effects on cancer.

AVR: Bremachlorin® has three components that target different aspects of cancer biology: (1) vascular damage, or interfering with angiogenesis, the growth of new blood vessels that in turn enable tumors to grow; (2) damage to the cell signaling system (by damaging the cancer cell's membranes), which is coupled with heightened recognition by the anti-cancer immune defenses; and (3) damage to the membranes of the cancer cell's internal structures, the organelles and in particular the mitochondria and DNA.

So, Bremachlorin® contains three components that provide this multi-faceted tumor-killing potential. First, there is chlorin e_6, which targets the blood vasculature. Second, there is chlorin p_6, which targets the plasma membrane or outer shell of the cancer cell. And third, there is purpurin 5, which targets the cancer cell's mitochondria and lysosomes and nucleus. When you examine the accumulation patterns, you see that it goes from the blood stream to the stroma. Within the first quarter of an hour, it goes to the blood, then relocates to the endothelium of blood vessels and stroma (i.e., the bulk of the tumor tissue), where it stays for about three hours. After that point, it detaches from various proteins and relocates to the cell membranes, finally reaching the cell organelles about six or seven hours from the time of intravenous administration.

Initially you see only chlorin e_6 in the vessels, and this causes the Von Willebrand Factor (Factor VII) to be released upon illumination. Then histamine is released and the blood vessels at first widen, causing damage along the vessel and resulting in the appearance of thrombosis (occlusions in the small blood vessels), and then a narrowing of the vessels (ischemic reaction), which is seen on the skin surface as a white rim around the illuminated tumor. This phenomenon happens if light is provided soon after administering the Bremachlorin® (within the first hour), and the reaction decreases with time, being fairly minimal or hard to see after four hours.

This prevents metastasis because the tumor essentially suffocates without oxygen or nutrients. However, the effect is only temporary, because the tumor can circumvent this event and continue growing around the periphery of the eliminated or dead (necrotic) tissue area. And this is why using pure chlorin e_6 (as is the case in some of the photosensitizers such as Fotolon and Fotoditazin), can lead to a tumor recurrence or relapse. Almost all such drugs have a very good partial response but a low complete response because they only address the first stage, i.e., suffocating the tumor by impeding angiogenesis. In most cases, the remission period is not very long because some cancer cells manage to survive.

That is why I had the idea that it would be helpful to make a further step and add another photosensitizer to the composition that would stay in the tissue longer and that would move from the vessels to the stroma. This idea was fully supported afterwards by Dr. Thierry Patrice of Nantes, France, a brilliant investigator and one of the top inventors. This is why we use in the composition chlorin p_6 —it sticks to oil and every kind of fat, so it has a stronger affinity for the lipoproteins (LDL)-food carriers, as well as macrophages highly concentrated in tumors. This is how it is able to go from the bloodstream into the tumor stroma, where it stays for some time before being taken up by the LDL receptors on cancer cells, then taken into lysosomes and digested by the cancer cells.

Now, light damages the membrane of the cancer cell because the photosensitizer is in the LDL receptor on the membrane. Microscopic photos have revealed that the light causes holes in the membrane, and when a critical number of holes is present, you have apoptosis, or programmed cell death or "cell suicide". When there are not enough holes, the cancer cells are able to recover from the apoptosis, using lipid reservoirs or "rafts" to fill the holes. The cancer cell is able to monitor the extent of damage. If too much damage has occurred, however, the cell will undergo suicide. This is how apoptosis takes place. If the damage can be repaired, the lipids will be distributed along the membrane to essentially plug the holes. (As an aside, a similar type of damage happens with PDT concerning the internal cell structures called lysosomes. When those structures are damaged, the lytic enzymes contained within them leak into the cytosol digesting everything around. This is how autophagy occurs.)

By the way, this is analogous to how the skin responds to sunlight. Getting brown is the body's way of protecting itself; but many people get sunburn because the UV damage is too extensive to repair. If you get burned, that is akin to the cell being unable to repair itself.

One additional point is that tumor cells may be thought of as adolescent teens who are out of balance. If they have enough resources or support from society, they will survive and continue to function and play a positive role in society. If they lack such support, they may have a tendency to be fairly destructive, self-destruct or even undergo suicide (apoptosis).

MNM: Please talk a bit more about the role of the second component, chlorin p_6.

AVR: Assuming that you give light at about three hours post-injection (PI), then you will have more effects. (Note: If you wait 5-6 hours or even within 25 hours PI, you can still have this effect.) At this point the chlorin p_6 is transported to the lysosome. If you give light, there is perforation of the lysosome, and thus the peroxides and other enzymes are released through the intracellular matrix, and the chlorin leaks into the cell and damages the skeleton (assembly of tubular proteins) within the cell upon light activation, causing the cell to collapse or shrink. There is slow dysfunction of the cell that eventually ends in apoptosis. The tumor slowly shrinks or is resorbed into the body. If you give the light at six hours, you get slower tumor resorption but also have less chance of repair (or reversal), so slowly but surely you get better results. This is why at six hours, one needs a three-fold lower light dose than if you irradiate at three hours following administration.

Note that normal, healthy cells have much lower accumulation of the chlorin p_6 and also light is not being shone on those (assuming localized light exposure, as in laser therapy), so this effect will not happen. However, if using pure chlorin p_6, people may not go in the sun for one month. Fortunately, this is not the case when combining it with chlorin e_6 as in Bremachlorin®.

MNM: What about Purpurin *5*, the third component?

AVR: This is easily oxidized and creates peroxide or CN bridges to the specific hydroxy and amino groups of proteins containing lysine, arginine or serine. Thus it becomes an ideal probe tightly bound to some proteins through the specific interactions. So its oxidized form first attaches to proteins or to lipoproteins, like a rider getting into the saddle of a horse. This can happen in the blood stream as well as on the plasma membrane of the tumor cell. There are then multiple transport paths into the cell because there are a variety of proteins entering the cell. Almost any protein can bear the -OH group or -NH_2. While inside the tumor, it causes further oxidation, through the peroxide cascade reactions (generation of the reactive oxygen species, ROS). This is another reason it is so important to have preferential accumulation in tumors, as long as you have the correct dosage.

After attaching to the protein, the Purpurin *5* is then transported into the cell. It stays connected or bound to fragments of protein until digestion starts. Even passing through the lysosome, there will be no cleavage of the bond between the protein and Purpurin *5*. This enables it to reach the mitochondria, where it becomes stuck to the mitochondrial membrane and stays there, interfering with the energy cycle of the cell. There are minor and major grooves on the mitochondrial DNA, so the Purpurin *5* can intercalate with the DNA. It also moves into the nuclear DNA as well. This genetic damage includes single and double strand damage to the DNA, so that the spiral is either split or cut. Note that single strand damage can be repaired, but not the double strand. When you provide the light treatment, you can demonstrate the damage in cancer cells but not in normal cells because the damage targets cancer cells and spares normal cells.

The Purpurin *5* is the most critical component in terms of finally killing the tumor. It is the dagger, the ultimate killing blow. The compound is highly chemically unstable, and for this reason has to be combined with the Ce_6 and Cp_6—yes, they stick to each other—in order to become stable. The Ce_6 and Cp_6 help to deliver the P*5* to the tumor. This ability to be transported into the tumor is essential to the success of the treatment. You could think of them as the Three Musketeers. And thanks to this wonderful trio, if you use them to do fluorescent diagnosis, initially the whole tumor will gleam, then individual cells, then the organelles.

MNM: What are the main limitations of Bremachlorin®?

AVR: Limitations are the same as for other photosensitizers, most notably the challenges of adequate light penetration and dealing with dense tumor structures such as sarcomas. Also, the selection criteria include having superficial tumors, with a tumor depth not more than seven millimeters, and not treating sarcomas or bone tumors because of problems with selective accumulations.

MNM: What about skin reactions using Fotonaflor®?

AVR: This will be given in the hospital in the context of either PDT or PIT. We have never seen any evidence that it has skin phototoxicity. If there are skin reactions, the patient must turn to his or her doctor and consult with them.

MNM: So to summarize the photodynamic effects of using Bremachlorin®: We have higher concentrations of photosensitizer in cancer cells, a dose- and time-dependent process that results in a greater likelihood of double-strand DNA breaks in the cancer cells. A longer period of accumulation and preferential accumulation in cancer cells seems to be the key. How do other chlorins on the market measure up to Bremachlorin®?

AVR: Many of these other chlorins are very expensive and also not stable or hard to deliver. Easy production technology is an important criterion, but many of these chlorins are not easy to produce.

MNM: Please talk about the effects of Bremachlorin® on the immune system in the context of light treatment.

AVR: There are three types of light dose with a single administration of 1 mg/kg Bremachlorin®: damaging, threshold, and stimulating light dose. The damaging light dose is 200-300 Joules per square cm. Above 300 J/cm^2, there is the risk of damaging the surrounding healthy tissues. Sometimes this is done to hit more aggressive tumors such as small-cell carcinoma of the lung, so they give 600 J/cm^2 even though it is damaging to some of the lung's healthy tissues. The damaging dose causes necrosis.

The threshold of light treatment is 20-100 Joules per square cm. This is between stimulation and suppression. The 20-50 J/cm^2 range is what is used for killing microbes. The laser fiber technology must be well-designed and very high quality in order to deliver a homogeneous light to the tumor. If the light beam is weak or light spot is irregular, it can actually stimulate the tumor, especially in the periphery.

MNM: Is there any therapeutic application for a dose below 20 J/cm^2?

AVR: Yes, there is. Below 20 J/cm^2 is stimulating to the macrophages and immune system, and also to the skin cells. In addition to boosting the immune system, this lower dose of light is useful for rejuvenation and regeneration. This is why you don't want people to get too much sunlight when they are trying to rejuvenate the skin. Excessive sun exposure accelerates the aging of the skin, as we discuss in Chapter 2. Similarly, an effective and safe photorejuvenation involves going out in the morning sun (before 10 a.m.) and then again in the evening light (after about 5 p.m.), for only an hour, while taking FloraDynamica or using our photoregenerative cosmetics.

If people need to stay in the sun longer than that, they need to protect the open areas with light clothes or UV-block (sunscreen) agents. Though UV-blocks are somewhat helpful, they also exclude other key wavelengths from the spectrum. So, they prevent any "additive" effects. The UV-blocks are helpful in case people get out in the sun longer than 1 hour a day after using FloraDynamica or our photoregenerative cosmetics.

MNM: You mentioned FloraDynamica®. Please describe this product and explain its advantages when compared to other photosensitizer agents.

AVR: In FloraDynamica®, the active component is the so-called Active Water-Soluble Chlorophyll—AWSC® in the liquid glycerol matrix. Both FloraDynamica® and AWSC® are trademarked. Even though this is chlorin e_6, we present it as chlorin with glycerol groups surrounding it. Simply speaking, this is a chlorophyll derivative. When taken orally, it is broken down by the digestive enzymes into a number of components that include Chlorin e_6, Chlorin p_6, purpurin 5 and others, but easy penetration (good bioavailability) is achieved through the glycerol delivery.

The main advantage of using FloraDynamica® is that it is not quickly cleared from the body because its dose is below the recognition threshold of the liver. Most drugs and medications have to bypass the liver. FloraDynamica® goes easily through the liver and into the bloodstream, and then takes about one week to build up in the body, with selective accumulation in abnormal tissues or mutated cells.

MNM: With FloraDynamica®, is there a risk of side effects?

AVR: Yes, with every photosensitizer, the amount plays a major role. Secondly, the light dose and light exposure are important. And thirdly, the individual's skin type and other individual factors may play a role. Allergic individuals may get skin reactions, such as blisters, redness, swelling, and basically changes that are similar to sunburn. The release of histamine makes it often look like a rash. When it appears, the person must discontinue use for a few days (or until the uncomfortable symptoms cease), but further use after that is possible. The light exposure and product intake should also be reduced. Also less getting out in the sun, and more use of dark clothes.

Other Thoughts and Comments

MNM: It's remarkable that so many excellent PDT agents come from the plant world. Perhaps you could speak a little to the point about how plants can teach us about PDT.

AVR: PDT reactions are going on all the time in green leaves but the singlet oxygen generated is being quenched by other pigments such as carotenoids, flavonoids (phenolic compounds) and saponins. Without those other pigments and other antioxidant compounds, the chlorophyll would generate too much singlet oxygen and the leaf would die. This is what happens in the fall as the leaf loses its pigments. Thus, plants have PDT going on all the time, but we only see its effects in the fall, when the leaf loses all the antioxidant systems that prevent the single oxygen-mediated damaging effects of chlorophyll.

If you remove iron from the heme in hemoglobin, you get a very nice photosensitizer called Protoporphyrin-IX (Pp-IX), a disodium salt. Pp-IX is naturally present in skin and prevents infection on the surface of the skin, upon reaction with sunlight. If the skin pores are blocked, however, you have to use external creams to help the skin pores open up, and restore the skin's natural, healthy homeostasis. This then enables the skin to restore its production of Pp-IX. We made such cosmetic creams and gels commercially available at our website www.lortic.ru.

MNM: A recent study showed that selenium synergistically enhanced the effectiveness of Radachlorin® in the context of PDT. This seems interesting given that selenium has prooxidative effects in cancer cells, which is thought to be how it may kill those cells. Also, selenium enhances anti-cancer immunity. Are there other agents that may also enhance these effects?

AVR: This is worth thinking about and trying to select some supplements that are compatible with PDT. We address this issue in Chapter 6, which focuses on dietary practice and supplements. Green tea, curcumin, St. John's Wort, Solanaceae, soy proteins, horse radish, vitamin K2, and high-dose vitamin C, all have pro-oxidant effects and may be taken concurrently with the PDT. Nicotinamide, a form of niacin or vitamin B3, may be useful for other reasons. Perhaps if people supplement with selenium or nicotinamide, we will see them respond better to PDT. And same can be said about certain immune-adjuvants. Also, two months after starting their PDT/PIT/SYLT, people may benefit from the use of antioxidant supplements to establish balance in the body, as the excessively long pro-oxidative action can be aging and should be neutralized by blueberry extract, grapeseed extract, low-dose vitamin C, and vitamin E in the form of mixed tocopherols.

MNM: Could you briefly address the effects of PDT on heart disease?

