Dermatologic Cryosurgery

William Abramovits
Gloria Graham
Yaron Har-Shai
Renata Strumia
Editors

Springer

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ISBN 978-1-4471-6764-8 ISBN 978-1-4471-6765-5 (eBook)
DOI 10.1007/978-1-4471-6765-5

Library of Congress Control Number: 2015960385

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer-Verlag London Ltd.

Preface

In dermatologic cryotherapy and cryosurgery, localized cold is used to improve some skin conditions or destroy and remove abnormal tissue. It utilizes cryogens to treat various benign non-cancerous, pre-cancerous, and cancerous lesions.

The advantages of cryosurgery include high success rates, few side effects of significance, relatively short recovery times, ease of performance, and reasonable cost. The disadvantages include frequent morbidity, lack of accurate margin of destruction control, and operator dependency.

Solid scientific grounds nowadays support the indications for cryosurgical and cryotherapeutic procedures, starting with understanding the mechanisms of action, the cellular and vascular events that occur during the processes of cooling and freezing, thawing and recovery, and ending with the statistical evidence of cure or relief.

This book is titled *Cryosurgery and Cryotherapy for Skin Diseases and Conditions* because in this way we address from the start semantic issues with the word cryotherapy, which we consider to be misused interchangeably with cryosurgery. For our purpose, the term "cryosurgery" is used to denote a primarily destructive procedure involving temperature reduction (such as for skin cancer), while "cryotherapy" is used to denote a therapeutic procedure where the tissues are taken to low temperature but are expected to survive (such as in pain reduction). A terminology compromise was accepted for those procedures where mechanisms of action where destruction and the involvement of immunity overlapped. We often respected the choice of words by the chapter authors.

An example of cryosurgery is the treatment of epithelial skin neoplasms by lowering them to temperatures that selectively destroy the cancer cells within them, while their surrounding tissue is spared lethal damage. Examples of cryotherapy include lowering skin temperature to induce anesthesia, preserving a severed finger for reattachment, or cooling a wart for a few seconds just to induce an immune response that hopefully will get rid of it.

It was 3 years ago that Mr. Grant Weston from Springer Publishers approached me after my almost yearly lecture on cutaneous cryosurgery at an Annual Meeting of the American Academy of Dermatology to suggest that I write the "definitive textbook" on the subject. That year another textbook (albeit not the definitive) on the same topic was just published, so I felt that the timing was suboptimal; the seed had been placed in nourishing ground. For the daunting task, it was tremendously gratifying to obtain the support of luminaries like Gloria Graham, MD; Renata Strumia, MD; and Yaron Har-Shai, MD, who became my co-editors.

Gloria needs no introduction in the world of dermatology, and she is without a doubt the Doyenne of Cryosurgery, having written many articles, edited textbooks, lectured innumerable times all over the world, treated many, and mentored a large cadre of practitioners of the trade. Dr. Graham kept motivating us by example; although she struggled with health issues, she never quit pressing us to edit and her many friends in the field to contribute.

Renata was introduced to me by Grant. He suggested that I read a book on cryosurgery she had just published in Italian. Dr. Strumia wrote that book pretty much all by herself, and it was very much to my liking. I contacted her, met her at congresses, learned firsthand of her competence, and asked her to join us as editor and contributor; she did so with remarkable eagerness and efficiency.

Yaron's name I kept running into while reviewing cryosurgery on PubMed; Dr. Har-Shai is a plastic surgeon in Israel who has a keen interest in the reduction of keloids and has developed innovative techniques. He was also a most efficient deliverer of contributions to our text, and he helped us recruiting erudite authors for several chapters. I would also want to give a special thanks to Dr. Robert Schwartz for his help in the final stretch of this book. He dedicated a lot of his time and his team's effort to complete chapters for which we had difficulties finding willing contributors.

I am in great debt to my co-editors for their efforts and collaboration. They all actively participated in the development of the content, wrote a great number of the chapters, and helped me greatly in the selection of contributors of the highest quality, expertise, and recognition in their respective fields.

