cryosurgical advances in dermatology and tumors of the head and neck

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Forewords by

John G. Bellows, M.D., Ph.D.

and

Edward A. Krull, M.D.

Clinical and scientific leaders from numerous surgical fields have joined together to produce this peerless compendium of cryosurgical methods for the treatment of benign and malignant neoplasia of the skin, head and neck. No detail has escaped their authoritative examination; no method is left unexplained. Cryosurgery has come of age, and the clinician will find this book indispensable as a source of reference for the practice of its various techniques.

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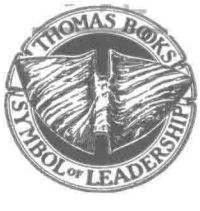

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I dedicate this book to my parents who early in my childhood nurtured my interest in medicine.

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FOREWORDS

Cryosurgical Advances in Dermatology and Tumors of the Head and Neck, the author's third book, is further proof that Doctor Setrag Zacarian is a leading expert on cryosurgery of the skin. Physicians, and especially cryosurgeons, are greatly indebted to Doctor Zacarian who was instrumental in developing the basic principles of cryosurgery. He was a pioneer in establishing the relationship of the freezing temperature, the length of time of the application, and the resulting cellular and tissue reactions. Before this, skin lesions that were destroyed by freezing depended upon the application to the skin of cotton swabs dipped into a cryogen.

Dr. Zacarian is not only preeminent in clinical cryosurgery of skin lesions, but also has contributed much to our knowledge through his work in experimental cryosurgery. Using his great energy and talents unsparingly, he has become the established leader in cryosurgery of the skin. In his classic studies of the cryolesion, he described the thermal gradients that exist in deepfreezing of biological systems; using thermocouples, he developed means of monitoring the temperature in the evolving cryolesion and demonstrated that the lowest temperatures occur near the heat sink. He emphasized that treating a skin malignancy without using thermocouple needles is unsatisfactory because the surgeon does not know the varying freezing temperatures of different parts of the tumor. Thus, many cancer cells can escape destruction. The author also demonstrated clinically the superiority of the wound healing which follows cryosurgery, in contrast to that which follows other methods of tumor removal.

Zacarian and his co-authors, who individually are experts in various scientific disciplines, in updating cryosurgery for head and neck tumors, oral tumors as well as eyelid neoplasms, have rendered a great service to patients and physicians alike.

John G. Bellows, M.D., Ph.D.
Editor-in-Chief:
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Doctor Setrag Zacarian is one of the foremost leaders in cryosurgery of skin tumors. His two previous books on cryosurgery have served both as a foundation for and major stimulus to the increasing scientific development and use of cryosurgery for cutaneous lesions. This book brings together the advances in the biology and techniques of cryosurgery, new instrumentation, and an in-depth study of the role and effectiveness of cryosurgery that have evolved in the intervening

years since his last text. It is significantly different from his other books and is an important contribution to our knowledge of cryosurgery of skin tumors.

Cryosurgery has been used by dermatologists for many years in a variety of benign cutaneous lesions without much concern about cryogenics and cryobiology. This knowledge seemed unnecessary when treating warts and seborrheic and actinic keratoses. The end result of the destruction of the lesion was obvious. However, the employment of cryosurgery in the treatment of malignant lesions has necessitated the investigation of cryobiology and its careful application and evaluation in clinical situations. Thus concepts of the cryolesion, critical temperatures for normal and malignant cell destruction, thermal gradients, freeze-thaw cycles, double freeze-thaw cycles have been of necessity studied in great detail. Doctor Zacarian has presented the fundamentals of cryobiology in a fascinating and clinically relevant manner.

The very simplicity of cryosurgical technique creates inherent problems of failing to utilize appropriate control systems. I think it is very important that Doctor Zacarian has stressed the necessity of thermocouple monitoring of tumor treatment by measuring the temperatures within the tissue to be certain that the critical levels necessary for tumor destruction are attained. Without the establishment of specific methods and temperature monitoring systems the interpretation of results would have much less scientific value and might be more variable and unpredictable.