AVR: We talk about PDT for atherosclerosis in Chapter 5. There is some evidence that SYLT can have hematoprotective action, improving blood circulation and making the blood less dense. It also helps to de-aggregate the platelets, so the Bremachlorophyll® (clinically proven) and FloraDynamica® are generally going to improve blood flow. There are published studies indicating effects on dendritic cells that may help reverse restenosis.

MNM: Are there any measurements that physicians and other health care professionals should take in order to make the photodynamic approach more effective?

AVR: We need to be able to measure two things. First, the concentration of the product in the blood stream or tissue can be easily measured in a non-invasive way through the skin, because of the fluorescing and phosphorescing ability of the drug. Secondly we need to be able to measure the antioxidant potential of the blood, or the oxidative index.[285] This will tell us how much a person needs to balance out the effects of treatment with antioxidant supplements and diet. This will help us fight cancer and rejuvenate without accelerating aging. Otherwise, there is the risk of having too much of a pro-oxidant effect in the blood, and this will accelerate the aging process. Too much oxidative stress also may encourage the genesis of diseases such as cancer, diabetes, stroke and heart disease.

I would like to thank Dr. Thierry Patrice for his discovering a technique for measuring the antioxidant potential of the blood, the importance of which cannot be overestimated. His insight was that the antioxidant power of any organism—from fish to human—can be of prognostic and diagnostic significance in relation to many metabolic disorders. So, we must find ways to efficiently balance between the pro-oxidant impact of PDT and nutritional antioxidants. Essentially, we are balancing our efforts to fight cancer and infection on the one hand, with promoting mutations, diseases and aging on the other.

MNM: Thanks so much for sharing this wealth of information along with your seasoned insights in the realm of photodynamic medicine. It's exciting to contemplate all the ways by which light-based technologies may improve cancer treatment and prevention as well, and I look forward to seeing how photomedicine evolves in the years ahead.

REFERENCES

1. Kennedy JC, Pottier RH, Pross DC. Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience. J Photochem Photobiol B. 1990 Jun;6(1-2):143-8.

2. Mead MN. Benefits of sunlight: a bright spot for human health. Environ Health Perspect. 2008 Apr;116(4):A160-7.

3. Marrelli M, Menichini G, Provenzano E, Conforti F. Applications of Natural Compounds in the Photodynamic Therapy of Skin Cancer. Curr Med Chem. 2013 Mar 15. [Epub ahead of print]

4. Phillips D. Light relief: photochemistry and medicine. Photochem Photobiol Sci. 2010 Dec; 9(12):1589-96.

5. Patel NS, Paghdal KV, Cohen GF. Advanced treatment modalities for vitiligo. Dermatol Surg. 2012 Mar;38(3):381-91. See also: Hamzavi IH, Lim HW, Syed ZU. Ultraviolet-based therapy for vitiligo: what's new? Indian J Dermatol Venereol Leprol. 2012 Jan-Feb;78(1):42-8

6. Dougherty TJ. Photodynamic therapy (PDT) of malignant tumors. Crit Rev Oncol Hematol. 1984;2(2):83-116

7. ZA 2003/8407, AU 2002212867, NZ 528237, GB 2389531, NO 327751, SE 01981209.8, IT 70446-BE/2009, HU P0400298, SK 2003-1348; SI, NL, IE, FR, DE, CH, BE 1380295 (RADA-PHARMA INTERNATIONAL B.V.). RU 2183956, BR PI0116952-1, IN 217695, US 6,969,765, CA 2,440,650, CN 258833, KR 10-0628548 (OOO RADA-FARMA) Priority of 2001-10-04 (Russia – 2001-03-30). Published on 2002-06-27. Reshetnickov AV, Zalevskiy ID et al. Photosensitizer, and a method thereof.

8. Pandi-Perumal SR, Srinivasan V, Spence DW, Cardinali DP. Role of the melatonin system in the control of sleep: therapeutic implications. CNS Drugs. 2007;21(12):995-1018.

9. Lindholm H, Sinisalo J, Ahlberg J, Hirvonen A, Hublin C, Partinen M, Savolainen A. Attenuation of vagal recovery during sleep and reduction of cortisol/melatonin ratio in late afternoon associate with prolonged daytime sleepiness among media workers with irregular shift work. Am J Ind Med. 2012 Jul;55(7):643-9

10. Gallucci S, Matzinger P. Danger signals: SOS to the immune system. Curr Opin Immunol. 2001 Feb;13(1):114-9. See also: Nace G, Evankovich J, Eid R, Tsung A. Dendritic cells and damage-associated molecular patterns: endogenous danger signals linking innate and adaptive immunity. J Innate Immun. 2012;4(1):6-15.

11. Etminan N, Peters C, Lakbir D, Bünemann E, Börger V, Sabel MC, Hänggi D, Steiger HJ, Stummer W, Sorg RV. Heat-shock protein 70-dependent dendritic cell activation by 5-aminolevulinic acid-mediated photodynamic treatment of human glioblastoma spheroids in vitro. Br J Cancer. 2011 Sep 27;105(7):961-9. See also: Multhoff G. Heat shock proteins in immunity. Handb Exp Pharmacol. 2006;(172):279-304.

12. Haraldsdóttir KH, Ivarsson K, Götberg S, Ingvar C, Stenram U, Tranberg KG. Interstitial laser thermotherapy (ILT) of breast cancer. Eur J Surg Oncol. 2008 Jul;34(7):739-45.

13. Lee SJ, Kim SY, Kim SD. A case of diode laser photocoagulation in the treatment of choroidal metastasis of breast carcinoma. Korean J Ophthalmol. 2008 Sep;22(3):187-9

14. Korbelik M. PDT-associated host response and its role in the therapy outcome. Lasers Surg Med. 2006 Jun;38(5):500-8

15. Mroz P, Szokalska A, Wu MX, Hamblin MR. Photodynamic therapy of tumors can lead to development of systemic antigen-specific immune response. PLoS One. 2010 Dec 14;5(12):e15194. See also: St Denis TG, Aziz K, Waheed AA, Huang YY, Sharma SK, Mroz P, Hamblin MR. Combination approaches to potentiate immune response after photodynamic therapy for cancer. Photochem Photobiol Sci. 2011 May;10(5):792-801. See also: Castano AP, Gad F, Zahra T, Hamblin MR. Specific anti-tumor immune response with photodynamic therapy mediated by benzoporphyrin derivative and chlorin (e6). Proc. SPIE 4961 (2003) 1-9.

16. Internet source: http://www.who.int/mediacentre/factsheets/fs194/en/

17. Klein EY, Smith DL, Laxminarayan R, Levin S. Superinfection and the evolution of resistance to antimalarial drugs. Proc Biol Sci. 2012 Jul 11; also see: Barnes KI, White NJ. Population biology and antimalarial resistance: The transmission of antimalarial drug resistance in Plasmodium falciparum. Acta Trop. 2005 Jun;94(3):230-40

18. Klein E, Smith DL, Laxminarayan R. Hospitalizations and deaths caused by methicillin-resistant Staphylococcus aureus, United States, 1999-2005. Emerg Infect Dis. 2007 Dec;13(12):1840-6.. Note: This includes individuals who were admitted to the hospital for treatment of an infection that was acquired or occurred outside the hospital.

19. Hansen S, Schwab F, Asensio A, Carsauw H, Heczko P, Klavs I, Lyytikäinen O, Palomar M, Riesenfeld-Orn I, Savey A, Szilagyi E, Valinteliene R, Fabry J, Gastmeier P. Methicillin-resistant Staphylococcus aureus (MRSA) in Europe: which infection control measures are taken? Infection. 2010 Jun;38(3):159-64

20. Internet source: http://www.who.int/mediacentre/factsheets/fs194/en/

21. Wagner H. Synergy research: approaching a new generation of phytopharmaceuticals. Fitoterapia. 2011 Jan;82(1):34-7. See also: Eumkeb G, Sakdarat S, Siriwong S. Reversing ß-lactam antibiotic resistance of Staphylococcus aureus with galangin from Alpinia officinarum Hance and synergism with ceftazidime. Phytomedicine. 2010 Dec 15;18(1):40-5.

22. Mead MN. Nutrigenomics: The genome-food interface. Environmental Health Perspectives. 2007; 115(12):582-589

23. Afaq F, Katiyar SK. Polyphenols: skin photoprotection and inhibition of photocarcinogenesis. Mini Rev Med Chem. 2011 Dec;11(14):1200-15

24. Filip A, Clichici S, Daicoviciu D, Adriana M, Postescu ID, Perde-Schrepler M, Olteanu D. Photochemoprevention of cutaneous neoplasia through natural products. Exp Oncol. 2009 Mar;31(1):9-15

25. Pilkington SM, Watson RE, Nicolaou A, Rhodes LE. Omega-3 polyunsaturated fatty acids: photoprotective macronutrients. Exp Dermatol. 2011 Jul;20(7):537-43

26. Bogh MK, Gullstrand J, Svensson A, Ljunggren B, Dorkhan M. Narrowband ultraviolet B three times per week is more effective in treating vitamin D deficiency than 1600 IU oral vitamin D_3 per day: a randomized clinical trial. Br J Dermatol. 2012 Sep; 167(3):625-30. See also: Ala-Houhala MJ, Vähävihu K, Hasan T, Kautiainen H, Ylianttila L, Viljakainen HT, Snellman E, Reunala T. Comparison of narrowband ultraviolet B exposure and oral vitamin D substitution on serum 25-hydroxyvitamin D concentration. Br J Dermatol. 2012 Jul;167(1):160-4.

27. Fayter D, Corbett M, Heirs M, Fox D, Eastwood A. A systematic review of photodynamic therapy in the treatment of pre-cancerous skin conditions, Barrett's oesophagus and cancers of the biliary tract, brain, head and neck, lung, oesophagus and skin. Health Technol Assess. 2010 Jul;14(37):1-288.

28. Zhao B, He YY. Recent advances in the prevention and treatment of skin cancer using photodynamic therapy. Expert Rev Anticancer Ther. 2010;10(11):1797-809

29. Price M, Heilbrun L, Kessel D. Effects of the oxygenation level on formation of different reactive oxygen species during photodynamic therapy. Photochem Photobiol. 2013 May;89(3):683-6. See also: Henderson BW, Gollnick SO, Snyder JW, Busch TM, Kousis PC, Cheney RT, Morgan J. Choice of oxygen-conserving treatment regimen determines the inflammatory response and outcome of photodynamic therapy of tumors. Cancer Res. 2004 Mar 15;64(6):2120-6.

30. Morton CA, Brown SB, Collins S, et al. Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group. Br J Dermatol 2002; 146: 552-67

31. Sidoroff A. Actinic keratosis. In: Calzavara-Pinton PG, Szeimies RM, Ortel B, eds. Photodynamic therapy and Fluorescence Diagnosis in Dermatology. Amsterdam: Elsevier, 2001: 199-216

32. Wiegell SR, Wulf HC, Szeimies RM, Basset-Seguin N, Bissonnette R, Gerritsen MJ, Gilaberte Y, Calzavara-Pinton P, Morton CA, Sidoroff A, Braathen LR. Daylight photodynamic therapy for actinic keratosis: an international consensus: International Society for Photodynamic Therapy in Dermatology. J Eur Acad Dermatol Venerol. 2012;26(6):673-9

33. Waibel JS. Photorejuvenation. Dermatol Clin. 2009 Oct;27(4):445-57

34. Kohl E, Karrer S. Photodynamic therapy for photorejuvenation and non-oncologic indications: overview and update. G Ital Dermatol Venereol. 2011 Dec;146(6):473-85.

35. Marmur ES, Phelps R, Goldberg DJ. Ultrastructural changes seen after ALA-IPL photorejuvenation: a pilot study. J Cosmet Laser Ther. 2005 Mar;7(1):21-4.

36. Alster TS, Tanzi EL, Welsh EC. Photorejuvenation of facial skin with topical 20 percent 5-aminolevulinic acid and intense pulsed light treatment: a split-face comparison study. J Drugs Dermatol. 2005 Jan-Feb;4(1):35-8.

37. Nootheti PK, Goldman MP. Aminolevulinic acid-photodynamic therapy for photorejuvenation. Dermatol Clin. 2007 Jan;25(1):35-45. See also: Seaton ED, Mouser PE, Charakida A, Alam S, Seldon PM, Chu AC. Investigation of the mechanism of action of nonablative pulsed-dye laser therapy in photorejuvenation and inflammatory acne vulgaris. Br J Dermatol. 2006 Oct;155(4):748-55.

38. Gold MH. Therapeutic and aesthetic uses of photodynamic therapy part one of a five-part series: the use of photodynamic therapy in the treatment of actinic keratoses and in photorejuvenation. J Clin Aesthet Dermatol. 2008 Jul;1(2):32-7

39. Babilas P, Schreml S, Landthaler M, Szeimies RM. Photodynamic therapy in dermatology: state-of-the-art. Photodermatol Photoimmunol Photomed. 2010 Jun;26(3):118-32

40. Kochneva EV, Filonenko EV, Vakulovskaya EG, Scherbakova EG, Seliverstov OV, Markichev NA, Reshetnickov AV. Photosensitizer Radachlorin®: Skin cancer PDT phase II clinical trials, Photodiagnosis and Photodynamic Therapy 2010; 7(4): 258-267.

41. Zeitouni NC, Shieh S, Oseroff AR. Laser and photodynamic therapy in the management of cutaneous malignancies. Clin Dermatol. 2001; 19: 328-338; See also: Basset-Seguin N, Ibbotson SH, Emtestam L, et al. Topical methyl aminolaevulinate photodynamic therapy versus cryotherapy for superficial basal cell carcinoma: a 5 year randomized trial. Eur J Dermatol. 2008; 18:547-553.

42. Privalov VA, Lappa AV, Kochneva EV. Five years' experience of photodynamic therapy with new chlorin photosensitizer. SPIE Proc. 2005; 5863 (II):186-198.

43. Basset-Seguin N, Ibbotson SH, Emtestam L, et al. Topical methyl aminolaevulinate photodynamic therapy versus cryotherapy for superficial basal cell carcinoma: a 5 year randomized trial. Eur J Dermatol. 2008;18(5):547–553

44. Wheless L, Black J, Alberg AJ. Nonmelanoma skin cancer and the risk of second primary cancers: a systematic review. Cancer Epidemiol Biomarkers Prev. 2010 Jul;19(7):1686-95

45. Rodust PM, Stockfleth E, Ulrich C, Leverkus M, Eberle J. UV-induced squamous cell carcinoma--a role for antiapoptotic signalling pathways. Br J Dermatol. 2009 Nov;161 Suppl 3:107-15.

