Dedication

This book is dedicated to Dr. Rodney Dawber. Cutaneous cryosurgery owes an enormous debt to Dr. Dawber who researched, practiced, and taught the subject to a generation of young dermatologists. He inspired and co-authored the first three editions of this book which achieved an international audience. Although he is now retired from medicine, his enthusiasm for cryosurgery lives on through the pages of this book.
Cutaneous Cryosurgery
Principles and Clinical Practice

Fourth Edition

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Preface

The first edition of *Cutaneous Cryosurgery* appeared in 1992 and set out to provide practical information for dermatologists and family doctors who were either already using cryosurgery or who wished to add this technique to their therapeutic options. The second and third editions were modified as new research and clinical studies became available, but also in response to comments from colleagues around the world. It has been helpful that national bodies have produced guidelines for the management of premalignant and malignant skin lesions, which include cryosurgery as appropriate treatment for some lesions; this cements the place of cryosurgery and renders *Cutaneous Cryosurgery* an invaluable practical guide.

Dr. Rodney Dawber was the chief architect of the first edition – a dermatologist who almost single-handedly brought cutaneous cryosurgery in the UK to respectability, through research and infectious enthusiasm. He had a wealth of publications to his name on all aspects of practical dermatology. It was typical of the man to be inclusive and he sought the help of Dr. Arthur Jackson, author of numerous articles on cryosurgery, who was already ahead of his time for the extensive use of cryosurgery in family medicine. In addition Dr. Graham Colver, who had trained under Dr. Dawber, was recruited as the third author. He is author of 10 books and chapters on aspects of skin cancer. Although these three physicians did not share exactly the same techniques and applications for cryosurgery, they agreed on a text for the book that represented a reasonable and safe approach to the subject. Sadly neither Dr. Dawber nor Dr. Jackson was available to be directly involved in this fourth edition. Of course some of the text and photographs from previous editions are used here so that extent their memory lives on. It has, however, created the perfect opportunity to diversify.

For this edition, Dr. Richard Usatine was asked to be the lead author. He is a Professor of Dermatology, Cutaneous Surgery, and Family Medicine in the USA. Although he was originally trained in family medicine, he is the Medical Director of the University Skin Clinic, as part of the University of Texas Health Science Center at San Antonio. He practices dermatology full time and works closely with his colleagues in the Division of Dermatology and Cutaneous Surgery at the University of Texas. Dr. Usatine has been the lead author of two major dermatology procedural textbooks and teaches dermatology procedures to family physicians in many settings.

Dr. Daniel Stulberg was asked to join us as the third author for this fourth edition. Dr. Stulberg has co-taught cryosurgery workshops for over 10 years with Dr. Usatine and was co-author of the last dermatology procedure book by Dr. Usatine. He is a natural fit to complete the talent and experience needed for this fourth edition. Having two new authors ensures that the emphasis, style, and content are significantly different. We have also expanded the book from seven to eleven chapters, including such new areas as the evidence behind cryosurgery and other cryosurgery methods outside of liquid nitrogen. We have adhered to the same philosophy that the contents of the entire book are agreed upon by all three authors.

The combined experience of the authors has allowed for a major change and increase in the number of clinical photographs in this edition. Research has led to a better understanding of the process of cell death and the effects at the periphery of the cryolesion, and these are discussed in the Introduction. The exponential growth in the utilization of cryosurgery, via insulated probes, for the treatment of solid tumors of the lung, kidney, and prostate has led to research to further our understanding of the complex events that occur when tissue is frozen.

This book is for use chiefly by dermatologists and family physicians but nurse practitioners, physician assistants, medical students, residents, and podiatrists will also find it useful. Appropriate management of many epidermal skin lesions, whether benign,
premalignant, or malignant, should take cryosurgery into consideration. This book should also be on the shelves of plastic surgeons, head and neck surgeons, and oculoplastic surgeons among others.

Graham Colver, MD
Richard Usatine, MD
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PERSONAL NOTE
In the mid-1990s I was working on my first skin surgery book and came across the first edition of *Cutaneous Cryosurgery, Principles and Clinical Practice*. I realized that I had come across a gem of a book providing great insight into the practice of cryosurgery based on the experiences and research of three talented men. It quickly became the major reference for the cryosurgery chapter of my first book *Skin Surgery: A Practical Guide*. Up to that point in my career, I did not realize the depth and breadth of clinical uses possible with cryosurgery. The clear text and excellent photographs in the book gave me the confidence to use cryosurgery as a therapeutic option for skin cancers. It also helped me learn the basic science behind cryosurgery, as well as how to treat benign and premalignant conditions with cryosurgery. The book explained the concept of freeze times, halo diameters, and thaw times better than any other article or book on the subject.