Finally, I must acknowledge the valuable participation and intense dedication and efforts of the team Alba Quiñones, MD (from Dermatology Treatment and Research Center) and Michael D. Sova (Developmental Editor for Springer Science) to whom this text owes its crystallization.

Hopefully the readers will find this book to be of value, as complete as possible, and enjoyable to read; it may not be the "definitive textbook" on the subject, but hopefully that is because the field continues to expand and progress.

Dallas, TX, USA William Abramovits

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Part I

History

The History of Dermatologic Cryosurgery

1

William Abramovits

Abstract

The therapeutic use of "extreme" cold dates from the mid nineteen century. For over a hundred years cryosurgery has been used to treat skin cancer; also skin infections, benign tumors, and a myriad of other conditions. Understanding of the mechanism by which cold affects the skin and other organs has led to the development of progressively better delivery systems, cryogens and monitorization equipment; all this thanks to the contributions of many bright medical and other scientific minds which we attempted to recognize in this chapter.

Keywords

History • Liquid air • Carbon dioxide • Liquid oxygen • Liquid nitrogen • Isotherms • Monitorization • Cryotherapy • Cryosurgery

Although the history of the use of lowered temperatures for therapeutic purposes may go as far back as ancient Egypt and Greece its early use, was intended to provide analgesia and inflammation relief. Frostbite, an injury due to ice crystal formation in superficial and deep tissues was appreciated long before; a 5,000-year-old mummy found in Chilean mountains represents the earliest documentation of its occurrence [1, 2].

Dermatologic cryosurgery textbooks and scholarly reviews credit James Arnott, with the first publication on the destruction of skin tissue by means of "extreme" cold (circa 1851), which he achieved by mixing finely crushed ice and sodium chloride, recommending it in acne, neuralgia and

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W. Abramovits et al. (eds.), *Dermatological Cryosurgery and Cryotherapy*,
DOI 10.1007/978-1-4471-6765-5_1

to anesthetize skin preoperatively; and supposed the curability of cancers by congelation [3].

Campbell White, in articles published in 1899 and 1901 advocated the use of liquid air for the treatment of a variety of skin conditions including lupus, herpes zoster, chancroid, nevi, warts, leg varicosities, carbuncles and epitheliomata. About the latter he said that treated early it will always be cured [4].

Whitehouse, H in 1907 reported on the use of liquid air on vascular nevi, lupus erythematosus and epitheliomata; about the latter he found it to be more successful at eradicating recurrences than repeat radiotherapy; that same year Bowen, JT and Towle, HP reported on the successful use of liquid air on vascular lesions [4–6].

Hall-Edwards, J in 1911 reported on the use of carbon dioxide (CO2) in many conditions, but most notably on "rodent ulcers" [7] an old term for ulcerated basal-cell carcinomas and on the same year Cranston-Low explained the results of cryosurgery as the sum of its directly injurious, thrombotic and inflammatory effects [3–5].

Gold, J in 1910 reported on the comparison of the effects of liquid air versus CO2 stating with "no hesitancy" that the former is "far preferable" [8].

In the 1920s and 1930s liquid oxygen was used for the treatment of acne.

Irvine, H and Turnacliffe, D in 1929 favored liquid air and oxygen over CO2, reporting on the use of the former in seborrheic and senile keratosis, lichen simplex, poison ivy dermatitis and herpes zoster; and of liquid oxygen for warts, including plantar [9, 10].

Pussey, W in 1935 popularizes the use of CO2 snow derived from steel cylinders that kept it in liquid state, which when allowed to escape, turns into a fine snow that can be compressed into shapes for particular treatments; Pussey successfully treated a large black hairy nevus on a girl's face, as well as warts, nevi and lupus erythematosus. He also recognized the low scarring potential of cryosurgery [6].