46. Morton CA. Methyl aminolevulinate: actinic keratoses and Bowen's disease. Dermatol Clin. 2007; 25: 81-87; Salim A, Leman JA, McColl JH, Chapman R, Morton CA. Randomized comparison of photodynamic therapy with topical 5-fluorouracil in Bowen's disease. Br J Dermatol. 2003; 148: 539-543

47. Calin MA, Diaconeasa A, Savastru D, Tautan M. Photosensitizers and light sources for photodynamic therapy of the Bowen's disease. Arch Dermatol Res. 2011 Apr;303(3):145-51

48. Shimizu I, Cruz A, Chang KH, Dufresne RG. Treatment of squamous cell carcinoma in situ: a review. Dermatol Surg. 2011 Oct; 37(10):1394-411

49. Privalov VA, et al. SPIE Proc. 2005; 5863 (II):186-198. OP CIT.

50. Volkov EI. Non-published data/personal communication by the author.

51. Maeurer MJ, Gollin SM, Storkus WJ, Swaney W, Karbach J, Martin D, Castelli C, Salter R, Knuth A, Lotze MT. Tumor escape from immune recognition: loss of HLA-A2 melanoma cell surface expression is associated with a complex rearrangement of the short arm of chromosome 6. Clin. Cancer Res. 1996;2:641–652

52. Baldea I, Filip AG. Photodynamic therapy in melanoma--an update. J Physiol Pharmacol. 2012 Apr;63(2):109-18.

53. RU 2345803 (BREMA PHARMA B.V.) Priority of 2006-11-30. Published on 2009-02-10 in Bull.4/2009. Vasiliev NE, Reshetnickov AV et al. Photoimmunotherapy treatment in a man by a photosensitizer activated with electromagnetic energy outside the body.

54. Baldea I, Filip AG. 2012. Op Cit

55. den Brok MH, Sutmuller RP, van der Voort R, Bennink EJ, Figdor CG, Ruers TJ, et al. In situ tumor ablation creates an antigen source for the generation of antitumor immunity. Cancer Res. 2004;64:4024–4029

56. Chen WR, Singhal AK, Liu H, Nordquist RE. Antitumor immunity induced by laser immunotherapy and its adoptive transfer. Cancer Res. 2001;61:459–461

57. Steinmann A, Funk JO, Schuler G, von den Driesch P. Topical imiquimod treatment of a cutaneous melanoma metastasis. J Am Acad Dermatol. 2000;43:555–556; Bong AB, Bonnekoh B, Franke I, Schön MP, Ulrich J, Gollnick H. Imiquimod, a topical immune response modifier, in the treatment of cutaneous metastases of malignant melanoma. Dermatology. 2002;205:135–138

58. Li X, Naylor MF, Le H, Nordquist RE, Teague TK, Howard CA, Murray C, Chen WR. Clinical effects of in situ photoimmunotherapy on late-stage melanoma patients: a preliminary study. Cancer Biol Ther. 2010;10(11):1081-7.

59. Korbelik M, Cooper PD. Potentiation of photodynamic therapy of cancer by complement: the effect of γ-inulin. Br. J. Cancer. 2007;96(1):67–72

60. Shurin MR, Naiditch H, Gutkin DW, Umansky V, Shurin GV. Chemo-ImmunoModulation: immune regulation by the antineoplastic chemotherapeutic agents. Curr Med Chem. 2012;19(12):1792-803; see also: Haynes NM, van der Most RG, Lake RA, Smyth MJ. Immunogenic anti-cancer chemotherapy as an emerging concept. Curr Opin Immunol. 2008 Oct;20(5):545-57.

61. Davids LM, Kleemann B. Combating melanoma: the use of photodynamic therapy as a novel, adjuvant therapeutic tool. Cancer Treat Rev. 2011 Oct;37(6):465-75

62. Shixiang Y, Xi S, Junliang L, Shanyi Z, Xingke X, Meiguang Z, Kai W, Fangcheng L. Antitumor efficacy of a photodynamic therapy-generated dendritic cell glioma vaccine. Med Oncol. 2011 Dec;28 Suppl 1:S453-61; see also: Rass K, Tilgen W. Treatment of melanoma and nonmelanoma skin cancer. Adv Exp Med Biol. 2008;624:296-318

63. Madhunapantula SV, Gowda R, Inamdar GS, Robertson GP. In situ photoimmunotherapy: a new hope for cutaneous melanoma patients. Cancer Biol Ther. 2010;10(11):1088-90

64. St Pierre SA, Rommel J, Ciurea A, Fife D, Yoo SS, Martini M, Kuzel TM, Wayne J, Rademaker A, West DP, Alam M. In situ photoimmunotherapy: a surgery- and limb-sparing approach to the treatment of cutaneous metastases in advanced melanoma. Arch Dermatol. 2010;146(8):831-4; Li X, Naylor MF, Le H, Nordquist RE, Teague TK, Howard CA, Murray C, Chen WR. Clinical effects of in situ photoimmunotherapy on late-stage melanoma patients: a preliminary study. Cancer Biol Ther. 2010;10(11):1081-7; Naylor MF, Chen WR, Teague TK, Perry LA, Nordquist RE. In situ photoimmunotherapy: a tumour-directed treatment for melanoma. Br J Dermatol. 2006;155(6):1287-92.

65. RU 2438604 (GBOU DPO RMAPO) Priority of 2010-06-11. Mumladze RB, Yakovlev VN, Dolidze DD, Herzen AV, Dzhigkaev TD, Reshetnickov AV, Vardanyan AB, Antysheva TYa. Thyroid benign nodular adenomatosis treatment.

66. Dzhigkaev TD, Dolidze DD, Antysheva TYa, Mumladze RB, Gertsen AV, Vardanyan AV, Lisitsin DV, Khamukova OS, Reshetnickov AV, Photodynamic therapy combined with percutaneous laser ablation of benign multiple adenomatosis of the thyroid: 3-year follow-up of 8 patients. The 13th IPA World Congress. May 10-14. Innsbruck, Austria. Book of abstracts. 2011:67. Dzhigkaev TD, Dolidze DD, Antysheva TYa, Mumladze RB, Gertsen AV, Reshetnickov AV, Photodynamic therapy combined with percutaneous laser ablation of benign multiple adenomatosis of the thyroid: 5-year follow-up of 8 patients. The 14th IPA World Congress. May 28-31. Seoul, South Korea. Book of abstracts. 2013:115.

67. Rothschild BM, Witzke BJ, Hershkovitz I. Metastatic cancer in the Jurassic. Lancet. 1999;354(9176):398

68. Rothschild BM, Tanke DH, Helbling M 2nd, Martin LD. Epidemiologic study of tumors in dinosaurs. Naturwissenschaften. 2003;90(11):495-500

69. Platek SM, Gallup GG Jr, Fryer BD. The fireside hypothesis: was there differential selection to tolerate air pollution during human evolution? Med Hypotheses. 2002 Jan;58(1):1-5.

70. Baramiya MG. Aging and carcinogenesis--insufficient metabolic cell repair as the common link. Gerontology. 2000 Nov-Dec;46(6):328-32

71. Lichtenstein AV. Cancer as a programmed death of an organism. Biochemistry (Mosc). 2005;70(9):1055-64; Lichtenstein AV. Cancer: shift of the paradigm. Med Hypotheses. 2008;71(6):839-50; Sommer SS. Does cancer kill the individual and save the species? Hum Mutat. 1994;3(2):166-9

72. Brinkley D, Haybittle JL. A 15 year follow up study of patients treated for carcinoma of the breast. Br J Radiol 1968;41:215-221

73. Páez D, Labonte MJ, Bohanes P, Zhang W, Benhanim L, Ning Y, Wakatsuki T, Loupakis F, Lenz HJ. Cancer dormancy: a model of early dissemination and late cancer recurrence. Clin Cancer Res. 2012;18(3):645-53; Uhr JW, Pantel K. Controversies in clinical cancer dormancy. Proc Natl Acad Sci U S A. 2011 Jul 26;108(30):12396-400

74. Demicheli R, Retsky MW, Hrushesky WJ, Baum M, Gukas ID. The effects of surgery on tumor growth: a century of investigations. Ann Oncol. 2008 Nov;19(11):1821-8.

75. Ehrlich P, Apolant H. Beobechtungen über maligne Mäusetumoren. Berl Klein Wchnshr 1905;42:871-874

76. Marie P, Clunet J. Fréquences des métastases viscérales chez les souris cancéreuses après ablation chirurgicale de leur tumeur. Bull Assoc Franç pour l'étude du cancer 1910;3:19-23; Tyzzer EE. Factors in the production and growth of tumor metastases. J Med Res 1913;23:309-332

77. Yamashita T, Hayakawa K, Hosokawa M, Kodama T, Inoue N, Tomita K, Kobayashi H. Enhanced tumor metastases in rats following cryosurgery of primary tumor. Gann. 1982 Apr;73(2):222-8

78. Keller R, Hess MW. Divergency between incidence of microscopic and macroscopic metastases. Virchows Arch A Pathol Anat Histopathol. 1982;398(1):33-43. See also: Keller R. Elicitation of macroscopic metastases via surgery: various forms of surgical intervention differ in their induction of metastatic outgrowth. Invasion Metastasis. 1983;3(3):183-92.

79. Retsky M. New concepts in breast cancer emerge from analyzing clinical data using numerical algorithms. Int J Environ Res Public Health. 2009;6(1):329-48

80. Goldstein MR, Mascitelli L. Surgery and cancer promotion: are we trading beauty for cancer? QJM. 2011;104(9):811-5

81. Park Y, Kitahara T, Takagi R, Kato R. Does surgery for breast cancer induce angiogenesis and thus promote metastasis? Oncology. 2011;81(3-4):199-205

82. Lejeune FJ. Is surgical trauma prometastatic? Anticancer Res. 2012 Mar;32(3):947-51

83. Demicheli R, Retsky MW, Hrushesky WJ, et al. Ann Oncol. 2008 Nov;19(11):1821-8. OP CIT.

84. Camara O, Kavallaris A, Nöschel H, Rengsberger M, Jörke C, Pachmann K. Seeding of epithelial cells into circulation during surgery for breast cancer: the fate of malignant and benign mobilized cells. World J Surg Oncol. 2006 26;4:67; Kasimir-Bauer S, Oberhoff C, Schindler AE, Seeber S. A summary of two clinical studies on tumor cell dissemination in primary and metastatic breast cancer: methods, prognostic significance and implication for alternative treatment protocols (Review). Int J Oncol. 2002;20(5):1027-34

85. Lacy AM, Garcia-Valdecasas JC, Delgado S, et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet 2002;359:2224-2229

86. Park Y, Kitahara T, Takagi R, Kato R. Does surgery for breast cancer induce angiogenesis and thus promote metastasis? Oncology. 2011;81(3-4):199-205

87. Castano AP, Mroz P, Hamblin MR. Photodynamic therapy and anti-tumour immunity. Nat Rev Cancer. 2006 Jul;6(7):535-45

88. Yanase S, Nomura J, Matsumura Y, Kato H, Tagawa T. Hyperthermia enhances the antitumor effect of photodynamic therapy with ALA hexyl ester in a squamous cell carcinoma tumor model. Photodiagnosis Photodyn Ther. 2012 Dec;9(4):369-75. See also: He Y, Ge H, Li S. Haematoporphyrin based photodynamic therapy combined with hyperthermia provided effective therapeutic vaccine effect against colon cancer growth in mice. Int J Med Sci. 2012;9(8):627-33. See also: Yanase S, Nomura J, Matsumura Y, Watanabe Y, Tagawa T. Synergistic increase in osteosarcoma cell sensitivity to photodynamic therapy with aminolevulinic acid hexyl ester in the presence of hyperthermia. Photomed Laser Surg. 2009 Oct;27(5):791-7. See also: Hirschberg H, Sun CH, Tromberg BJ, Yeh AT, Madsen SJ. Enhanced cytotoxic effects of 5-aminolevulinic acid-mediated photodynamic therapy by concurrent hyperthermia in glioma spheroids. J Neurooncol. 2004 Dec;70(3):289-99.

89. Klotz L. Cancer overdiagnosis and overtreatment. Curr Opin Urol. 2012 May;22(3):203-9.

90. Garg AD, Nowis D, Golab J, Agostinis P. Photodynamic therapy: illuminating the road from cell death towards anti-tumour immunity. Apoptosis. 2010;15(9):1050-71

91. Allison R, Moghissi K, Downie G, Dixon K. Photodynamic therapy (PDT) for lung cancer. Photodiagnosis Photodyn Ther. 2011 Sep;8(3):231-9

92. Endo C, Miyamoto A, Sakurada A, et al. Results of long-term follow-up of photodynamic therapy for roentgenographically occult bronchogenic squamous cell carcinoma. Chest. 2009; 136: 369-375

93. Usuda J, Ichinose S, Ishizumi T, et al. Outcome of photodynamic therapy using NPe6 for bronchogenic carcinomas in central airways >1.0 cm in diameter. Clin Cancer Res. 2010; 16: 2198-2204

94. Simone CB 2nd, Friedberg JS, Glatstein E, Stevenson JP, Sterman DH, Hahn SM, Cengel KA. Photodynamic therapy for the treatment of non-small cell lung cancer. J Thorac Dis. 2012 Feb;4(1):63-75

95. Moghissi K, Dixon K. Update on the current indications, practice and results of photodynamic therapy (PDT) in early central lung cancer (ECLC). Photodiagnosis Photodyn Ther. 2008 Mar;5(1):10-8

96. Casas A, Di Venosa G, Hasan T, Al Batlle. Mechanisms of resistance to photodynamic therapy. Curr Med Chem. 2011;18(16):2486-515

97. Hill BT. Differing patterns of cross-resistance resulting from exposures to specific antitumour drugs or to radiation in vitro. Cytotechnology. 1993;12(1-3):265-88.

98. Crescenzi E, Chiaviello A, Canti G, Reddi E, Veneziani BM, Palumbo G. Low doses of cisplatin or gemcitabine plus Photofrin/photodynamic therapy: Disjointed cell cycle phase-related activity accounts for synergistic outcome in metastatic non-small cell lung cancer cells (H1299). Mol Cancer Ther. 2006 Mar;5(3):776-85.