You can imagine my delight in 2013 when Robert Peden from Taylor & Francis publishing group contacted me to ask if I would consider being the lead author/editor of the fourth edition of this book. I learned that two of the three original authors were no longer going to be involved. My introduction to the remaining original author, Graham Colver, confirmed that he would stay on to provide the continuity and expertise needed to keep the book true to its original roots. Although I was involved in the development of two new books at the time that Robert Peden contacted me, I could not say no to this offer. At this point in my life I was already a serious medical writer and had six published medical books on the market, so why not add a third book to the two I was developing? I have never regretted saying yes to this offer.

The teaching of cryosurgery is near and dear to my heart. I have been teaching cryosurgery workshops since the year 2000 to family physicians at the American Academy of Family Physicians Scientific Assembly. My last skin surgery book called *Dermatologic and Cosmetic Procedures in Office Practice* had a robust chapter on cryosurgery. But a chapter is nothing like a whole book. We hope that you will find this book to be the gem that I found 20 years ago when looking for a resource to advance my skills of cryosurgery.

Richard Usatine, MD
EARLY HISTORY
Written history does not relate the first encounters of Homo sapiens with cold temperatures. But in the last ice age they would have been well aware of the risks attached to prolonged exposure to extreme cold and possibly the benefits such as storage of food produce and analgesic effects. Frostbite and hypothermia have hampered exploration and warfare throughout the ages. Military campaigns have been severely prejudiced by the freezing temperatures found at high altitude and there are well-documented examples such as Hannibal’s crossing of the Alps in 218 BC. To this day the destructive effects of unintentional exposure to cold are seen in climbers and polar explorers in the form of frostbite (Figure 1.1).

Over the last few thousand years humans have experimented with and recorded potentially beneficial outcomes of exposure to cold temperatures. The analgesic and anti-inflammatory properties were recorded by the Egyptians. A papyrus document from 3500 BC described the use of cold to reduce inflammation, particularly for fractures of the skull and trauma sustained during battle. At first glance it is not clear how ice or snow would have been available at such latitudes, but even in hot countries there were means of acquiring it. Ice could be stored, from the winter time, in ice houses where it was packed in large quantities and covered with straw or other insulating materials. Alternatively runners were sent up the mountains to acquire a fresh supply of snow or ice when it was required for medical or refreshment purposes. Ingenuity was at its foremost when methods were developed to produce ice or slush in desert areas when the extreme low temperatures at night were manipulated to freeze evaporating water. The Romans and later Iranians would dig a pit and line it with insulating straw. In it was placed a water container and the opening was covered by sun-reflecting shiny metal in the day but open to the elements at night. Evaporation at night led to ice forming around the edge of the container. This was collected and stored.

And so from very ancient times it is clear that cryotherapy, or the therapeutic use of low temperatures in medicine, was an active discipline. In the fifth century BC Hippocrates noted that cold could be used therapeutically to treat inflammation in joints and to reduce bleeding, bruising, and swelling. He also commented on the anesthetic effects of freezing. Over the next 1000 years there were attempts to move the science forward but there is scant literature on the subject. One account stands out, for it not only reiterated the known analgesic properties of cold but also emphasized the hemostatic effect. This was the wartime experience of Baron Dominique Jean Larrey, the military surgeon of Napoleon’s army. During the retreat of the armies of Napoleon from Moscow in the winter campaign of 1812, he noted that a limb could be amputated almost painlessly and with minimal hemorrhage if the part concerned was covered with ice or snow before the operation took place.

EARLY SCIENTIFIC ENDEAVOR AND CRYOGENS
Shepherd and Dawber have recorded the scientific developments in the world of subzero temperatures as applied to animal and human skin. There had been little scientific advance until 1777 when John Hunter, in London, recognized the effects of low temperature applied to animal tissues, observing local necrosis, vascular stasis, and

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**Figure 1.1** (a) Gangrene of digits after prolonged high altitude exposure. (b) Same digits seen 2 years later.
excellent healing. These three features of cryosurgery are equally pertinent today. Scientific observations had become more relevant after the invention of the thermometer in the early eighteenth century. It allowed researchers to strive to produce lower and lower temperatures and helped to pinpoint at what temperature certain biologic events took place. Studies on the controlled destruction of living tissue followed closely upon improved methods of generating colder temperatures. Important work on human tissue began with James Arnott, an English physician from Brighton, during the period 1845–1851. He developed a special device that allowed him to apply directly a mixture of various salts and crushed ice to achieve local temperatures of around −18°C. He demonstrated this equipment at the Great Exhibition of London in 1851 and enjoyed considerable acclaim. He used his method to treat advanced uterine tumors. This resulted in a reduction in pain, regression of the tumor, and control of symptoms. Arnott did not claim that his treatment was curative but did note some histological changes and suggested that solid carbon dioxide might be used to achieve even more effective cryotreatment. He also used cold for the treatment of cancer of the breast, headaches and neuralgia.