Allington, HV in 1950 is the first to publish on the satisfactory use of liquid nitrogen in the treatment of warts, keratosis, superficial hemangiomas, leukoplakia, keloids, acute contact dermatitis, lichen simplex and planus, pyogenic granulomas, discoid lupus and acne. His cure rates treating common warts surpassed 90 % in three treatments done dipping cotton swabs into thermos bottles containing liquid nitrogen. Besides his elegant description of the method he used, histologic findings of post-cryosurgery were reported in the article [11].

In the 1960s several reports are made of the use of CO2 from dry ice, pulverized and wrapped into bags (golf ball size) lined with gauze, sometimes mixed with precipitated sulfur, and doused with acetone, in acne therapy.

Cooper, IS in 1963 reported on the use of liquid nitrogen to destroy or extirpate benign and malignant skin lesions; he had developed an apparatus to deliver liquid nitrogen targeted for neurosurgical use [13].

Torre, D [14] in 1965 and Zacarian, S [15] in 1967 presented hand held devices to spray liquid nitrogen that were particularly well suited to the dermatology practice; later on both dermatologists wrote extensively on the subject, particularly Zacarian who published a textbook on Cryosurgery of Skin Cancer, and Cryogenic Techniques in Dermatology in 1969 and two other in 1977 and 1985 [16–18]. Torre edited an issue of the Journal of Dermatologic Surgery and Oncology wholly dedicated to cryosurgery in 1983 [19].

Gage, AA in 1965 [20] writes on cryosurgery of the lip and oral cavity, later on benign and malignant lesions of the mouth; then on its use for pilonidal cysts, basal and squamous cell carcinoma, lentigo maligna, and on ear cancer. His body of work exceeds 70 papers listed in the PubMed database and many textbook chapters.

Gage has made major contributions to the field of cryobiology, the understanding of the mechanisms by which cryosurgery works, and to its monitorization.

Graham, GF in 1971 [21] reviews the use of cryosurgery in the treatment of malignant lesions of the skin and later publishes on the success rates of this modality for the ablation of basal cell carcinomas. Graham, GF writes and lectures extensively; in 1994 she was the Chair of the Task Force that developed the American Academy of Dermatology Guidelines of Care of Cryosurgery.

Other distinguished and contemporaneous contributors to the field of dermatologic cryosurgery include: Emmanuel Kuflik, Rodney Dawber, Gilberto Castro-Ron, Reimo Suhonen, Ronald Lubritz, Lazlo Biro, José M. Férnandez-Vozmediano, Peter Nordin, CC Zouboulis, José Carlos d'Almeida-Gonçalves and my co-editors and chapter writers for this textbook.

A PubMed review of a cross search of cryosurgery and dermatology found the following list of diseases as one time or another since 1963 when the database began to have been reported as amenable to cryosurgery treatment [12]:

Molluscum Contagiosum, Actinic Keratosis, Elastosis Perforans Serpiginosa, Basal and Squamous Cell Carcinomas, Lentigo Maligna, Lentigo Maligna Melanoma, Melanoma Maligna, Hemangiomas, Trichoepitheliomas, Porokeratosis of Mibelli, Kaposi's Sarcoma, Mucous Cyst, Hemorrhoids, Pilonidal Cysts, Nevus Flammeus, Condyloma, Cylindroma, Herpes Simplex, Telangiectasia, Atypical Fibroxanthoma, Bowen's Disease, Angiofibromas of Tuberous Sclerosis, Cherry and Capillary Angiomas, Cavernous Hemangiomas, Epidermal Nevus, Keloids, Lichen Sclerosus and Atrophicans, Erythroplasia of Queyrat, Verruciform Epidermodysplasia of Lewandowski and Lutz, Extramammary Paget's Disease, Actinic Comedonal Plaque, Prurigo Nodularis, Tattoos, Pigmented Nevi, Carbuncles, Clear Cell Acanthomas, Trichiasis, Dermatofibromas, Sebaceous Hyperplasia, Angiolymphoid Hyperplasia, Tricoepithelioma, Chalazion, Neurodermatitis, Bowenoid Papulosis, Leishmaniasis, Lupus Erythematosus, Idiopathic Guttate Hypomelanosis, Lymphocytoma Cutis, Leukoplakia, Hypertrophic Scars, Xanthogranulomas, Cutaneous Larva Migrans, Granuloma Annulare, Facial Eosinophilic Granuloma, Xanthelasma, Leiomyosarcoma, Actinic Cheilitis, Pearly Penile Papules, Venous Lakes, Granuloma Faciale, Giant Cell Tumor, Milia, Rhinophyma, Pyogenic Annulare, Chomomycosis, Epidermodysplasia Verruciformis, Verrucous Hyperplasia and Carcinoma, Acrokeratosis Verruciformis of Hopf, Seborrheic Keratosis, Merkel Cell Carcinoma, Keratocanthoma, Myasis, Multinucleate Cell Angiohistiocytoma, Blue Rubber Bleb Nevus Syndrome, Lobomycosis, PTEN Hamartoma Tumor Syndrome, Oral and Acral Pigmentation of Laugier-Hunziker Syndrome, Xeroderma Pigmentosa, and Kindler Syndrome.