99. Diaz-Jimenez JP, Martinez-Ballarin JE, Llunell A, Farrero E, Rodriguez A, Castro MJ. Efficacy and safety of photodynamic therapy versus Nd-YAG laser resection in NSCLC with airway obstruction. Eur Respir J. 1999; 14: 800-805

100. Freitag L, Ernst A, Thomas M, Prenzel R, Wahlers B, Macha HN. Sequential photodynamic therapy (PDT) and high dose brachytherapy for endobronchial tumour control in patients with limited bronchogenic carcinoma. Thorax. 2004 Sep;59(9):790-3

101. Biel MA, Kim T, Trump MJ. Effect of radiation therapy and Photofrin on tissue response in a rat model. Lasers Surg Med 1993;13:672–6. See also: Dobler-Girdziunaite D, Burkard W, Haller U, et al. Combined treatment of breast carcinoma cells in vitro by photodynamic therapy and ionizing radiation. Strahlenther Onkol 1995;171:622–9.

102. Lam S, Muller NL, Miller RR, et al. Laser treatment of obstructive endobronchial tumors: factors which determine response. Lasers Surg Med. 1987; 7: 29-35

103. Okunaka T, Hiyoshi T, Furukawa K, Yamamoto H, Tsuchida T, Usuda J, Kumasaka H, Ishida J, Konaka C, Kato H. Lung cancers treated with photodynamic therapy and surgery. Diagn Ther Endosc. 1999;5(3):155-60

104. Weinberg BD, Allison RR, Sibata C, Parent T, Downie G. Results of combined photodynamic therapy (PDT) and high dose rate brachytherapy (HDR) in treatment of obstructive endobronchial non-small cell lung cancer (NSCLC). Photodiagnosis Photodyn Ther. 2010; 7: 50-58

105. Sokolov VV, Telegina LV, Trakhtenberg AKh, Kolbanov KI, Pikin OV, Frank GA. [Endobronchial surgery and photodynamic therapy for the treatment of multiple primary lung cancer] Khirurgiia (in Russian) 2010;(7):28–31

106. RU 2345803 (BREMA PHARMA B.V.) Priority of 2006-11-30. Published on 2009-02-10 in Bull.4/2009. Vasiliev NE, Reshetnickov AV et al. Photoimmunotherapy treatment in a man by a photosensitizer activated with electromagnetic energy outside the body. Op Cit.

107. Pass HI, Temeck BK, Kranda K, Thomas G, Russo A, Smith P, Friauf W, Steinberg SM. Phase III Randomized Trial of Surgery With or Without Intraoperative Photodynamic Therapy and Postoperative Immunochemotherapy for Malignant Pleural Mesothelioma. Ann. Surg. Oncol. 1997;4:628–633. See also: Moskal TL, Dougherty TJ, Urschel JD, Antkowiak JG, Regal AM, Driscoll DL, Takita H. Operation and Photodynamic Therapy for Pleural Mesothelioma: 6-year Follow-up. Ann. Thorac. Surg. 1998;66:1128–1133; See also: Schouwink H, Rutgers ET, van der Sijp J, Oppelaar H, van Zandwijk N, van Veen R, Burgers S, Stewart FA, Zoetmulder F, Baas P. Intraoperative Photodynamic Therapy After Pleuropneu-monectomy in Patients with Malignant Pleural Mesothelioma: Dose Finding and Toxicity Results. Chest. 2001;120:1167–1174; See also: Bonnette P, Heckly GB, Villette S, Fragola A. Intrauperative Photodynamic Therapy After Pleuropneumonectomy for Malignant Pleural Mesothelioma. Chest. 2002;122:1866–1867

108. Moskal TL, Dougherty TJ, Urschel JD, et al. Operation and photodynamic therapy for pleural mesothelioma: 6-year follow-up. Ann Thorac Surg. 1998; 66: 1128-1133

109. Chen Q, Huang Z, Chen H, Shapiro H, Beckers J, Hetzel FW. Improvement of Tumor Response by Manipulation of Tumor Oxygenation During Photodynamic Therapy. Photochem. Photobiol. 2002;76:197-203; Huang Z, Chen Q, Shakil A, Chen H, Beckers J, Shapiro H, Hetzel FW. Hyperoxygenation Enhances the Tumor Cell Killing of Photofrin-mediated Photodynamic Therapy. Photochem. Photobiol. 2003;78:496–502

110. Matzi V, Maier A, Sankin O, Lindenmann J, Woltche M, Smolle J, Smolle-Juttner FM. Photodynamic Therapy Enhanced by Hyperbaric Oxygenation in Palliation of Malignant Pleural Mesothelioma: Clinical Experience. Photodiag. Photodyn. Therapy. 2004;1:57–64

111. Friedberg JS, Cengel KA. Pleural malignancies. Semin Radiat Oncol. 2010; 20: 208-214

112. Stepp H, Beck T, Pongratz T, Meinel T, Kreth FW, Tonn JCh, Stummer W. ALA and malignant glioma: fluorescence-guided resection and photodynamic treatment. J Environ Pathol Toxicol Oncol. 2007;26(2):157-64. See also: Aziz F, Telara S, Moseley H, Goodman C, Manthri P, Eljamel MS. Photodynamic therapy adjuvant to surgery in metastatic carcinoma in brain. Photodiagnosis Photodyn Ther. 2009;6(3-4):227-30

113. Eljamel MS, Goodman C, Moseley H. ALA and Photofrin fluorescence-guided resection and repetitive PDT in glioblastoma multiforme: a single centre Phase III randomised controlled trial. Lasers Med Sci. 2008 Oct;23(4):361-7.

114. Kostron H. Photodynamic diagnosis and therapy and the brain. Methods Mol Biol. 2010;635:261-80

115. Madsen S, Hirschberg H. Photodynamic therapy and detection of high-grade gliomas. J Environ Pathol Toxicol Oncol. 2006;25(1-2):453-66; see also: Stepp H, Beck T, Pongratz T, Meinel T, Kreth FW, Tonn JCh, Stummer W. ALA and malignant glioma: fluorescence-guided resection and photodynamic treatment. J Environ Pathol Toxicol Oncol. 2007;26(2):157-64.

116. Kurzhupov MI, Zaitsev AM, Loshakov VA, Filonenko EV. The role of intraoperative photodynamic therapy in complex treatment of cerebral metastases. Zh Vopr Neirokhir Im N N Burdenko. 2010;(3):62-5; also see: Zilidis G, Aziz F, Telara S, Eljamel MS.Fluorescence image-guided surgery and repetitive Photodynamic Therapy in brain metastatic malignant melanoma. Photodiagnosis Photodyn Ther. 2008 Dec;5(4):264-6

117. Eljamel S. Photodynamic applications in brain tumors: a comprehensive review of the literature. Photodiagnosis Photodyn Ther. 2010;7(2):76-85

118. Whelan HT. High-grade glioma/glioblastoma multiforme: is there a role for photodynamic therapy? J Natl Compr Canc Netw. 2012 Oct 1;10 Suppl 2:S31-4

119. Jerjes W, Upile T, Hamdoon Z, Alexander Mosse C, Morcos M, Hopper C. Photodynamic therapy outcome for T1/T2 No oral squamous cell carcinoma. Lasers Surg Med. 2011 Aug;43(6):463-9

120. Biel MA. Photodynamic therapy and the treatment of head and neck neoplasia. Laryngoscope. 1998; 108: 1259-1268; Biel M. Advances in photodynamic therapy for the treatment of head and neck cancers. Lasers Surg Med. 2006; 38: 349-355.

121. Biel M. Advances in photodynamic therapy for the treatment of head and neck cancers. Lasers Surg Med. 2006; 38: 349-355; Keller GS, Doiron DR, Fisher GU. Photodynamic therapy in otolaryngology-head and neck surgery. Arch Otolaryngol. 1985; 111: 758-761; Feyh J, Goetz A, Muller W, Konigsberger R, Kastenbauer E. Photodynamic therapy in head and neck surgery. J Photochem Photobiol B. 1990; 7: 353-358; Feyh J, Gutmann A, Leunig A. A photodynamic therapy in head and neck surgery. Laryngol Rhinol Otol. 1993; 72: 273-278.

122. Jerjes W, Upile T, Akram S, Hopper C. The surgical palliation of advanced head and neck cancer using photodynamic therapy. Clin Oncol (R Coll Radiol). 2010; 22: 785-791; Bredell MG, Besic E, Maake C, Walt H. The application and challenges of clinical PD-PDT in the head and neck region: a short review. J Photochem Photobiol B. 2010; 101: 185-190

123. Li LB, Luo RC, Liao WJ, Zhang MJ, Luo YL, Miao JX. Clinical study of Photofrin photodynamic therapy for the treatment of relapse nasopharyngeal carcinoma. Photochem Photobiol Ther. 2006; 3: 266-271

124. D'Cruz AK, Robinson MH, Biel MA. mTHPC-mediated photodynamic therapy in patients with advanced, incurable head and neck cancer: a multicenter study of 128 patients. Head Neck. 2004; 26: 232-240

125. Fan KF, Hopper C, Speight PM, Buonaccorsi G, MacRobert AJ, Bown SG. Photodynamic therapy using 5-aminolevulinic acid for premalignant and malignant lesions of the oral cavity. Cancer. 1996; 78: 1374-1383; Grant WE, Hopper C, MacRobert AJ, Speight PM, Bown SG. Photodynamic therapy of oral cancer: photosensitisation with systemic aminolaevulinic acid. Lancet. 1993; 342: 147-148; Sieron A, Namyslowski G, Misiolek M, Adamek M, Kawczyk-Krupka A. Photodynamic therapy of premalignant lesions and local recurrence of laryngeal and hypopharyngeal cancers. Eur Arch Otorhinolaryngol. 2001; 258: 349-352

126. Copper MP, Triesscheijn M, Tan IB, Ruevekamp MC, Stewart FA. Photodynamic therapy in the treatment of multiple primary tumours in the head and neck, located to the oral cavity and oropharynx. Clin Otolaryngol. 2007; 32: 185-189

127. Pera M, Manterola C, Vidal O, Grande L. Epidemiology of esophageal adenocarcinoma. J Surg Oncol. 2005 Dec 1;92(3):151-9; Powell J, McConkey CC, Gillison EW, et al Continuing rising trend in oesophageal adenocarcinoma. Int J Cancer 2002;102:422-7

128. Selvasekar CR, Birbeck N, McMillan T, Wainwright M, Walker SJ. Photodynamic therapy and the alimentary tract. Aliment Pharmacol Ther. 2001 Jul;15(7):899-915

129. Filonenko EV, Sokolov VV, Chissov VI, Lukyanets EA, Vorozhtsov GN. Photodynamic therapy of early esophageal cancer. Photodiagnosis Photodyn Ther. 2008 Sep;5(3):187-90

130. Wolfsen HC, Hemminger LL, Wallace MB, Devault KR. Clinical experience of patients undergoing photodynamic therapy for Barrett's dysplasia or cancer. Aliment Pharmacol Ther. 2004; 20: 1125-1131

131. Corti L, Skarlatos J, Boso C, et al. Outcome of patients receiving photodynamic therapy for early esophageal cancer. Int J Radiat Oncol Biol Phys. 2000; 47: 419-424

132. Overholt BF, Wang KK, Burdick JS, et al. Five-year efficacy and safety of photodynamic therapy with Photofrin in Barrett's high-grade dysplasia. Gastrointest Endosc. 2007; 66: 460-468

133. Wang KK, Lutzke L, Borkenhagen L, Westra W, Song MW, Prasad G, Buttar NS. Photodynamic therapy for Barrett's esophagus: does light still have a role? Endoscopy. 2008 Dec;40(12):1021-5.

134. Maier A, Tomaselli F, Anegg U, Rehak P, Fell B, Luznik S, Pinter H, Smolle-Jüttner FM. Combined photodynamic therapy and hyperbaric oxygenation in carcinoma of the esophagus and the esophago-gastric junction. Eur J Cardiothorac Surg. 2000 Dec;18(6):649-54

135. Sánchez A, Reza M, Blasco JA, Callejo D. Effectiveness, safety, and cost-effectiveness of photodynamic therapy in Barrett's esophagus: a systematic review. Dis Esophagus. 2010 Nov;23(8):633-40

136. Lipson RL, Blades EJ, Gray MJ. Hematopophyrin derivative for the detection and management of cancer. Cancer 1967; 20: 2255–7

137. Gregorie HB Jr, Horger EO, Ward JL, et al. Hematoporphyrin-derivative fluorescence in malignant neoplasms. Ann Surg 1968; 167: 820–8

138. Von Holstein CS, Nilsson AM, Andersson-Engels S, et al. Detection of adenocarcinoma in Barrett's oesophagus by means of laser induced fluorescence. Gut 1996; 39: 711–6.

139. V.V.Sokolov, E.V.Filonenko, L.V.Telegina, D.G.Sukhin, A.B.Grishajeva, R.V.Ylianov, V.V.Chissov, N.N.Bulgakova. Local Fluorescence Spectroscopy for Cancer Detection: 15 Years Clinical Experience. The 11th IPA World Congress. Shanghai, China. Book of abstracts. 2007:74. See also: Kochneva EV, Filonenko EV, Vakulovskaya EG, Scherbakova EG, Seliverstov OV, Markichev NA, Reshetnickov AV. Photosensitizer Radachlorin®: Skin cancer PDT phase II clinical trials, Photodiagnosis and Photodynamic Therapy 2010; 7(4): 258-267. OP CIT. See also: V.I.Chissov, V.V.Sokolov, E.V.Filonenko, R.I.Yakubovskaya, E.A.Lukyanets, S.G.Kuzmin, G.N.Vorozhtsov, E.G.Vakulovskaya, S.S.Kharnas. Fluorescence Diagnosis (FD) and Photody-

namic Therapy (PDT) of Malignant Tumors: 15-Years' Clinical Experience in Moscow. The 11th IPA World Congress. Shanghai, China. Book of abstracts. 2007:154. See also: E.V.Filonenko. Ph.D. Thesis (Medicine – Oncology). Moscow, Russia 14.00.14, 2006, 195 p, See also: R.N.Krupnov. Ph.D. Thesis (Medicine – Oncology). Moscow, Russia 14.00.14, 2006.