At the end of the nineteenth century Cailletet demonstrated the liquefaction of oxygen at the French Academy of Science and von Linde produced commercial quantities of liquid air. Dewar liquefied hydrogen in 1898 and soon developed the Dewar vacuum flask for the storage and transport of these fluids. This had the immediate benefit of allowing therapeutic use of cold liquids away from the laboratory. The first clinical application of liquid air was carried out by the dermatologist, Campbell White, in New York in 1899. The liquid was applied with a swab and used to treat skin lesions, including basal cell skin cancers, nevi, verrucae and lupus vulgaris. He was excited by the possibilities of this approach and stated: "I can truly say today that I believe that epithelioma, treated early in its existence by liquid nitrogen, will always be cured and that many inoperable cases can also be cured by its application.”

In 1907 Bowen and Towle reported the use of liquid air to treat pigmented hairy nevi, vascular skin lesions, and lymphangiomas. It was becoming apparent that cryotherapy of skin lesions led to better cosmetic results, with less scarring, than other treatments. Whitehouse, in 1907, developed a simple spray made from a wash bottle with two tubes through the cork and used this to treat patients with basal cell carcinomas, lupus erythematosus, and vascular nevi. He treated recurrences of basal cell carcinomas after radiotherapy and found it to be more successful than repeat radiotherapy.

Around this time Dr. William Pusey, in Chicago, popularized the use of carbon dioxide snow (or carbonic acid snow) in preference to a salt and ice mixture. It had become readily available thanks to the carbonated mineral water industry. Liquid carbon dioxide gas was supplied in steel cylinders under pressure and, when expelled into a soft material, produced a fine snow that could be molded into suitable shapes for application to the skin. One of his cases involved treating a large black hairy nevus on a young girl’s face and he made the important observations that melanocytes were particularly sensitive to cold and that there was little thickening or scarring of tissues after even deep freezing techniques. He successfully treated other nevi, warts, and lupus erythematosus. Pusey stated of carbon dioxide snow that "we have found a destructive application whose action can be accurately gauged and is therefore controllable.” Hall-Edwards of Birmingham, in 1913, described his extensive use of carbon dioxide treatments, which was all the more remarkable because he was a respected radiotherapist. He detailed many conditions in which treatment was effective but was particularly struck by its efficacy in rodent ulcers (basal cell carcinoma.)

Carbon dioxide slush, a mixture of carbon dioxide and acetone, was used extensively for acne. As the use of carbon dioxide snow became more widespread so did the range of conditions treated. De Quervain reported the successful use of carbonic snow for bladder papillomas and bladder cancers in 1917.

Carbon dioxide cryotherapy had limitations because the lowest temperatures that it recorded on the surface were around −79°C and this did not penetrate more than 2 mm into the tissue. Nevertheless it was a great step forward and found great favor up to the 1960s. Meanwhile in the 1920s liquid oxygen became available, achieving temperatures of −183°C, and this was used by Irvine and Turnacliff to treat a range of conditions including warts, lichen planus, herpes zoster, and contact dermatitis. Its failure to achieve more widespread use lay mainly with the attendant fire risks.

Between 1920 and 1945 few advances occurred in the field. There were no technological or refrigerant advances and people concentrated on the use of carbon dioxide

<p>| Table 1.1 Cryogenic Materials Used by Physicians Over the Years |
|----------------|----------------|-------|</p>
<table>
<thead>
<tr>
<th>Cryogen</th>
<th>Introduced by</th>
<th>Year</th>
</tr>
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<tbody>
<tr>
<td>Ice</td>
<td>Ancient Egyptians</td>
<td></td>
</tr>
<tr>
<td>Ice/salt mix</td>
<td>Arnott</td>
<td>1851</td>
</tr>
<tr>
<td>Ether</td>
<td>Openchowski</td>
<td>1883</td>
</tr>
<tr>
<td>Liquid air</td>
<td>White</td>
<td>1899</td>
</tr>
<tr>
<td>Solid carbon dioxide</td>
<td>Pusey</td>
<td>1907</td>
</tr>
<tr>
<td>Freon</td>
<td>Hall</td>
<td>1942</td>
</tr>
<tr>
<td>Liquid nitrogen</td>
<td>Allington</td>
<td>1950</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>Amoils</td>
<td>1964</td>
</tr>
<tr>
<td>Argon</td>
<td>Torre</td>
<td>1970</td>
</tr>
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pencils and slush to treat conditions such as acne and post-acne scarring. Other reasons for stagnation in cryosurgery were the development of radiotherapy for cancers and the increasing sophistication of excisional surgery, together with the relative safety of general anesthesia.