Cryosurgery is one of a number of physical modalities that is successfully used in the treatment of skin malignancies. Simplicity of techniques, possible better cosmetic results, relative preservation of the lacrimal duct system, avoidance of chondronecrosis and perforation of the ear and nose are some of the benefits of this treatment method.

But there has been some question about cure rates of basal cell and squamous cell carcinoma treated with cryosurgery. Doctor Zacarian's long-term statistics have established that cryosurgery, if properly used in appropriate circumstances, has a cure rate equal to that of x-ray, electrosurgery, and excision surgery.

The most frequent use and perhaps the main application of cryosurgery is for benign skin lesions such as warts, actinic and seborrheic keratoses, sebaceous hyperplasia, dermatofibromas, and acne. All physicians treating skin lesions should become familiar with the indications and use of cryosurgery for these lesions.

Cryosurgery knows no specialty restriction. Any tissue that is accessible to cryosurgical application may be amenable to this treatment. Doctor Zacarian has drawn together contributors from surgery, plastic surgery, otolaryngology, and ophthalmology, as well as dermatology to present the scope of current cryosurgical usage and to stress its potential value for other specialties.

Doctor Zacarian continues with this book his important contribution to cryosurgery. It is very well written, with a broad scope and a meaningful organization of material. It combines in a most understandable and interesting fashion the biology and techniques of cryosurgery, thus affording a guide to practical treatment and development of the foundations from which future investigations and new clinical application may be derived.

I strongly recommend Doctor Zacarian's excellent new book to all physicians treating skin and oral lesions—the family practitioner, surgeon, plastic surgeon, otolaryngologist, oral surgeon, ophthalmologist, gynecologist and the dermatologist—and to those who might conceive of even other roles in medicine for cryosurgery.

Doctor Zacarian is to be congratulated on his outstanding book and his abiding scientific endeavors in cryosurgery.

Edward A. Krull, M.D.
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Preface

Cryosurgery is not only an established technical procedure but also an accepted medical discipline for the effective treatment of benign and malignant neoplasia. In some instances freezing or cryogenics has replaced the traditional scalpel, irradiation and other conventional modalities for the ablation of unwanted tumors. The therapeutic effects of subzero temperatures for various medical disorders was known to Hippocrates and his followers. However, it was not until the turn of the century that the use of extremely cold refrigerants became available to the physician and were enthusiastically explored by the dermatologists. The application of liquid nitrogen with a cotton swab upon benign and precancerous growths of the skin was passed on from one generation of dermatologists to another for almost sixty years.

During this same period of time, cryobiologists diligently investigated and observed the effects of subzero temperatures upon plant and animal cells. Subsequently, the new science of cryopreservation of living cells, tissues, and organ systems was evolved. Indirectly they paved the way and contributed to our own divergent specific interests in cryogenics, not to preserve tissues but to destroy them.

Fifteen years ago there emerged an imaginative clinician and investigator, Doctor Irving S. Cooper, who employed a sophisticated cryogenic instrument which delivered liquid nitrogen to freeze a specific focal area of the basal ganglia, to relieve the symptoms of Parkinson's Disease and other neurological disorders. Through his pioneering research and extensive clinical studies, he promulgated the modern science of cryogenic surgery. This new technical skill very rapidly made inroads to almost all of our surgical specialties, including dermatology. The cotton swab was soon replaced by various sophisticated instruments which delivered liquid nitrogen with greater precision and offered a sustained heat sink to eradicate malignant tumors of the skin, the oral cavity, and selected head and neck tumors. The high cure rate, simplicity of application, and superb cosmetic end results from freezing, and the added role as a useful modality for palliation of external neoplasms, has brought cryogenic surgery into the forefront with other contemporary medical disciplines.

You may well ask, why then have I authored and helped edit a third book? The desire to familiarize the physician and the clinical investigator with the fundamental pathogenesis of freezing temperatures upon normal and malignant tissue was foremost in my mind. I want to stir his imagination to explore and elucidate the enigmas of superb wound healing following cryogenic surgery and to make him aware of the specific selectivity of various cells to freezing temperature.