140. Messmann H, Knuchel R, Baumler W, et al. Endoscopic fluorescence detection of dysplasia in patients with Barrett's esophagus, ulcerative colitis, or adenomatous polyps after 5-aminolevulinic acid-induced protoporphyrin IX sensitization. Gastrointest Endosc 1999; 49: 97–101

141. McCaughan Jr JS, Mertens BF, Cho C, et al. Photodynamic therapy to treat tumors of the extrahepatic biliary ducts. A case report. Arch Surg 1991;126(1):111—3.

142. Lau SH, Lau WY. Current therapy of hilar cholangiocarcinoma. Hepatobiliary Pancreat Dis Int. 2012;11(1):12-7

143. Burke EC, Jarnagin WR, Hochwald SN, Pisters PW, Fong Y, Blumgart LH. Hilar Cholangiocarcinoma: patterns of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system. Ann Surg. 1998;228:385–394

144. Ortner ME, Caca K, Berr F, et al. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. Gastroenterology. 2003;125:1355–1363

145. Zoepf T, Jakobs R, Arnold JC, Apel D, Riemann JF. Palliation of nonresectable bile duct cancer: improved survival after photodynamic therapy. Am J Gastroenterol. 2005;100:2426–2430

146. Witzigmann H, Berr F, Ringel U, et al. Surgical and palliative management and outcome in 184 patients with hilar cholangiocarcinoma: palliative photodynamic therapy plus stenting is comparable to r1/r2 resection. Ann Surg. 2006; 244: 230-239; Pereira SP, Ayaru L, Rogowska A, Mosse A, Hatfield AR, Bown SG. Photodynamic therapy of malignant biliary strictures using meso-tetrahydroxyphenylchlorin. Eur J Gastroenterol Hepatol. 2007; 19: 479-485

147. Cheon YK, Lee TY, Lee SM, Yoon JY, Shim CS. Long-term outcome of photodynamic therapy compared with biliary stenting alone in patients with advanced hilar cholangiocarcinoma. HPB (Oxford). 2012 Mar;14(3):185-93

148. Prasad GA, Wang KK, Baron TH, et al. Factors associated with increased survival after photodynamic therapy for cholangio- carcinoma. Clin Gastroenterol Hepatol 2007;5(6):743-8.

149. Sergeeva ON, Dolgushin BI, Panov VO, Kukushkin AV, Reshetnickov AV. Photodynamic action combined with pro-Immune therapeutics in hilar cholangiocarcinoma patients. The 13th IPA World Congress. May 10-14. Innsbruck, Austria. Book of abstracts. 2011:67. See also: Sergeeva ON, Dolgushin BI, Panov VO, Kukushkin AV, Reshetnickov AV. Immuno-PDT in hilar cholangiocarcinoma patients. The 14th IPA World Congress. May 28-31. Seoul, South Korea. Book of abstracts. 2013:119.

150. Yow CM, Wong CK, Huang Z, Ho RJ. Study of the efficacy and mechanism of ALA-mediated photodynamic therapy on human hepatocellular carcinoma cell. Liver Int. 2007;27(2):201-8; see also: Seitz G, Krause R, Fuchs J, Heitmann H, Armeanu S, Ruck P, Warmann. In vitro photodynamic therapy in pediatric epithelial liver tumors promoted by hypericin. Oncol Rep. 2008 Nov;20(5):1277-82

151. Park KC, Kim SY, Kim DS. Experimental photodynamic therapy for liver cancer cell-implanted nude mice by an indole-3-acetic acid and intense pulsed light combination. Biol Pharm Bull. 2009;32(9):1609-13

152. Zhang H, Ma W, Li Y Generation of effective vaccines against liver cancer by using photodynamic therapy. Lasers Med Sci. 2009 Jul;24(4):549-52

153. Loh CS, Bliss P, Bown SG, Krasner N. Photodynamic therapy for villous adenomas of the colon and rectum. Endoscopy. 1994; 26: 243-246; See also: Nakamura T, Fukui H, Ishii Y, Ejiri K, Ejiri M. Photodynamic therapy with polypectomy for rectal cancer. Gastrointest Endosc. 2003; 57: 266-269; See also: Spinelli P, Mancini A, Dal Fante M. Endoscopic treatment of gastrointestinal tumors: indications and results of laser photocoagulation and photodynamic therapy. Semin Surg Oncol. 1995; 11: 307-318; See also: Abulafi AM, Dejode M, Allardice JT, Ansell J, Rogers J, Williams NS. Adjuvant intraoperative photodynamic therapy in experimental colorectal cancer. Br J Surg. 1995; 82: 178-181

154. Stukavec J, Duchac V, Horak L, Pouckova P. Photodynamic Therapy of a Human Colorectal Carcinoma Cell Line. Photomed Laser Surg. 2008 Aug 8; Jalili A, Makowski M, Switaj T, Nowis D, Wilczynski GM, Wilczek E, Chorazy-Massalska M, Radzikowska A, Maslinski W, Biały L, Sienko J, Sieron A, Adamek M, Basak G, Mróz P, Krasnodebski IW, Jakóbisiak M, Gołab J. Effective photoimmunotherapy of murine colon carcinoma induced by the combination of photodynamic therapy and dendritic cells. Clin Cancer Res. 2004 Jul 1;10(13):4498-508

155. Del Governatore M, Hamblin MR, Shea CR, Rizvi I, Molpus KG, Tanabe KK, Hasan T Experimental photoimmunotherapy of hepatic metastases of colorectal cancer with a 17.1A chlorin(e6) immunoconjugate. Cancer Res. 2000 Aug 1;60(15):4200-5

156. Dohmoto M, Hunerbein M, Schlag PM. Palliative endoscopic therapy of rectal carcinoma. Eur J Cancer 1996; 32A: 25–9

157. Barr H, Krasner N, Boulos PB, et al. Photodynamic therapy for colorectal cancer: a quantitative pilot study. Br J Surg 1990; 77: 93–6

158. McCaughan JS. Photodynamic therapy. A review. Drugs Aging 1999; 15: 49–68

159. Mlkvy P, Messmann H, Debinski H, et al.Photodynamic therapy for polyps in familial adenomatous polyposis—a pilot study. Eur J Cancer 1995; 31A: 1160–5

160. Herrera-Ornelas L, Petrelli NJ, Mittelman A, et al. Photodynamic therapy in patients with colorectal cancer. Cancer 1986; 57: 677–84

161. McCaughan JS. Photodynamic therapy. A review. Drugs Aging 1999; 15: 49–68

162. Allison RR. Sheng C, et al. Photodynamic therapy for anal cancer. Photodiagnosis and Photodynamic Therapy (2010) 7, 115-119

163. Wust P, Hildebrandt B, Sreenivasa G, Rau B, Gellermann J, Riess H, Felix R, Schlag PM. Hyperthermia in combined treatment of cancer. Lancet Oncol. 2002;3(8):487-97; Falk MH, Issels RD. Hyperthermia in oncology. Int J Hyperthermia. 2001 Jan-Feb;17(1):1-18

164. Dieing A, Ahlers O, Hildebrandt B, Kerner T, Tamm I, Possinger K, Wust P. The effect of induced hyperthermia on the immune system. Prog Brain Res. 2007;162:137-52; Baronzio G, Gramaglia A, Fiorentini G.Hyperthermia and immunity. A brief overview. In Vivo. 2006;20(6A):689-95; Skitzki JJ, Chen Q, Wang WC, Evans SS.Primary immune surveillance: some like it hot. J Mol Med. 2007 Dec;85(12):1361-7.

165. Zhang HG, Mehta K, Cohen P, Guha C. Hyperthermia on immune regulation: A temperature's story. Cancer Lett. 2008 Jun 30

166. Sun G, Anderson MA, Gorospe EC, Leggett CL, Lutzke LS, Wong Kee Song LM, Levy M, Wang KK. Synergistic effects of photodynamic therapy with hpph and gemcitabine in pancreatic cancer cell lines. Lasers Surg Med. 2012 Sep 27

167. Xie Q, Jia L, Liu YH, Wei CG. Synergetic anticancer effect of combined gemcitabine and photodynamic therapy on pancreatic cancer in vivo. World J Gastroenterol. 2009;15(6):737-41

168. Celli JP, Solban N, Liang A, Pereira SP, Hasan T. Verteporfin-based photodynamic therapy overcomes gemcitabine insensitivity in a panel of pancreatic cancer cell lines. Lasers Surg Med. 2011;43(7):565-74.

169. Samkoe KS, Chen A, Rizvi I, O'Hara JA, Hoopes PJ, Pereira SP, Hasan T, Pogue BW. Imaging tumor variation in response to photodynamic therapy in pancreatic cancer xenograft models. Int J Radiat Oncol Biol Phys. 2010;76(1):251-9

170. Fan BG, Andrén-Sandberg A. Photodynamic therapy for pancreatic cancer. Pancreas. 2007 May;34(4):385-9.

171. Bown SG, Rogowska AZ, Whitelaw DE, Lees WR, Lovat LB, Ripley P, Jones L, Wyld P, Gillams A, Hatfield AW. Photodynamic therapy for cancer of the pancreas. Gut. 2002;50(4):549-57

172. Ayaru L, Bown SG, Pereira SP. Photodynamic therapy for pancreatic and biliary tract carcinoma. Int J Gastrointest Cancer. 2005;35(1):1-13; Liu CD, Kwan D, Saxton RE, McFadden DW. Hypericin and photodynamic therapy decreases human pancreatic cancer in vitro and in vivo. J Surg Res. 2000;93(1):137-43; Hajri A, Coffy S, Vallat F, Evrard S, Marescaux J, Aprahamian M. Human pancreatic carcinoma cells are sensitive to photodynamic therapy in vitro and in vivo. Br J Surg. 1999;86(7):899-906

173. Ell C, Gossner L, May A, et al. Photodynamic ablation of early cancers of the stomach by means of mTHPC and laser irradiation: preliminary clinical experience. Gut. 1998;43:345–349

174. Kim JH, Park JJ. The Effects of Photodynamic Therapy in Upper-Gastrointestinal Malignant Diseases. Gut Liver. 2010; 4(Suppl. 1): S39–S43

175. Romanov VA, Reshetnickov AV. PDT of stomach cancer with photosensitizer Bremachlorin®: a pilot trial. The 14th IPA World Congress. May 28-31, 2013. Seoul, South Korea. Book of abstracts. 2013:53.

176. Park S, Hong SP, Oh TY, Bang S, Chung JB, Song SY. Paclitaxel augments cytotoxic effect of photodynamic therapy using verteporfin in gastric and bile duct cancer cells. Photochem Photobiol Sci. 2008 Jul;7(7):769-74.

177. Yanai H, Kuroiwa Y, Shimizu N, Matsubara Y, Okamoto T, Hirano A, Nakamura Y, Okita K, Sekine T. The pilot experience of immunotherapy-combined photodynamic therapy for advanced gastric cancer in elderly patients. Int J Gastrointest Cancer. 2002;32(2-3):139-42.

178. Etzioni R, Penson DF, Legler JM, et al. Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer incidence trends. J Natl Cancer Inst. 2002;94:981–990

179. Sultan SM, El-Doray AA, Hofstetter A, Abdel-Gawad O, El-Mahdy Ael-D, Khoder W. Photodynamic selectivity of 5-aminolevulinic acid to prostate cancer cells. J Egypt Natl Canc Inst. 2006;18(4):382-6

180. Lecornet E, Ahmed HU, Moore C, Emberton M. Focal therapy for prostate cancer: a potential strategy to address the problem of overtreatment. Arch Esp Urol. 2010;63(10):845-52

181. Eggener SE, Coleman JA. Focal treatment of prostate cancer with vascular-targeted photodynamic therapy. ScientificWorldJournal. 2008;8:963-73.

182. Donaldson MS. Nutrition and cancer: a review of the evidence for an anti-cancer diet. Nutr J. 2004;3:19

183. Cohen JH, Kristal AR, Stanford JL. Fruit and vegetable intakes and prostate cancer risk. J Natl Cancer Inst. 2000;92:61–68

184. Moore CM, Emberton M, Bown SG. Photodynamic therapy for prostate cancer--an emerging approach for organ-confined disease. Lasers Surg Med. 2011;43(7):768-75

185. Trachtenberg J, Bogaards A, Weersink RA, et al. Vascular targeted photodynamic therapy with palladium-bacteriopheophorbide photosensitizer for recurrent prostate cancer following definitive radiation therapy: assessment of safety and treatment response. Journal of Urology. 2007;178(5):1974–1979

186. Patel H, Mick R, Finlay J, Zhu TC, Rickter E, Cengel KA, Malkowicz SB, Hahn SM, Busch TM. Motexafin lutetium-photodynamic therapy of prostate cancer: short- and long-term effects on prostate-specific antigen. Clin Cancer Res. 2008;14(15):4869-76.

187. Dhom G. Epidemiologic aspects of latent and clinically manifest carcinoma of the prostate. J Cancer Res. Clin Oncol 1983; 106: 210-218; See also: Breslow N. Chan CW. Dhom G et al. Latent carcinoma of the prostate at autopsy in seven areas. Int J Cancer 1977; 20: 680-688

188. Yip I. Aronson W. Heber D. Nutritional approaches to the prevention of prostate cancer progression. Advances in Experimental Medicine & Biology. 1996; 399:173-81

189. Fair WR. Fleshner NE. Heston W. Cancer of the prostate: a nutritional disease? Urology 1997; 50(6): 840-8; See also: Wynder EL. Fair WR. Editorial: prostate cancer—nutrition adjunct therapy. J Urol 1996; 156: 1364-5

190. Mori M, Masumori N, Fukuta F, Nagata Y, Sonoda T, Sakauchi F, Ohnishi H, Nojima M, Tsukamoto T. Traditional Japanese diet and prostate cancer. Mol Nutr Food Res. 2009;53(2):191-200

191. Marugame T, Mizuno S. Comparison of prostate cancer mortality in five countries: France, Italy, Japan, UK and USA from the WHO mortality database (1960–2000) Jpn J Clin Oncol. 2005;35:690–691

192. Chan JM, Gann PH, Giovannucci EL. Role of diet in prostate cancer development and progression. J Clin Oncol. 2005 Nov 10;23(32):8152-60

193. Ploeg M, Aben KK, Kiemeney LA. The present and future burden of urinary bladder cancer in the world. World J Urol. 2009;27(3):289-93; See also:: IARC. GLOBOCAN 2002. Cancer Incidence, Mortality and Prevalence Worldwide (2002 estimates) http://globocan.iarc.fr/

194. Sylvester RJ, van der Meijden APM, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. European Urology. 2006;49(3):466–475

195. Dindyal S, Nitkunan T, Bunce CJ. The economic benefit of photodynamic diagnosis in non-muscle invasive bladder cancer. Photodiagnosis Photodyn Ther. 2008;5(2):153-8

196. Ahmad S, Aboumarzouk O, Somani B, Nabi G, Kata SG. Oral 5-aminolevulinic acid in simultaneous photodynamic diagnosis of upper and lower urinary tract transitional cell carcinoma - a prospective audit. BJU Int. 2012 Jul 3.