**The Impact of Liquid Nitrogen**

After World War II liquid nitrogen (−196°C) became widely available and Allington used this on a swab applicator to treat some benign skin lesions, including warts, keratoses, leukoplakia, hemangiomas, and keloids. Liquid nitrogen had similar properties to liquid air and oxygen but was much safer to use. Studies comparing liquid nitrogen swabs and solid carbon dioxide showed that liquid nitrogen provided more effective heat exchange, largely due to its lower boiling point. The swab method, however, has a limited freezing capacity due to its low thermal mass and the poor conductivity between swab and skin. Zacarian and Adham attempted to overcome these limitations by applying solid copper cylinders, cooled in liquid nitrogen, directly to the skin. The improved heat exchange and thermal mass enabled them to achieve freezing to a depth of 7 mm compared with the 2 mm achieved with swabs.

The next major developments in the use of cryosurgery took place in the early 1960s when various cryoprobes were developed. Cooper and Lee, in 1961, developed a liquid nitrogen (−196°C)-cooled probe that was capable of controlled freezing of tissues of the brain. The probe consisted of three concentric tubes, with the central tube carrying liquid nitrogen from a pressurized cylinder to a chamber at the probe tip where the nitrogen vaporized and gaseous nitrogen was returned via the middle channel. The outer channel consisted of vacuum insulation, which ensured that freezing took place only at the probe tip. The probe was used for neurological treatment of Parkinson’s disease and other neuromuscular disorders. In 1964, Amoils and Walker developed an improved probe in which cooling was achieved by the Joule–Thomson effect on compressed nitrous oxide, for the treatment of ophthalmologic conditions. This probe provided more rapid cooling and did not require thermal insulation. Compressed gas was supplied to the probe and expanded through a small orifice, close to the probe tip. Temperatures of −70°C could be achieved and the system was highly controllable.

Douglas Torre, the New York dermatologist, developed a liquid nitrogen spray, which could be used with a variety of tips, allowing areas of different sizes to be treated. The spray could be operated with one hand and the closed system provided by the tip gave greater cooling capacity and allowed a wider range of conditions to be treated. Dr. Zacarian developed the first handheld spray in 1968. In 1968, Michael D Bryne developed the handheld “Kryospray” unit (Figure 1.2), which was the start of Brymill, a leading company providing cryosurgery systems throughout the world. This was when the term “cryosurgery” (“cold handiwork”) was first used in practice. In the USA some key figures practiced and taught cryosurgical techniques once the cryospray was widely available – these included Zacarian, Torre, Gage, Kuflik, Graham, Lubritz, Elton, and Spiller. In the UK the inclusion of cryosurgery training in surgery workshops was popularized by Dawber and others, and with time the popularity of cryosurgery spread around the world. The range of lesions that can be treated with cryosurgery is now wide and includes many benign, premalignant, and malignant conditions.

**BIOLOGY OF CELLULAR INJURY**

The study of cryobiology can be divided into two main areas. Cell preservation covers areas such as the preservation of blood products, gametes, embryos, and organs for transplantation. Cell destruction deals with cold-induced cell and tissue damage, and this underpins the discipline of cryosurgery. Understanding the mechanisms of cell damage is important if maximum benefit is to be gained from treatments. The tissue response to cold injury, which can range from inflammation to total destruction, depends on the severity of freezing. The lesion created by freezing is
characterized by coagulation necrosis in the central region with a surrounding, relatively thin, peripheral region in which cell death is apparent. The effects are described as either early, direct or delayed, indirect. Before a detailed description is given it is important to emphasize that the effects of cryosurgery are not uniform across the treated area. In the border, or peripheral, zone the cooling rate is slow, the duration of freezing is short, the final temperature is in the range 0 to −10°C, and warming is rather rapid. In this zone, some cells are necrotic, others are apoptotic, and others may survive. Many cells close to the 0°C isotherm will survive and it is in this range that differences in cell sensitivity to freezing injury become evident. Much of the basic science in this area is “cell” science and not necessarily directly applicable to whole tissues and organs. It will be seen how delayed changes such as hypoxia then influence the damage done by the primary effects of ice formation.

Early Effects
Cooling cells to a temperature of about −10°C causes little damage because the cell is protected for a period of time from the effects of low temperature by the cell contents, mainly the cytoplasm. As the temperature falls further, ice crystals form and this has more serious consequences for cell viability. During slower freezing, crystals initially form in the extracellular spaces at temperatures of around −15°C or below. As they form from pure water, the extracellular solute concentration increases. This creates an osmotic potential and leads to net movement of water from the intracellular to the extracellular spaces. The resulting high intracellular solute concentration damages the enzyme systems and destabilizes the cell membrane.