It is extremely important to understand the development of the cryolesion,

temperature gradients, and the importance of freeze-thaw cycles. The clinician should not embark upon cryogenic surgery if he does not understand these important parameters clearly outlined in the first chapter.

The need to learn from each other and share our experiences in diverse medical and surgical disciplines is extremely important if medicine is to advance. In this monograph I have brought together the expertise of not only the dermatologist, but also the general surgeon, the plastic surgeon, the ophthalmologist, and the head and neck surgeon. We have described the various cryosurgical instrumentations that have evolved in the past fifteen years as well as their specific use in various medical disorders. Some of the complications and limitations of cryogenic surgery have not been deleted. Since my two monographs in 1969 and 1973, a larger number of patients with skin cancers have been cryosurgically treated by this author and others. The follow-ups and cure rates, therefore, are more meaningful now and give further impetus to this new technology. This treatise also presents the effects of freezing through the tarsal plate of dogs and lacrimal duct with preservation of these vital structures. Freeze-thaw cycles have been further defined both upon canine skin and HeLa cells as they would relate to human experience. Several authors present their experience in cryosurgery for lentigo maligna which appears to be very promising.

We have touched upon the possible implications of cryoimmunology, a fertile field, yet unexplored and unchartered in the management of human malignancy. Cryogenic surgery is still in its infancy, but it has already proven its usefulness as a therapeutic regimen for most primary neoplasia of the skin and selected lesions of the oral cavity. It has its place as an adjunctive modality for advanced carcinomas when there is no other recourse. The cryosurgical approach for the management of eyelid cancers is both provocative and promising. Throughout the chapters there may be some differences among the authors as to critical temperatures, single versus double freeze-thaw cycles, as well as success and failure of specific malignant tumors of the skin and their location. These divergent views need not necessarily confuse the reader but may clarify the dynamic phase of this new burgeoning technology.

The future of cryosurgery is as limited as the myoptic vision of the physician and as unlimited as his imagination, curiosity and clinical investigation. I am reminded of Edgar Allan Poe who said, "Those who dream by day are cognizant of many things which escape those who dream only by night."

If this monograph stimulates and inspires others in the pursuit of truth and advancement of this new technique for the benefit of mankind, this alone will have sufficed to fulfill my goal and purpose and that of the contributing authors.

Our ultimate desire is for the physican who is unacquainted with cryogenic surgery to consider its usefulness in the management of human malignancy. Was it not Alexander Pope who said, "Be not the first by whom the new attract, nor yet the last to lay the old aside."

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Acknowledgments

WRITING A BOOK is a prodigious undertaking, particularly in a field of medicine where changes and innovations are capricious and concepts and therapeutic indications are so ephemeral. Cryogenic surgery, an established medical and surgical discipline, is very much alive. Clinical investigators are developing new ideas and exploring fertile fields in our struggle against human disorders. I am indeed fortunate and most grateful to the contributing authors, who have kindly consented to share their expertise in cryogenic surgery to make this monograph the most complete and contemporary in its field. Each author has been a pioneer in this new technology and has authored many papers and promulgated important principles in cryosurgery.

The invaluable help and advice of Dr. Charles D. Cox, Chairman of the Department of Microbiology at the University of Massachusetts at Amherst is herein acknowledged and much appreciated. I also thank Miss Ann Progluske and Mary Lee Noden at the University of Massachusetts for their technical assistance.

The first chapter would have been totally incomplete and inadequate without the help and contributions of Dr. Joseph T. Giammalvo, Pathologist-in-Chief of the Providence Hospital in Holyoke, Massachusetts. His meticulous interpretations in the pathogenesis of human carcinoma of the skin and specimens of in vivo freezing of dog integument with variant cryogenic techniques was both informative and stimulating. I am genuinely indebted to him.