197. Yavari N, Andersson-Engels S, Segersten U, Malmstrom PU. An overview on preclinical and clinical experiences with photodynamic therapy for bladder cancer. Can J Urol. 2011;18(4):5778-86.

198. Agostinis P, Berg K, Cengel KA, Foster TH, et al. Photodynamic therapy of cancer: an update. CA Cancer J Clin. 2011;61(4):250-81.

199. Burger M, Grossman HB, Droller M, Schmidbauer J, Hermann G, Drăgoescu O, Ray E, Fradet Y, Karl A, Burgués JP, Witjes JA, Stenzl A, Jichlinski P, Jocham D. Photodynamic Diagnosis of Non-muscle-invasive Bladder Cancer with Hexaminolevulinate Cystoscopy: A Meta-analysis of Detection and Recurrence Based on Raw Data. Eur Urol. 2013 Apr 8. [Epub ahead of print]

200. Jocham D, von Wietersheim J, Pfluger H, et al. BCG versus photodynamic therapy (PDT) for nonmuscle invasive bladder cancer-a multicentre clinical phase III study [in German]. Aktuelle Urol. 2009; 40: 91-99

201. Pinthus JH, Bogaards A, Weersink R, Wilson BC, Trachtenberg J. Photodynamic therapy for urological malignancies: past to current approaches. J Urol. 2006; 175: 1201-1207; See also: Skyrme RJ, French AJ, Datta SN, Allman R, Mason MD, Matthews PN. A phase-1 study of sequential mitomycin C and 5-aminolaevulinic acid-mediated photodynamic therapy in recurrent superficial bladder carcinoma. BJU Int. 2005; 95: 1206-1210

202. Prout GR Jr, Lin CW, Benson R Jr, et al. Photodynamic therapy with hematoporphyrin derivative in the treatment of superficial transitional-cell carcinoma of the bladder. N Engl J Med. 1987; 317: 1251-1255; See also: Uchibayashi T, Koshida K, Kunimi K, Hisazumi H. Whole bladder wall photodynamic therapy for refractory carcinoma in situ of the bladder. Br J Cancer. 1995; 71: 625-628

203. Lamm DL, Riggs DR, Shriver JS, vanGilder PF, Rach JF, DeHaven JI. Megadose vitamins in bladder cancer: a double-blind clinical trial. J Urol. 1994 Jan;151(1):21-6

204. Berger AP, Steiner H, Stenzl A, Akkad T, Bartsch G, Holtl L. Photodynamic therapy with intravesical instillation of 5-aminolevulinic acid for patients with recurrent superficial bladder cancer: a single-center study. Urology. 2003; 61: 338-341; See also: Waidelich R, Beyer W, Knuchel R, et al. Whole bladder photodynamic therapy with 5-aminolevulinic acid using a white light source. Urology. 2003; 61: 332-337.

205. Szliszka E, Czuba ZP, Kawczyk-Krupka A, Sieron-Stoltny K, Sieron A, Krol W. Chlorin-based photodynamic therapy enhances the effect of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in bladder cancer cells. Med Sci Monit. 2012;18(1):BR47-53

206. IARC. World Cancer Report. International Agency for Research on Cancer, World Health Organization; 150, cours Albert-Thomas 69372 Lyon Cedex 08, France. 2008

207. Ladner DP, Steiner RA, Allemann J, Haller U, Walt H. Photodynamic diagnosis of breast tumours after oral application of aminolevulinic acid. Br J Cancer. 2001; 84(1):33-7

208. Lapes M, Petera J, Jirsa M. Photodynamic therapy of cutaneous metastases of breast cancer after local application of meso-tetra-(para-sulphophenyl)-porphin (TPphotosensitizer4). J Photochem Photobiol B. 1996;36(2):205-7

209. Ahn TG, Lee BR, Choi EY, Kim DW, Han SJ. Photodynamic therapy for breast cancer in a BALB/c mouse model. J Gynecol Oncol. 2012;23(2):115-9; See also: Hoi SW, Wong HM, Chan JY, Yue GG, Tse GM, Law BK, Fong WP, Fung KP. Photodynamic therapy of Pheophorbide a inhibits the proliferation of human breast tumour via both caspase-dependent and -independent apoptotic pathways in in vitro and in vivo models. Phytother Res. 2012;26(5):734-42

210. Tong ZS, Miao PT, Liu TT, Jia YS, Liu XD. Enhanced antitumor effects of BPD-MA-mediated photodynamic therapy combined with adriamycin on breast cancer in mice. Acta Pharmacol Sin. 2012 Jul 30; See also: Yoon JH, Yoon HE, Kim O, Kim SK, Ahn SG, Kang KW. The enhanced anti-cancer effect of hexenyl ester of 5-aminolaevulinic acid photodynamic therapy in adriamycin-resistant compared to non-resistant breast cancer cells. Lasers Surg Med. 2012;44(1):76-86; See also: Duanmu J, Cheng J, Xu J, Booth CJ, Hu Z. Effective treatment of chemoresistant breast cancer in vitro and in vivo by a factor VII-targeted photodynamic therapy. Br J Cancer. 2011;104(9):1401-9; See also: Crescenzi E, Varriale L, Iovino M, Chiaviello A, Veneziani BM, Palumbo G. Photodynamic therapy with indocyanine green complements and enhances low-dose cisplatin cytotoxicity in MCF-7 breast cancer cells. Mol Cancer Ther. 2004 May;3(5):537-44

211. Hu Z, Rao B, Chen S, Duanmu J. Selective and effective killing of angiogenic vascular endothelial cells and cancer cells by targeting tissue factor using a factor VII-targeted photodynamic therapy for breast cancer. Breast Cancer Res Treat. 2011;126(3):589-600; Hu Z, Rao B, Chen S, Duanmu J. Targeting tissue factor on tumour cells and angiogenic vascular endothelial cells by factor VII-targeted verteporfin photodynamic therapy for breast cancer in vitro and in vivo in mice. BMC Cancer. 2010;10:235

212. Wise-Milestone L, Akens MK, Lo VC, Yee AJ, Wilson BC, Whyne CM. Local treatment of mixed osteolytic/osteoblastic spinal metastases: is photodynamic therapy effective? Breast Cancer Res Treat. 2012;133(3):899-908; Won E, Wise-Milestone L, Akens MK, Burch S, Yee AJ, Wilson BC, Whyne CM. Beyond bisphosphonates: photodynamic therapy structurally augments metastatically involved vertebrae and destroys tumor tissue. Breast Cancer Res Treat. 2010;124(1):111-9; Won E, Akens MK, Hardisty MR, Burch S, Bisland SK, Yee AJ, Wilson BC, Whyne CM. Effects of photodynamic therapy on the structural integrity of vertebral bone. Spine (Phila Pa 1976). 2010;35(3):272-7.

213. Cuenca RE, Allison RR, Sibata C, Downie GH. Breast cancer with chest wall progression: treatment with photodynamic therapy. Ann Surg Oncol. 2004;11(3):322-7

214. Allison R, Mang T, Hewson G, Snider W, Dougherty D. Photodynamic therapy for chest wall progression from breast carcinoma is an underutilized treatment modality. Cancer. 2001;91(1):1-8

215. Taber SW, Fingar VH, Wieman TJ. Photodynamic therapy for palliation of chest wall recurrence in patients with breast cancer. J Surg Oncol. 1998;68(4):209-14

216. Mang TS, Allison R, Hewson G, Snider W, Moskowitz R. A phase II/III clinical study of tin ethyl etiopurpurin (Purlytin)-induced photodynamic therapy for the treatment of recurrent cutaneous metastatic breast cancer. Cancer J Sci Am. 1998;4(6):378-84

217. Wyss P, Schwarz V, Dobler-Girdziunaite D, Hornung R, Walt H, Degen A, Fehr M. Photodynamic therapy of locoregional breast cancer recurrences using a chlorin-type photosensitizer. Int J Cancer. 2001;93(5):720-4.

218. Ford ES, Capewell S. Coronary heart disease mortality among young adults in the US from 1980 through 2002: concealed leveling of mortality rates. J Am Coll Cardiol. 2007;50(22):2128–2132. See also: O'Flaherty M, Ford E, Allender S, Scarborough P, Capewell S. Coronary heart disease trends in England and Wales from 1984 to 2004: concealed levelling of mortality rates among young adults. Heart. 2008;94(2):178–181. doi: 10.1136/hrt.2007.118323.

219. Weber C, Noels H. Atherosclerosis: current pathogenesis and therapeutic options. Nat Med. 2011;17(11):1410-22.

220. Kossodo S, LaMuraglia GM. Clinical potential of photodynamic therapy in cardiovascular disorders. Am J Cardiovasc Drugs. 2001;1(1):15-21

221. Mansfield R, Bown S, McEwan J. Photodynamic therapy: shedding light on restenosis. Heart. 2001;86(6):612-8.

222. Usui M, Miyagi M, Fukasawa S, Hara T, Ueyama N, Nakajima H, Takata R, Sasame A, Tamura K, Naitou Y, Yamashina A. A first trial in the clinical application of photodynamic therapy for the prevention of restenosis after coronary-stent placement. Lasers Surg Med. 2004;34(3):235-41; see also: Jenkins MP, Buonaccorsi GA, Raphael M, et al. Clinical study of adjuvant photodynamic therapy to reduce restenosis following femoral angioplasty. Br J Surg 1999;86:1258–63

223. Waksman R, McEwan PE, Moore TI, Pakala R, Kolodgie FD, Hellinga DG, Seabron RC, Rychnovsky SJ, Vasek J, Scott RW, Virmani R. PhotoPoint photodynamic therapy promotes stabilization of atherosclerotic plaques and inhibits plaque progression. J Am Coll Cardiol. 2008;52(12):1024-32.

224. Peng C, Li Y, Liang H, Cheng J, Li Q, Sun X, Li Z, Wang F, Guo Y, Tian Z, Yang L, Tian Y, Zhang Z, Cao W. Detection and photodynamic therapy of inflamed atherosclerotic plaques in the carotid artery of rabbits. J Photochem Photobiol B. 2011;102(1):26-31

225. Drakopoulou M, Toutouzas K, Michelongona A, Tousoulis D, Stefanadis C. Vulnerable plaque and inflammation: potential clinical strategies. Curr Pharm Des. 2011 Dec;17(37):4190-209. See also: Muller JE. New light on an old problem photodynamic therapy for atherosclerosis. J Am Coll Cardiol. 2008 Sep 16;52(12):1033-4

226. Rockson SG, Kramer P, Razavi M, Szuba A, Filardo S, Fitzgerald P, Cooke JP, Yousuf S, DeVault AR, Renschler MF, Adelman DC. Photoangioplasty for human peripheral atherosclerosis: results of a phase I trial of photodynamic therapy with motexafin lutetium (Antrin). Circulation. 2000;102(19):2322-4

227. Seaman DR. The diet-induced proinflammatory state: a cause of chronic pain and other degenerative diseases? J Manipulative Physiol Ther. 2002 Mar-Apr;25(3):168-79; Watzl B. Anti-inflammatory effects of plant-based foods and of their constituents. Int J Vitam Nutr Res. 2008 Dec;78(6):293-8

228. Ozdemir H, Karacorlu SA, Karacorlu M. Early optical coherence tomography changes after photodynamic therapy in patients with age-related macular degeneration. Am J Ophthalmol. 2006;141(3):574-6.

229. Verteporfin In Photodynamic Therapy Study Group.Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization--verteporfin in photodynamic therapy report. Am J Ophthalmol. 2001;131(5):541-60.

230. Couch SM, Bakri SJ. Review of combination therapies for neovascular age-related macular degeneration. Semin Ophthalmol. 2011; 26(3):114-20; see also: Kaiser PK, Boyer DS, Cruess AF, Slakter JS, Pilz S, Weisberger A; DENALI Study Group. Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month results of the DENALI study. Ophthalmology. 2012 May;119(5):1001-10.

231. Sadda SR, Stoller G, Boyer DS, Blodi BA, Shapiro H, Ianchulev T. Anatomical benefit from ranibizumab treatment of predominantly classic neovascular age-related macular degeneration in the 2- year anchor study. Retina. 2010;30(9):1390-9; see also: Parodi MB, Iacono P, Kontadakis DS, Zucchiatti I, Cascavilla ML, Bandello F. Bevacizumab vs photodynamic therapy for choroidal neovascularization in multifocal choroiditis. Arch Ophthalmol. 2010;128(9):1100-3

232. Mennel S, Barbazetto I, Meyer CH, Peter S, Stur M. Ocular photodynamic therapy--standard applications and new indications (part 1). Review of the literature and personal experience. Ophthalmologica. 2007;221(4):216-26

233. RU 2233146 (OOO RADA-FARMA) Priority of 2002-21-10. Egorov EA, Prokof'eva MI, Novoderyozhkin VV, Reshetnickov AV. Cystic filtering bleb treatment.

234. Prasad photosensitizer, Schwartz SD, Hubschman JP. Age-related macular degeneration: current and novel therapies. Maturitas. 2010;66(1):46-50

235. Chakravarthy U, Soubrane G, Bandello F, Chong V, Creuzot-Garcher C, Dimitrakos SA 2nd, Korobelnik JF, Larsen M, Monés J, Pauleikhoff D, Pournaras CJ, Staurenghi G, Virgili G, Wolf S. Evolving European guidance on the medical management of neovascular age related macular degeneration. Br J Ophthalmol. 2006 Sep;90(9):1188-96.

236. Spencer EH, Ferdowsian HR, Barnard ND. Diet and acne: a review of the evidence. Int J. Dermatol 2009; 48(4):339-347

237. Kim RH, Armstrong AW. Current state of acne treatment: highlighting lasers, photodynamic therapy, and chemical peels. Dermatol Online J. 2011;17(3):2.