The second major mechanism of direct cell destruction is intracellular ice formation. This effect is more dominant with rapid cooling rates and occurs once the temperature falls to between −20 to −40°C. Rapid cooling enables ice crystals to nucleate within the cell before the process of osmotic dehydration has occurred, trapping water in the cell. The crystals damage cell organelles and membranes causing cell death. The relative importance of these two mechanisms will depend on the rate of cooling. Very rapid cooling leads to intracellular ice formation and relatively slow rates of cooling cause cell damage by solute effects. Some of these effects may be mediated by the cold denaturation of proteins, whereby the three-dimensional conformation of proteins is altered by cooling and dehydration.\(^2\)

A further damaging effect to cell viability is found during the thawing process. Extracellular ice melts before intracellular ice, creating an osmotic fluid shift of water into damaged cells, causing swelling and bursting. Also as the temperature rises, recrystallization takes place, whereby smaller ice crystals fuse to form larger, more thermodynamically stable ones. The larger crystals have a physically damaging effect on the cell membrane. Slow or spontaneous thawing will maximize recrystallization, mechanical damage, and hence cell destruction. The temperature at which maximum intracellular ice crystal formation is found is between −20 and −25°C.\(^3\) When the ice crystals melt, this releases a flood of pure water, causing the cell to become hypotonic for a short period and may cause the cell to burst. The damage caused by freezing will involve more than one of these mechanisms and the predominant one will depend on the time–temperature history of the tissue. In any tissue treated with cryosurgery, the temperature experienced by different areas will vary widely. Areas adjacent to a cryoprobe will attain temperatures close to the cryogen temperature, whereas areas at the periphery of the lesion will be at temperatures closer to the freezing point or normal tissue temperature. The regions will also experience different rates of cooling and warming, depending on their distance from the probe.

Delayed Effects
The major delayed effect, which occurs some hours after cryosurgery, is vascular damage. The initial vascular response to cold is vasoconstriction followed by a cessation of blood supply as the temperature falls into the freezing range. This leads to tissue ischemia during the freezing process. As thawing takes place blood vessel endothelial cells reveal damage.\(^4\)

This leads to platelet aggregation and microthrombus formation. The vessels become occluded, resulting in further ischemia and necrosis. The effects are greater in venules where blood flow is slower. Freezing also increases the permeability of the vessel walls and causes tissue edema. These changes enhance the hypoxic environment and lead to increased cell death.

There is evidence to suggest that some cells undergo apoptosis (gene-regulated cell death) when exposed to temperatures around −6 to −10°C. This could be an important mechanism of cell death for cells at the periphery of the ice ball, although much of the research on apoptosis and low temperatures has been carried out in vitro and its importance in vivo requires further work.\(^5\)

Immunological Effects
Most of the work on this topic relates to large tumors and metastases in liver, prostate, kidney, and breast cancer, but it gives insight to the mechanisms that may be important in dermatologic practice. The mechanism is thought to be the development of sensitivity to the tissue destroyed by cryosurgery. It has been proposed that larger numbers of apoptotic cells might cause tissue protection and lead to immunosuppression whereas larger numbers of necrotic cells could serve as immunostimulators.\(^2\) More recent work has, however, shown that apoptotic cells may at times have an immunostimulatory role.\(^7\) In another study on breast
cancer and cryoablation, the rate of freezing influenced T-cell recruitment. It may be that the timing of the assessment is important such that early assessment might miss antitumor activity. Later evaluation may be more relevant. In dermatology, anecdotal clinical examples cited are the disappearance of distant viral warts after local freezing of a few lesions only and clearance of cutaneous metastases of malignant melanoma after freezing a solitary lesion. In the laboratory, evidence of this immunological protective effect for melanoma was found by Redondo et al. They showed that cryosurgery led to destruction of implanted melanoma cells in mice and led to a 70% protection effect from attempts at further implantation. When, in addition, imiquimod was applied to the cryosurgically treated site, the degree of protection rose to 90%.

CRYOSENSITIVITY AND MAXIMIZING CELL DEATH

In vivo experiments have shown great diversity in the sensitivity of different cell types to low temperatures with estimates of −4°C for melanocytes to −60°C for some cancer cells. However, gauging the lethal temperature for tissues as a whole is much more complex. To some extent it depends on the free water content so that skin, mucous membranes, and granulation tissue are cryosensitive whereas fibrous tissue, fat, and bone are relatively resistant. The sensitivity of melanocytes and resistance of connective tissue can be seen in freeze branding of cattle where the pigment has disappeared but there is no distortion of the treated area (Figure 1.3). Every facet of the freeze–thaw cycle may produce injury to the tissue, and all may be manipulated. There are five phases, and knowledge of the effect of each phase of the cycle is critical, whether the goal is complete or selective tissue destruction:

1. The rate of cooling varies throughout the tissue and only the part in direct contact with the cryogen or probe freezes at maximum rate. Slow cooling tends to produce extracellular ice, which is less destructive except perhaps in highly cellular tissues. However, some intracellular ice does form even at slow cooling rates. The cooling rate at the periphery slows as the volume of frozen tissue expands until no further expansion can occur. The cooling rate is not the most important factor.