Dr. Joseph M. Stoyak, a veterinarian in Springfield, Massachusetts, worked diligently with me to help with the experimental studies on freeze-thaw cycles and the effects of freezing upon the eyelids and lacrimal apparatus of dogs. He has contributed much to elucidate the effects of cryogenic surgery as it may relate to humans. In his own right, Dr. Stoyak is a pioneer in veterinary cryogenic surgery in the United States.

I acknowledge with thanks the help of Mrs. Jean E. Scougall and the library staff of the Bay State Medical Center. The assistance offered by Mr. Joseph Stumpf, Joseph Andera, and Robert Eisenberg from the Engineering Department of Frigitronics, Inc. of Shelton, Connecticut were invaluable in the final modifications and implementations of the templates to measure central and peripheral depth of the cryolesion during freezing and also in the development of the new C-76 portable unit.

This author expresses his gratitude to the Zacarian Cancer Research Foundation for the financial support it has given to pursue the experimental studies at the University of Massachusetts, and the studies pertinent to the pathogenesis of cryonecrosis of malignant tumors of the skin and the canine experiments. This Foundation has also helped to defray the cost of many of the color plates

in this monograph along with the Rudolph Ellender Medical Foundation through the efforts of Dr. Joseph A. Baldone, President. The following pharmaceutical companies have generously contributed toward the colored plates: Cooper Laboratories; Dermik Laboratories; Dome Laboratories, Division of Miles Laboratories; Herbert Laboratories; Johnson & Johnson; Lederle Laboratories, Division of American Cyanamid; Owen Laboratories; Pfizer Laboratories, Inc.; J. B. Roerig; Reed and Carnrick; Schering Corporation; E. R. Squibb and Sons, Inc.; Stiefel Laboratories; Syntex Laboratories; Texas Pharmacal, Division of Warner Lambert; and Westwood Pharmaceuticals, Inc. to each, I express my sincere thanks.

The commercial art work of Patricia Dupont and the excellent reproduction of many prints rendered by Armen Tashjian are herein acknowledged with appreciation. I also want to thank the staff of Charles C Thomas, Publisher, in particular, William H. Bried who worked diligently in the preparation of this treatise and made special efforts to reproduce the excellent quality of the color plates which have enhanced this monograph. I thank Miss Teresa C. Boylam for the preparation of the subject and author indices.

Last but not least, I am grateful to my wife, Rocky, who not only served as my sounding board, but also tolerated my incessant long hours, the cluttered study, and reediting and retyping the mountainous hand-scribbled notes of my manuscript to its final revision.

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Contents

Cryosurgical Advances in Dermatology and Tumors of the Head and Neck

CHAPTER ONE

Cryogenics, the Cryolesion and the Pathogenesis of Cryonecrosis

SETRAG A. ZACARIAN, M.D., F.A.C.P.

I. CRYOGENICS

WHILE CRYOBIOLOGY RELATES to the effects of subzero temperatures upon a living system, cryogenics primarily concerns itself in the development of freezing temperatures within a biological system. The physical basis by which freezing is accomplished within a living tissue or a cell is essentially the withdrawal of heat from that medium. This heat exchange is dependent in part upon the underlying tissue environment, its water content and the degree of its vascularity. Equally important is the type of refrigerant or cryogen employed. The lower the boiling point of refrigerant, greater is its capacity to freeze in both depth and volume; for example, Freon 12® with a boiling point of −29.8°C is not cold enough to freeze malignant tumors of the skin, yet is quite effective for freezing the lens of patients with cataracts, referred to as cryoextraction. Liquid nitrogen, on the other hand, with a lower boiling point of −195.6°C has the capacity to freeze not only benign but malignant neoplasia of the skin, oral cavity and bone as well.

The birth of modern cryogenics, interestingly enough, came on Christmas Eve in the year 1877. Two papers were delivered before the French Academy of Sciences, one by the French scientist Louis Cailletet and the second by the Swiss engineer Raul Pictet. Cailletet had liquefied small quantities of oxygen and carbon monoxide by expansion of the gases from extremely high pressures.[1] Pictet demonstrated his experiments wherein he had liquefied oxygen by means of a mechanical refrigeration cascade, by employing sulfur dioxide and carbon dioxide, boiled under reduced pressures.[2] Two Polish scientists, Wroblewski and Olszewski, in 1883, successfully converted oxygen and nitrogen into a liquid state.[3] The commercial production of large quantities of liquid air and subsequent extraction of liquid nitrogen were the contributions of Linde in 1895.