238. Dai T, Huang YY, Hamblin MR. Photodynamic therapy for localized infections--state of the art. Photodiagnosis Photodyn Ther. 2009;6(3-4):170-88

239. Sakamoto FH, Torezan L, Anderson RR. Photodynamic therapy for acne vulgaris: a critical review from basics to clinical practice: part II. Understanding parameters for acne treatment with photodynamic therapy. J Am Acad Dermatol. 2010;63(2):195-211

240. Sakamoto FH, Lopes JD, Anderson RR. Photodynamic therapy for acne vulgaris: a critical review from basics to clinical practice: part I. Acne vulgaris: when and why consider photodynamic therapy? J Am Acad Dermatol. 2010;63(2):183-93

241. Bissonnette R. Treatment of acne with photodynamic therapy. G Ital Dermatol Venereol. 2011;146(6):445-56. See also: Piérard-Franchimont C, Paquet P, Piérard GE. New approaches in light/laser therapies and photodynamic treatment of acne. Expert Opin Pharmacother. 2011;12(4):493-501; Elsaie ML, Choudhary S. Photodynamic therapy in the management of acne: an update. J Cosmet Dermatol. 2010;9(3):211-7

242. RU 2379073 (OOO RADA-FARMA) Priority of 2007-11-09. Pykhteeva EN, Reshetnickov AV, et.al. Chronic tonsillitis laser treatment using a photosensitizer.

243. Biel MA, Sievert C, Usacheva M, Teichert M, Balcom J. Antimicrobial photodynamic therapy treatment of chronic recurrent sinusitis biofilms. Int Forum Allergy Rhinol. 2011 Sep-Oct;1(5):329-34

244. RU 2228775 (OOO RADA-FARMA) Priority of 2002-01-10. Nasedkin AN, Reshetnickov AV, et.al. Purulent acute and chronic sinusitis photodynamic treatment.

245. Johnson-Huang LM, Lowes MA, Krueger JG. Putting together the psoriasis puzzle: an update on developing targeted therapies. Dis Model Mech. 2012; 5(4):423-33

246. Kostović K, Pasić A. Phototherapy of psoriasis: review and update. Acta Dermatovenerol Croat. 2004;12(1):42-50

247. Issa MC, Manela-Azulay M. Photodynamic therapy: a review of the literature and image documentation. An Bras Dermatol. 2010;85(4):501-11; Gupta AK, Ryder JE. Photodynamic therapy and topical aminolevulinic acid: an overview. Am J Clin Dermatol. 2003;4(10):699-708

248. Rama Sastry CV, Kar PK. A study of psoralen photochemotherapy with topical tar in the management of psoriasis vulgaris. Indian J Dermatol Venereol Leprol. 2001;67(6):305-8

249. Tandon YK, Yang MF, Baron ED. Role of photodynamic therapy in psoriasis: a brief review. Photodermatol Photoimmunol Photomed. 2008;24(5):222-30

250. Dayal S; Mayanka, Jain VK. Comparative evaluation of NBUVB phototherapy and PUVA photochemotherapy in chronic plaque psoriasis. Indian J Dermatol Venereol Leprol. 2010 Sep-Oct;76(5):533-7; see also: Dayal S; Mayanka, Jain VK. Comparative evaluation of NBUVB phototherapy and PUVA photochemotherapy in chronic plaque psoriasis. Indian J Dermatol Venereol Leprol. 2010 Sep-Oct;76(5):533-7.

251. Wolters M. Diet and psoriasis: experimental data and clinical evidence. Br J Dermatol. 2005 Oct;153(4):706-14. See also: Wolters M. The significance of diet and associated factors in psoriasis. Hautarzt. 2006 Nov;57(11):999-1004. [Article in German]

252. Ricketts JR, Rothe MJ, Grant-Kels JM. Nutrition and psoriasis. Clin Dermatol. 2010 Nov-Dec;28(6):615-26

253. Seaman DR. The diet-induced proinflammatory state: a cause of chronic pain and other degenerative diseases? J Manipulative Physiol Ther. 2002; 25(3):168-79. See also: Watzl B. Anti-inflammatory effects of plant-based foods and of their constituents. Int J Vitam Nutr Res. 2008 Dec;78(6):293-8. See also: Pan MH, Lai CS, Ho CT. Anti-inflammatory activity of natural dietary flavonoids. Food Funct. 2010 Oct;1(1):15-31.

254. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol. 2010 Jan;6(1):149-63.

255. Aggarwal BB, Gehlot P. Inflammation and cancer: how friendly is the relationship for cancer patients? Curr Opin Pharmacol. 2009 Aug;9(4):351-69. See also: McMillan DC. An inflammation-based prognostic score and its role in the nutrition-based management of patients with cancer. Proc Nutr Soc. 2008 Aug;67(3):257-62.

256. Aggarwal BB. Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals. Annu Rev Nutr. 2010 Aug 21;30:173-99.

257. Lindeberg S. Paleolithic diets as a model for prevention and treatment of Western disease. Am J Hum Biol. 2012 Mar-Apr;24(2):110-5

258. O'Keefe JH Jr, Cordain L. Cardiovascular disease resulting from a diet and lifestyle at odds with our Paleolithic genome: how to become a 21st-century hunter-gatherer. Mayo Clin Proc. 2004 Jan;79(1):101-8

259. Kello M, Mikes J, Jendzelovský R, Koval J, Fedorocko P. PUFAs enhance oxidative stress and apoptosis in tumour cells exposed to hypericin-mediated PDT. Photochem Photobiol Sci. 2010 Sep 24;9(9):1244-51. OP CIT.

260. Wendel M, Heller AR. Anticancer actions of omega-3 fatty acids--current state and future perspectives. Anticancer Agents Med Chem. 2009 May;9(4):457-70

261. Shirakami Y, Shimizu M, Moriwaki H. Cancer chemoprevention with green tea catechins: from bench to bed. Curr Drug Targets. 2012 Dec;13(14):1842-57; also see: Yang CS, Wang H, Li GX, Yang Z, Guan F, Jin H. Cancer prevention by tea: Evidence from laboratory studies. Pharmacol Res. 2011 Aug;64(2):113-22.

262. Ogunleye AA, Xue F, Michels KB. Green tea consumption and breast cancer risk or recurrence: a meta-analysis. Breast Cancer Res Treat. 2010;119(2):477-84

263. Suganuma M, Saha A, Fujiki H. New cancer treatment strategy using combination of green tea catechins and anticancer drugs. Cancer Sci. 2011 Feb;102(2):317-23.

264. Arab L. Epidemiologic evidence on coffee and cancer. Nutr Cancer. 2010;62(3):271-83. See also: Jiang W, Wu Y, Jiang X. Coffee and caffeine intake and breast cancer risk: An updated dose-response meta-analysis of 37 published studies. Gynecol Oncol. 2013 Mar 25. [Epub ahead of print]; See also: Discacciati A, Orsini N, Andersson SO, Andrén O, Johansson JE, Mantzoros CS, Wolk A. Coffee consumption and risk of localized, advanced and fatal prostate cancer: a population-based prospective study. Ann Oncol. 2013 Mar 18. [Epub ahead of print]

265. Goun EA, Petrichenko VM, Solodnikov SYu, Suhinina TV, Kline MA, Cunningham G, Nguyen C, Miles DH. Anticancer and Antithrombin activity of Russian Plants. Journal of Ethnopharmacology 2002, 81, 337-342.

266. Laviano A, Rianda S, Molfino A, Fanelli FR. Omega-3 fatty acids in cancer. Curr Opin Clin Nutr Metab Care. 2013 Jan 8. [Epub ahead of print]; also see: Calviello G, Serini S, Piccioni E, Pessina G. Antineoplastic effects of n-3 polyunsaturated fatty acids in combination with drugs and radiotherapy: preventive and therapeutic strategies. Nutr Cancer. 2009;61(3):287-301

267. Mandal CC, Ghosh-Choudhury T, Yoneda T, Choudhury GG, Ghosh-Choudhury N. Fish oil prevents breast cancer cell metastasis to bone. Biochem Biophys Res Commun. 2010 Nov 26;402(4):602-7; see also: Patterson RE, Flatt SW, Newman VA, Natarajan L, Rock CL, Thomson CA, Caan BJ, Parker BA, Pierce JP. Marine fatty acid intake is associated with breast cancer prognosis. J Nutr. 2011 Feb;141(2):201-6.

268. Serna-Marquez N, Villegas-Comonfort S, Galindo-Hernandez O, Navarro-Tito N, Millan A, Salazar EP. Role of LOXs and COX-2 on FAK activation and cell migration induced by linoleic acid in MDA-MB-231 breast cancer cells. Cell Oncol (Dordr). 2013 Feb;36(1):65-77.

269. Nishioka N, Matsuoka T, Yashiro M, Hirakawa K, Olden K, Roberts JD. Linoleic acid enhances angiogenesis through suppression of angiostatin induced by plasminogen activator inhibitor 1. Br J Cancer. 2011 Nov 22;105(11):1750-8.

270. Booyens J, van der Merwe CF, Katzeff IE. Chronic arachidonic acid eicosanoid imbalance: a common feature in coronary artery disease, hypercholesterolemia, cancer and other important diseases. Significance of desaturase enzyme inhibition and of the arachidonic acid desaturase-independent pathway. Med Hypotheses. 1985 Sep;18(1):53-60. See also: Patel MI, Kurek C, Dong Q. The arachidonic acid pathway and its role in prostate cancer development and progression. J Urol. 2008 May;179(5):1668-75.

271. Calder PC.The relationship between the fatty acid composition of immune cells and their function. Prostaglandins Leukot Essent Fatty Acids. 2008 Sep-Nov;79(3-5):101-8; see also: Cai J, Jiang WG, Mansel RE. Inhibition of angiogenic factor- and tumour-induced angiogenesis by gamma linolenic acid. Prostaglandins Leukot Essent Fatty Acids. 1999 Jan;60(1):21-9.

272. Sabaté J. The contribution of vegetarian diets to human health. Forum Nutr. 2003;56:218-20. See also: Ginter E. Vegetarian diets, chronic diseases and longevity. Bratisl Lek Listy. 2008;109(10):463-6.

273. Malter M, Schriever G, Eilber U. Natural killer cells, vitamins, and other blood components of vegetarian and omnivorous men. Nutr Cancer. 1989;12(3):271-8. See also: Hebert JR, Barone J, Reddy MM, Backlund JY. Natural killer cell activity in a longitudinal dietary fat intervention trial. Clin Immunol Immunopathol. 1990 Jan;54(1):103-16.

274. Timmons BW, Cieslak T. Human natural killer cell subsets and acute exercise: a brief review. Exerc Immunol Rev. 2008;14:8-23. See also: Na YM, Kim MY, Kim YK, Ha YR, Yoon DS. Exercise therapy effect on natural killer cell cytotoxic activity in stomach cancer patients after curative surgery. Arch Phys Med Rehabil. 2000 Jun;81(6):777-9.

275. Fang CY, Reibel DK, Longacre ML, Rosenzweig S, Campbell DE, Douglas SD. Enhanced psychosocial well-being following participation in a mindfulness-based stress reduction program is associated with increased natural killer cell activity. J Altern Complement Med. 2010 May;16(5):531-8.

276. Kris-Etherton PM, Taylor DS, Shaomei Y-P, Huth P, Moriarty K, Fishell V, Hargrove RL, Zhao G and Etherton TD. Polyunsaturated fatty acids in the food chain in the United States. Am J Clin Nutr. 2000; 71: 179-188.

277. Simopoulos AP. The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. Exp Biol Med (Maywood). 2008 Jun;233(6):674-88.

278. Gleissman H, Johnsen JI, Kogner P. Omega-3 fatty acids in cancer, the protectors of good and the killers of evil? Exp Cell Res. 2010 May 1;316(8):1365-73.

279. Rock CL. Diet and breast cancer: can dietary factors influence survival? J Mammary Gland Biol Neoplasia. 2003 Jan;8(1):119-32; Rock CL, Flatt SW, Natarajan L, Thomson CA, Bardwell WA, Newman VA, Hollenbach KA, Jones L, Caan BJ, Pierce JP. Plasma carotenoids and recurrence-free survival in women with a history of breast cancer. J Clin Oncol. 2005 Sep 20;23(27):6631-8

280. Xue F, Michels KB. Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. Am J Clin Nutr. 2007; 86(3):s823-35.

281. RU 2359711 (Brema Pharma B.V.) Priority of 2007-25-04. Armichev AV, Reshetnickov AV, et.al. Device to produce and photoactivate an aerosol.

282. Rama Sastry CV, Kar PK. A study of psoralen photochemotherapy with topical tar in the management of psoriasis vulgaris. Indian J Dermatol Venereol Leprol. 2001;67(6):305-8. OP CIT.

283. Adams, D.O. Molecular biology of macrophage activation: a pathway where by psychosocial factors can potentially affect health. Psychosomatic Medicine. 1994; 56: 316-327. See also: Adams DO and Hamilton TA. T he cell biology of macrophage activation. Annual Review of Immunology, 1984; 2: 283–318.

284. RU 2345803 (BREMA PHARMA B.V.) Priority of 2006-11-30. Published on 2009-02-10 in Bull.4/2009. Vasiliev NE, Reshetnickov AV et al. Photoimmunotherapy treatment in a man by a photosensitizer activated with electromagnetic energy outside the body. OP CIT.

285. Douillard S, Lhommeau I, Foursac A, Aillet L, Bigot E, Patrice T. Biophysical parameters influencing secondary oxidants activation in human serum exposed to singlet oxygen. J Photochem Photobiol B. 2011 Mar 2;102(3):22

GLOSSARY OF TERMS

Acne *n.* Localized skin inflammation resulting from overactivity of oil glands at the base of hair follicles; most common skin disorder worldwide.

Actinic *adj.* Produced or resulting from solar irradiation especially in the visible and ultraviolet parts of the spectrum.

Aminolevulinic acid *n.* A naturally occurring chemical that is converted to protoporphyrin IX in the body. Protoporphyrin IX is a photosensitizer or light-sensitive compound; also denoted as 5-aminolevulinic acid or 5-ALA.

Antibiotics *n.* A group of drugs used to treat bacterial infections; chemical substances produced by microorganisms that are harmful to other microorganisms.

Arthritis *n.* Inflammation of one or more joints, often resulting in stiffness, warmth, swelling, and redness around the joint areas; there are several primary types, including rheumatoid arthritis (a painful autoimmune condition affecting the joints), osteoarthritis (affecting the bones and joints), and psoriatic arthritis (affecting the skin and joints).