2. The lethal temperature for a tissue is different from the cell sensitivity because secondary changes of vascular stasis and hypoxia have a major impact on survival. It is important, when dealing with neoplasms, to achieve maximum cell death and temperatures of −20°C may not be adequate. Currently the consensus is that temperatures of −40°C are probably sufficient for direct killing but the secondary hypoxic changes may allow for successful cell death at the warmer, more distant parts of the tumor.

3. The practical application of the freeze–thaw cycle is discussed elsewhere but one of the measurements is the length of time that the tissue is maintained in the frozen state. Some authors pay little regard to this because they are using monitoring and aim to achieve only a certain temperature. However, experiments have shown that prolongation of the frozen state increases the destructive effect. This effect may be unimportant at temperatures colder than −50°C.

4. Slow thawing enhances the destructive effect considerably and should be as slow as possible. Experience with frostbite and cryopreservation has shown that rapid warming increases the chance of cell survival.

5. If a second freezing cycle is undertaken, the ice formation upon thawing is even greater than after the first cycle, so repeat cycles are thought to be more effective at tumor destruction. The interval between cycles has received little attention but if time permitted it is likely that waiting for 10 min or more would be more effective. In summary, the optimal technique for the destruction of tumors is fast freezing of the tissue to an appropriate low temperature, slow thawing, and repetition of the freeze–thaw cycle.

WOUND HEALING AFTER CRYOSURGERY

The pattern of healing reflects the cryosensitivity of the tissues treated. Minor freezing injury, such as that produced by short exposure to a temperature of about −10°C, is likely to result in little tissue loss and will heal quickly. Lower temperatures are associated with degrees of tissue loss, depending on the temperature achieved and the time frame. After the production of coagulation necrosis there begins an infiltration of neutrophils, then mononuclear cells, starting at the wound edge and stimulated by the mediators of inflammation. The underlying
collagen is relatively resistant to damage\textsuperscript{14} as seen in the electron micrograph (Figure 1.4), so there remains a scaffold around which healing can take place. Granulation tissue forms, fibroblasts differentiate into myofibroblasts, and gradually normal vasculature is seen together with epithelialization.\textsuperscript{15} Direct observation of healing using reflectance confocal microscopy has allowed researchers to visualize the process from the earliest edema and vasodilation through to the healing phase with finger-like projections into the wound bed.\textsuperscript{16}

Clinical wound healing after cryosurgery is slow. The diseased part has been destroyed in situ and it takes time to remove all the necrotic tissue whether by slough or resorption, so healing is slow in comparison to excision and primary suture of a wound. Immediately after freezing, there is erythema and edema, often with blister formation. As necrosis sets in, the surface ulcerates and a purulent discharge occurs. This stage may last for weeks with an eschar developing, only to be shed and replaced by another as the wound gradually stabilizes. The final scar is often pale with slight atrophy but has a softer, almost normal consistency and texture. This advantageous feature of cold-induced scars is in contrast to those induced by hot thermal burns. Work on rat skin demonstrated much more collagen production in hot- compared with cold-induced burns.\textsuperscript{17}

**PHYSICS**

Research into the biology and physics of cutaneous cryosurgery has led to important areas of greater understanding but has its limitations. Experimental cryosurgery allows for control of most parameters and precise measurement. However, in vivo there are factors of infinite variability such as room and skin temperature, skin thickness, and blood flow. Tissue below the surface and at the periphery cools at a slower rate than those elements in direct contact with the refrigerant, and ice crystal formation has different effects in living tissue compared with cell suspensions.