The same review found the following as complications of cryosurgery: Pruritus, neuropathy, residual tumor, relapses and recurrences, loss of pigment, reactive lentiginous hyperpigmentation, delayed wound healing, hypopigmented, hypertrophic and depressed scars, retraction at the free margins of lips and eyelids, pseudoepitheliomatous hyperplasia, hyperemia, erythema, edema, bullae, loss of lashes, hairs and meibomian glands, damage to the lacrimal system, bacterial and viral transfer risk, erosive pustular dermatosis of the scalp, amelanotic melanoma at recurrence.

A progressive understanding of the mode of action of cryosurgery includes reports on cryogen induced low temperatures on animal and human skin, measurements of temperatures below the skin surface, the influence of blood flow on freezing and thawing times [13], the evaluation of circulatory events during and after cryosurgery versus before it, the histopathology of the cryo-lesion, the finding of the minimal temperature lowering leading to epidermal necrosis, the effect of cryoprotective agents, the determination of the temperatures lethal do different cells, comparative histologic observations between thermo and cryonecrosis, vascular induction of cryolesions by thrombotic events, the mediators of pain during and post-cryosurgery, the effect of anesthesia and epinephrine on cryolesions, the detection of antibodies to epidermal cytoplasmatic antigens and cell mediated immunity post procedure, induction of stress (heat shock) proteins, immunomodulatory effects of cryosurgery on melanoma response, wound healing and scarring from different freezing protocols, long-term effects of cryosurgery on cutaneous sensation, the ablative effects of freeze-thaw times and cycle repetition, the use of clobetasol [14] and antimicrobials to reduce inflammation and infections post-procedure, the differential effects of various refrigerants.

An array of methods have evolved from the times that a simple thermometer was used to read the skin temperature at the site of application of cryogens or of the cryogens themselves; monitorization has progressed from the visual and tactile estimation of frozen skin margins, and the duration of freeze and thaw times, to the use of thermocouple needles that allow for more accurate estimation of temperatures below the surface and at expected lesion depth [15, 16]. Other modalities currently being used to estimate depth and intensity of freeze and to match those to targets include: Measurements of electrical impedance [17] and current flow, ultrasound and echography to estimate tumor extent, increase the precision of thermocouple placement and detection of a match of cryodestructive isotherms and tumor extension [18], The use of magnetic resonance imaging (MRI) [19], optical coherence and impedance tomography, real time infrared guidance, second-harmonic generation microscopy and in vivo reflectance confocal microscopy.

Other ways to optimize the success of cryosurgery evolving over the years include combinations with supervoltage, curettage and radiofrequency for preoperative debulking, the use of epinephrine in the local anesthetics, retinoids orally and topically, chemotherapeutic agents, non-steroidal anti-inflammatories, immune-stimulatory agents including imiquimod and tumor necrosis factor alpha, and tagging tumor cells with metallic nanoparticles, and sclerosing agents.

The incessant understanding of the mechanisms of action of lower temperatures and of the imaging technologies lead the way to increasing success for cryotherapy and cryosurgery.

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Part II

Physics