II. DEVELOPMENT OF THE CRYOLESION

Refrigerants in current use today are essentially capable of producing cryolesions of varying magnitude. However, the rapidity of its formation, its volume, depth, and the intensity of achieving subzero temperatures below the skin and neoplasia vary with the refrigerant selected and its boiling point. Insofar as the following chapter discusses at length various cryogens and instrumentations, the author will confine his remarks to the capacitance of liquid nitrogen.

The development of the cryolesion is interdependent upon the applicator used and probe size (Figures 1-1 and 1-2). If one

Figure 1-1. The extent and depth of the cryolesion is dependent upon the refrigerant and composition of the heat sink. Liquid nitrogen chilled copper disc will offer a greater degree of conduction and retention of the cryogen than cotton swab. From S. Zacarian, *Cryosurgery of Skin Cancer*, 1969. Courtesy of Charles C Thomas, Publisher, Springfield, Illinois.

employs an open system, the aperture size of the interchangeable plastic needle for the refrigerant spray is to be considered. The duration of freeze time (Figures 1-3 and 1-4), thermal conductivity, cellular composition and osmolality, and the underlying vascularity of the given tissue subjected to freezing will govern the extent of the cryolesion. The velocity of cooling inevitably closely correlates with the degree and depth of cryonecrosis which subsequently follows. The more rapid the rate of cooling, more profound is the underlying tissue destruction.[4-6] The heat generated during the cooling process with conversion of water to ice is referred to as the *latent heat of fusion.* As water is transformed into ice, one can measure

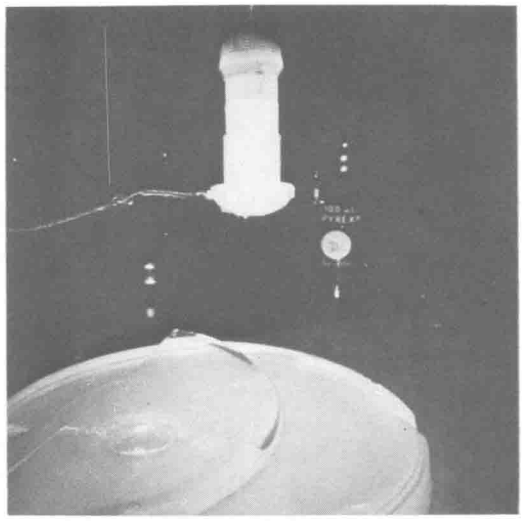

Figure 1-2. The classic hemisphere of a cryolesion produced in a gelatin mold as it would evolve in vivo. From S. Zacarian, *Cryosurgery of Skin Cancer*, 1969. Courtesy of Charles C Thomas, Publisher, Springfield, Illinois.

the production of heat equivalent to eighty calories per gram of water.

The survival or demise of normal or malignant cells is closely related to the velocity of the cooling experience to which they are subjected. Among cryobiologists there is no uniformity of opinion as to what constitutes rapid, moderately rapid,

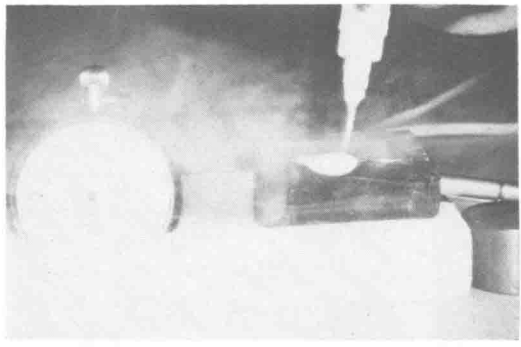

Figure 1-3. The early development of a cryolesion within thirty seconds of liquid nitrogen spray upon a gelatin mold with an open spray unit.