**Shape of the Ice Ball**

The shape of the expanding ice ball is important in our understanding of tissue destruction. To the novice it may appear that a visible, spreading icefield is represented, below the surface, by a similar area of ice formation. This is far from the truth. Rather than an iceberg effect, in which a greater part of the damage would be seen below the surface, there is instead a roughly hemispheric ice ball. This may not be important in the treatment of entirely superficial lesions but becomes important when treating deeper disease. The importance of this can be demonstrated by considering an infiltrative basal cell carcinoma. Its growth pattern may produce deep extensions that spread laterally beyond the visible lateral margin, whereas the depth of a therapeutic ice ball is less than the diameter of its visible lateral margin. The shape of the ice ball and the isotherms (lines linking all points of equal temperature) within it vary according to the shape and size of the probe (or spray), the rapidity of freezing, and the pressure exerted on the surface. A pointed probe, pressed lightly on the surface, produces a roughly hemispheric ice ball whereas a disc-shaped probe produces a flatter and less deep ice front. Sprays, when used with the spot freeze method, are more akin to the pointed probe initially producing a hemispheric shape. For a small increase in lateral spread there is a larger increase in depth, especially at the center. During the early stage of freezing the lateral spread of ice from the edge of the probe or cone is approximately equal to the depth of freeze (Figure 1.5). For this reason large lesions should generally not be treated with a single probe or spray application. It may not be possible to achieve sufficient lateral spread and, even if it were possible, it may be associated with greater deep destruction than is needed. Multiple, overlapping applications of the probe or spray are usually a better option. Another option would be a spray paint or spiral application of a cryospray (see Chapter 5).

![Figure 1.5 Early on the lateral ice spread is similar to the depth of freeze.](image)
Our knowledge of icefields comes from observation and measurement. The simplest model to observe the shape of the ice ball induced by various refrigerants is a gelatin block (Figure 1.6). When viewed from the side, the spreading ice ball can be seen clearly. These observations cannot be fully extrapolated to living tissues, principally because a blood supply has a profound effect on the spread of cold. Studies designed to elucidate the interrelationship of surface temperature, lateral spread, and depth of freeze have relied on thermocouple devices to monitor temperature.

When a tissue is cooled, the rate of heat exchange depends on water content, blood supply, thermal conductivity of the tissue, rate of freeze, and temperature of the refrigerant, among other variables. There are no formulae by which cell death can be predicted and further study is still required to produce ideal treatment protocols for the reproducible, consistent destruction of benign and malignant tumors. Much of the information accrued to date, which has led to the present state of the art, comes from experimental work on, for example, pigskin, with temperature monitoring and histological assessment. There are differences between the effects of a probe and a spray and between an open compared with a funneled spray technique (as with a neoprene cone). However, the important data that have led to the modern approach to cryosurgical practice can be summarized as follows:

- An open spray gives the most rapid drop in temperature. It will freeze to a greater depth than a closed probe unless pressure is exerted on the probe. However, the shape of the ice ball is approximately similar for the two methods. Up to depths of about 6 mm the contour of the ice ball is rounded but below this it becomes more triangular in shape at 1 min (Figure 1.7). The isotherms lie closer together when the rate of freezing is rapid.

- Assessment of the actual temperature at varying depths of the skin using an open spray gives some confidence as to the killing ability of the treatment protocol. Work by Dawber and Shepherd using live pigskin with thermocouple monitoring and a surface icefield 2 cm in diameter, maintained for 30 seconds, found temperatures < −40°C at the periphery and < −50°C at least 5 mm below the surface (Figure 1.8).

![Figure 1.6](image)

**Figure 1.6** A gelatin block (gel pad) is a simple model to observe the shape of the ice ball induced by various refrigerants. When viewed from the side, the spreading ice ball can be seen clearly. In this case, a bent tip extension has sprayed liquid nitrogen on the gel for 60 seconds, forming a hemispheric ice ball.

![Figure 1.7](image)

**Figure 1.7** Evolution of ice ball with continuous freezing. Note how the shape starts out as hemispheric and becomes more triangular with greater depth in the center at 1 min. (Adapted from Breitbart EW. Cryosurgery in the treatment of cutaneous malignant melanoma. Clin Dermatol 1990;8:96–100.)
CRYOSURGERY IN OTHER SPECIALTIES

Improving technology has helped to develop the dermatologic applications of cryosurgery, but in other specialties the technology has leapt forward even more. The practical applications for various anatomic sites have been reviewed by Gage et al. Using ultrasound intraoperatively to monitor the accurate placement of cryoprobes, and the freezing process developed in the 1990s, allowed use of cryosurgery deep in visceral tissues. Closed cryoprobe systems have utilized multiple cryoprobes that are controlled using a computer microprocessor to allow fine-tuned control of the freezing process. Long, thin probes can be inserted deep into the prostate, lung, or kidney with percutaneous access. Commonly used cryogens are pressurized, supercooled liquid nitrogen and argon gas. Liquid nitrogen systems supercool the cryogen and then force it under pressure through the cryoprobes. In contrast, argon gas-based systems operate by supplying high-pressure gas to the cryoprobes through a Joule–Thompson port, resulting in ablative temperatures.

It is now considered useful for the destruction of hepatocellular carcinoma, some renal tumors, and tumors in lung, prostate, pancreas, rectum, breast, brain, and oral cavity.

It is interesting to read the assessment of cryosurgical practice across many disciplines by Korpan. He believes that, in the future, cryosurgical techniques will be complementary to conventional surgery but also in some situations superior to it by nature of either the disease process or the condition of the patient. He reminds us that it is inexpensive and quick, and can be performed as an outpatient. However, he cautions that the apparent simplicity of the technique may lead some physicians, especially those with little experience, to misinterpret the results.