Autoimmune disorders *n.* Any of a large group of diseases characterized by abnormal functioning of the immune system that causes the system to produce antibodies against the body's own tissues.

Calcidiol *n.* This is a prehormone that is produced in the liver by hydroxylation of vitamin D3 (cholecalciferol) by the enzyme cholecalciferol 25-hydroxylase; it is also known as Calcifediol, 25-hydroxycholecalciferol, or 25-hydroxyvitamin D [abbreviated 25(OH)D], and widely regarded as a good serum indicator of past sunshine exposure.

Calcitriol *n.* This is the hormonally active form of vitamin D with three hydroxyl groups [abbreviated 1,25-(OH)2D3 or simply 1,25(OH)2D]. Also called 1,25-dihydroxycholecalciferol or 1,25-dihydroxyvitamin D3, this "secosteroid" hormone increases the level of calcium (Ca2+) in the blood by two methods: (1) increasing the uptake of calcium from the gut into the blood, and (2) at higher levels, increasing the release of calcium into the blood from bone.

Cancer *n.* A pathological condition characterized by malignant growth, namely by the proliferation of anaplastic (mutated) cells that tend to invade surrounding tissue and metastasize to new body sites. Over 200 different types of cancer have been identified.

Cardiovascular disease *n.* A disease of the heart or blood vessels.

Dendritic cells n. Antigen-presenting cells, which means immune cells that function to process antigens and present them on the surface to other cells of the immune system. Dendritic cells function as messengers between the innate and adaptive immunity, and they play a critical role in anti-tumor immunity.

Fluorescence imaging *n.* Describes the field of imaging technologies designed to visualize a pathological lesion by detection of substances that emit fluorescence (result in the emission of visible light); increasingly used in medical diagnosis of cancer and infectious diseases.

Free radical *n.* An atom or group of atoms that has at least one unpaired electron and is therefore in most cases highly unstable and reactive. In human or animal tissues, free radicals can damage cells and play a role in activation and suppression of cancer, cardiovascular disease, and age-related diseases.

Heat shock proteins *n.* A class of functionally related proteins involved in the folding and unfolding of other proteins, and also in modulation of the anti-cancer immune defenses. Their expression is increased when cells are exposed to elevated temperatures or other stress such as heat, surgery, or photosensitization of tissue.

Heliotherapy *n.* This is the classical term for light therapy or phototherapy and consists of exposure to daylight or sunlight; modern forms include exposure to specific wavelengths of light using lasers or special light sources.

Hematoporphyrin IX *n.* A porphyrin formed by the acid hydrolysis of hemoglobin; this was the first porphyrin isolated by treatment of blood with concentrated sulfuric acid. Hematoporphyrin has been used as an antidepressant and antipsychotic since the 1920s.

Hematoporphyrins *n.* Iron-free and hydrated derivatives of heme; some of these photosensitizing agents are used in the light-based treatment of cancers.

Heme *n.* Insoluble iron protoporphyrin IX constituent of hemoglobin, other respiratory pigments and of most animal organisms and cells.

Hemoglobin *n.* A red protein containing iron ions and protoporphyrin IX; found in red blood cells of vertebrates and plasma of annelids and mollusks.

Hyperthermia *n.* Use of heat for therapeutic purposes; can be either localized or whole-body hyperthermia. Widely considered by European oncologists to be the "fourth arm" of cancer treatment following surgery, radiation and chemotherapy.

Infrared *n.* A type of electromagnetic radiation. Infrared light has a frequency below the frequency of red light (which has the longest wavelength human eyes can see). Infrared waves are between 750 nm and 1 mm, are invisible to the human eye, and are sensed by the human body as heat.

Laser *n.* Originally an acronym for "Light Amplification by Stimulated Emission of Radiation", this refers to a device that emits light through a process stimulated by electrical current or electromagnetic waves in dyes, ionized and gaseous media, or semi-conductor materials resulting in amplification (amplitude summation) of generated waves in a very narrow range. Lasers are different from other sources of light because they emit light coherently (in a very narrow range of wavelengths, ± 5 nm).

Laser photocoagulation *n.* A surgical procedure that uses the heat from a laser to destroy abnormal tissue (e.g. tumor or hyper vascularized area), seal leaking blood vessels in the retina; increasingly used to treat a number of eye diseases.

Laser-induced thermotherapy *n.* A low-invasive technique for the destruction of tumors. Consists in tissue overheating above 60-1000C, by means of laser light energy transmission, often through an optical fiber inside the tissue.

LEDs *n.* An acronym for light-emitting diodes; a semiconductor light source used as indicator lamps in many devices and increasingly used for other lighting, including medicine.

LDL *n.* Low-density lipoproteins; a light fraction of fats conjugated to proteins and circulating in the bloodstream. They mainly play a transport role for food molecules.

MTT-test *n.* A colorimetric assay for measuring the activity of cellular enzymes that reduce the tetrazolium dye, MTT, to its insoluble formazan, giving a purple color. It measures cellular metabolic activity via NAD(P)H-dependent cellular oxidoreductase enzymes and may, under defined conditions, reflect the number of viable cells present. It can also be used to measure cytotoxicity (loss of viable cells) or cytostatic activity (shift from proliferative to resting status) of potential medicinal agents.

Oxide *n.* The chemical combination of a substance with oxygen.

Oxidation *n.* A reaction in which the atoms in a molecule lose electrons and the oxidation degree of the element is correspondingly increased.

Oxidative *adj.* Relating to the process of oxidation, a reaction taking place in the presence of oxygen.

Photoaging *n.* A process of aging of the skin attributed to continuous, long-term exposure to ultraviolet radiation (approximately 300–400 nm), natural or synthetic, on an intrinsically aged skin (most evident on the face, ears, neck and hands).

Photochemotherapy *n.* 1. A phototherapy approach in which treatment is carried out using specific drugs that react to ultraviolet radiation or sunlight; commonly used for skin disorders such as psoriasis. 2. In Western Europe often used as a synonym of PDT.

Photodamage *n.* Structural and functional deterioration of the skin related to excessive exposure to light, especially to the sun's ultraviolet radiation; consequences of photodamage include wrinkling, roughness, altered texture, discoloration, acral lentigines, mottled hyperpigmentation, and other changes. Photodamage is considered to be an aspect of photoaging (sun-related skin damage linked with aging).

Photodiagnosis *n.* Use of photosensitizer compounds for diagnostic purposes. Also referred to as fluorescence diagnosis or photodynamic diagnosis.

Photodynamic *adj.* 1. Of or pertaining to the energy of light; 2. Enhancing or strengthening the effects of light, or inducing a specific therapeutic reaction to light, notably ultraviolet light.

Photodynamic therapy *n.* A form of treatment that employs a photosensitizing agent, administered by mouth, topically or intravenously, which concentrates selectively in abnormal tissue (e.g., malignant tumor); subsequent exposure of the abnormal tissue to a special light source (e.g., laser light of a definite wavelength) enables selective destruction or modification of the abnormal tissue.

Photoimmunotherapy *n.* Use of light to help the immune system better detect cancer and destroy cancer. In one PIT approach, the photosensitizer is exposed to light outside the body and then injected in its oxidized form into the body, where it then changes the presentation of the tumor antigens so that the immune system can detect the cancer and eliminate it. Another PIT approach entails a light-based, molecular-targeted cancer therapy that enables the selective destruction of cancer cells without damage to normal ones. The monoclonal antibody-coupled photosensitizer, when interacts with the target molecule on the cancer cellular membrane, is only activated by near infrared light and thus enables a highly targeted treatment. This approach is also often called Antibody-targeted photolysis (ATP).

Photomedicine *n.* A field of medicine that encompasses the positive and negative effects of light on human health; includes the use of light for diagnostic purposes, and the use of both lasers and non-laser light for therapeutic purposes.

Photo-oxidative *adj.* Referring to an oxidative reaction triggered by light.

Photoprotective *adj.* Conferring protection against the harmful effects of excessive exposure to sunlight; refers to a group of mechanisms that nature has developed to minimize the damage that the human body suffers when exposed to UV radiation

Photorejuvenation *n.* The process of using laser and light sources for restoring skin to a more youthful appearance.

Photosensitizer *n.* A light-harvesting compound; a compound that sensitizes the targeted cells to light, rendering them vulnerable to the destructive effects of the light's energy.

Photosynthesis *n.* Synthesis of biological compounds upon exposure to light.

Phototoxic *n.* Capable of triggering a toxic reaction upon exposure to light.

Phthalocyanines *n.* Intensely blue-green colored aromatic macrocyclic compounds that are widely used in dyeing.

Porphycenes *n.* Structural isomers of porphyrins that act as photosensitizers.

Porphyrins *n.* A group of compounds containing the porphyrin structure, four pyrrole rings connected by methine bridges in a cyclic configuration to which a variety of side chains are attached. A porphyrin, in combination with iron, forms the heme component in biologically significant compounds such as hemoglobin and myoglobin. Examples of porphyrins include protoporphyrin, hematoporphyrin, uroporphyrin, benzoporphyrin, etc.

Protoporphyrin IX *n.* A photosensitizing pigment derived from 5-aminolevulinic acid (5-ALA) and naturally present in the body.

Protoporphyrins *n.* porphyrins whose iron complexes united with proteins occur in hemoglobin, myoglobin, and certain respiratory pigments.

Psoralens *n.* Weak photosensitizer that sensitizes the skin to the sun's rays; abundant in certain plants such as parsley, parsnip, carrots and celery.

ROS *n.* Reactive oxygen species; oxygen-containing atoms, free-radicals and molecules with a high oxidizing potential.

SYLT *n.* An acronym for Systemic Light Treatment; involves light-based activation of the immune system on a systemic or whole-body level as the photosensitizer circulates through the bloodstream.

Thermal ablation *n.* A surgical procedure in which heat is used to destroy tissue. Thermal ablation treats cancer tumors using heat-generating probes applied over the surface or inserted directly into malignant tissue.

Uroporphyrins *n.* Produced during the synthesis of natural porphyrins; excreted in urine.

RESOURCES

The Natural Health Foundation (www.naturalhealthfoundation.com)
The Natural Health Foundation (NHF) is an international non-profit organization originally established in The Netherlands in September 2003 following an international conference devoted to new developments in cancer treatment. This was an international gathering of physicians, scientists, journalists, and businessmen in The Hague on August 22 and 23. The NHF is dedicated to informing the general public and health care community about novel, non-toxic methods of cancer treatment and prevention. We are interested in supporting the research and development of holistic, humane and effective approaches to cancer, some of which may complement or, in some cases, substitute for mainstream modalities such as surgery, radiotherapy and chemotherapy. On the NHF website, you will find detailed information about these innovative methods as well as a directory of clinics and practitioners offering Photodynamic Therapy.

EuroPDT (www.euro-pdt.org)
According to founding president Lasse R. Braathen, MD, PhD, the purpose of EuroPDT is to become a communications platform between researchers working with fluorescence diagnosis and photodynamic therapy and to promote international cooperation among clinical researchers focusing on PDT in Europe. EuroPDT aspires "to become instrumental in the process of shortening the communication lines and time between clinical research results and clinical application and to promote cross fertilisation between FD & PDT specialists in Europe." EuroPDT also offers presentations of advances in clinical research and clinical application and progress, and invites researchers as well as clinicians from all over Europe.

International Society for Photodynamic Therapy (www.i-pdt.org)
The aim of the International Society for Photodynamic Therapy (I-PDT) is to promote the evidence-based use of PDT in dermatology and to be a forum for the exchange of knowledge and scientific data, as well as clinical use and techniques. On 29 January 2005, the I-PDT board invited a number of well-known clinicians and scientists to a launch meeting in Rome, Italy, where an executive committee of I-PDT was established. In addition to elucidating the aims and working procedures of the Society, I-PDT is considering the possibility of publications, courses and congresses in the near future.

European Platform for Photodynamic Medicine (www.eppm-photomedicine.org)
The European Platform for Photodynamic Medicine (EPPM) was founded by Keyvan Moghissi, Heinrich Walt, Giulio Jori and Patrice Jiclinski in 2006. The primary purpose of the organization is to bring together scientists and clinicians to further the evolution of photodynamic medicine. The EPPM is devoted to the promotion of Photodiagnosis (PDD) and Photodynamic Therapy (PDT) throughout Europe. Since 2009, the peer-reviewed medical journal, Photodiagnosis and Photodynamic Therapy has been the official journal of EPPM. This is an international journal for the dissemination of scientific knowledge and clinical developments of PDD and PDT in all medical specialties. The journal publishes original articles, review articles, case presentations, "how-to-do-it" articles, Letters to the Editor, short communications and relevant images with short descriptions. The journal was initiated in 2004 by Keyvan Moghissi (Ref: Moghissi K. Photodian Photodyn Therap, 2004;1:1-1) and continues to be published by Elsevier. IPA has been affiliated with the journal since 2012.

International Photodynamic Association (IPA)
Founded in 1986, the IPA's membership consists of the most prominent international clinicians and scientists involved in performing and researching photodynamic therapy (PDT) and photodiagnosis (PD). The main purpose of the association is to promote the study of PDT and PD, and to disseminate such information to the members of the IPA, the medical community and the general public. Every two years, the IPA organizes an International Congress as a unique opportunity to present research activities in the clinical and basic research aspects of PDT.

INDEX

D

E

F

G

H

I

J

L

M

N

O

P

R

S

T

U

V

W

X

Y

Z

ANDREI RESHETNICKOV, PhD, is a bioorganic chemist who has developed a wide range of leading-edge photosensitizers and other light-based medical technologies. An expert reviewer for the journal *Photodiagnosis and Photodynamic Therapy,* he conducts ongoing studies on photodynamic medicine in Moscow.

MARK NATHANIEL MEAD, MSc, is a nutrition research consultant and medical writer who has contributed to numerous health-related books as well as *Natural Health, Integrative Cancer Therapies, International Journal of Cancer, Cancer Treatment Reviews,* and many other publications.

POETRY CREDITS (page 25):

Annie Dillard quote, from *Pilgrim at Tinker Creek* (1974)
Mary Oliver quote, excerpted from her poem, "Poppies"
Shakespeare quote, from *The Two Gentlemen of Verona*
Walt Whitman quote, from *Leaves of Grass* (1855)
Ralph Waldo Emerson quote, from "The Over-Soul" (1841)
William Blake quote, from "To Thomas Butts"
Kahlil Gibran quote, source unknown