MONITORING METHODS

The newest method to monitor cryosurgery involves the use of infrared sensing available on the Brymill Cry-Ac TrackerCam device. This is a non-invasive method of monitoring surface temperature and is discussed in Chapter 3. This method has been calibrated and tested with thermocouple technology for accuracy of measurement (Figure 1.9).

Figure 1.9 Using thermocouple technology and infrared sensors to measure temperatures during freezing with liquid nitrogen.
less experience, to deviate from the protocol and to blame poor results on the method rather than questioning their skill level or technical knowledge. This warning should be also heeded by dermatologists.

REFERENCES

2 Use in clinical practice

INDICATIONS
Cryosurgery is a therapeutic technique used on the skin by dermatologists, family physicians, nurses, podiatrists, and many other clinicians. All clinicians who deal with skin disease should be aware of the treatment options available and should be able to practice with a wide “surgical repertoire.” Then the informed patient can be offered the most appropriate treatment. Cryosurgery is one of the options and the decision whether to use it will depend on characteristics of the lesion, patient-specific factors, and operator experience. When specific skin conditions are discussed in Chapters 8–10 it is not assumed that cryosurgery is the only option, but that it is appropriate and will achieve the desired outcome. In some cases, eg seborrheic keratosis, curettage or shave excisions may give equally good results both cosmetically and for cure rates. In other cases, there may be a specific reason to avoid more invasive techniques even if cryosurgery does not give an ideal outcome. When dealing with malignant lesions excisional surgery may produce the highest cure rates but cryosurgery still has a role for less aggressive tumors and in a palliative setting. It is paramount that the patient is aware of the benefits and risks and the comparative cure rates (where known) for different therapeutic options. Side effects may sway an individual to opt for one modality over another.

Whereas most individuals understand the concept of excisional surgery, they are less likely to readily comprehend what is intended with cryosurgery. Treatment that produces localized frostbite, leading to delayed inflammation, swelling, and necrosis, is not immediately understood by many patients. There can even be confusion about the word freezing because some people equate this with the numbing effect of local anesthetic.

Modes of Application
Freezing refrigerants are now so portable that cryotherapy is often the easiest treatment to offer. It is literally at hand in the office and can be applied without the patient having to move.

The choice of spray, probe, or forceps may be determined by the nature of the lesion. Compressible lesions such as angiomas are best treated by a probe, so that pressure can be exerted to partially empty the vessels at the time of freezing. Forceps application is particularly suited to polypoid lesions but is also very good for anxious patients for whom the sound and feel of the spray, especially when directed to the face, causes concern. Angulated (bent) spray tips are ideal for work on the undersurface of the chin or around the canthus. The rate at which refrigerant is delivered to the skin surface can be adjusted greatly by use of various diameter spray tips.

Epidermal Lesions
Generally, cryosurgery is best suited to the management of epidermal lesions such as keratoses. Indeed it is hard to imagine clinical practice without ready access to a liquid nitrogen source. It is a standard approach for viral warts, actinic keratosis, and molluscum contagiosum. However, keratin is a good insulator and markedly hyperkeratotic lesions will not respond so well. Bowen's disease may be amenable to treatment, but once the disease has spread down the hair shaft it is a less effective method.

Non-epidermal Lesions
Freeze times are generally longer for lesions arising in the dermis or the appendages.

- It can be very effective for acrochordons and may shrink or cure such lesions as angiomas, chondrodermatitis, labial mucoid cysts, and sebaceous hyperplasia. There are many other indications discussed in detail in later chapters. Inevitably longer freeze times will result in increased morbidity and the destructive effects of liquid nitrogen should not be underestimated.

CONTRAINDICATIONS

Operator Factors
Cryosurgery is a destructive treatment, which can do great harm if used inappropriately. The ease with which it can be obtained leads many to believe that it is a therapy that is simple and easy to learn. Inexperienced clinicians should be just as wary about the use of liquid nitrogen as they would be about excisional surgery. Adequate training will help to avoid the complications discussed in Chapter 11.

Inappropriate Lesions
There are no absolute contraindications to cryosurgery but some skin lesions are better dealt with in other ways. It would be inappropriate to freeze a suspected invasive malignant melanoma because the evidence and standards of care support excisional surgery. More generally, cryosurgery should not be used without previous histologic confirmation of a diagnosis that may be malignant.

Cryosurgery should rarely if ever be used to treat morpheiform, infiltrative, micronodular, or recurrent basal cell carcinoma. Cryosurgery should not be used to treat poorly differentiated or recurrent squamous cell carcinoma.