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CRYOTHERAPY

AN INDISPENSABLE TOOL IN DERMATOLOGY PRACTICE

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Foreword
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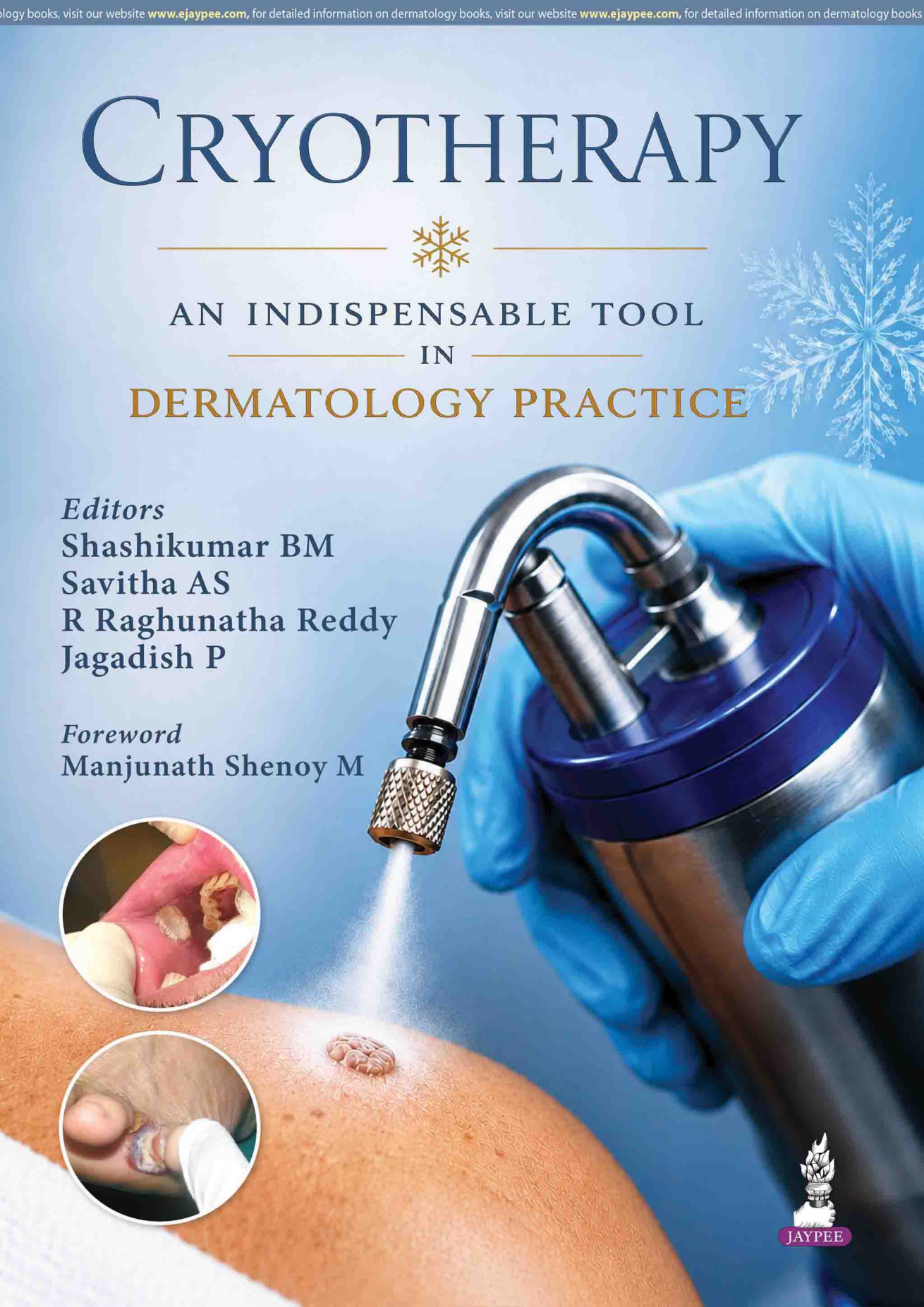

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3

Cryogen

Shashikumar BM, Savitha AS

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KEY POINTS

- Liquid nitrogen is the gold-standard cryogen in dermatology.
- The effectiveness of a cryogen depends on its heat extraction capacity.
- Lower boiling points produce deeper and more effective freezing.
- Different cryogens have specific indications and limitations.
- Safe storage, transport, and handling are essential for cryogen use.

INTRODUCTION

In dermatological surgery, a cryogen is defined as a substance used to produce extremely low temperatures for the purpose of tissue destruction. The term "cryogen" is Greek in origin, where *cryo*, meaning "very cold", and *gen*, meaning "to produce". The clinical efficacy of a cryogen is determined not just by its absolute temperature, but by its capacity to extract heat from the skin.

This heat extraction is most potent during a phase change (liquid to gas), a high-energy thermodynamic event. While the boiling point is a critical factor, effective freezing is also governed by interface heat transfer; occasionally, rapid boiling can create an insulating vapor layer (the Leidenfrost effect) that may paradoxically reduce heat flux.[1]

CHARACTERISTICS OF AN IDEAL CRYOGEN

- *Low boiling point:* To ensure a significant thermal gradient.
- *High latent heat:* To maximize the energy extracted from tissue during evaporation.
- *Safety profile:* Must be nontoxic (no toxic fumes) and nonflammable.
- *Logistics:* Must be cost-effective, storable, and easy to transport.

Liquid Nitrogen

Liquid nitrogen is the gold standard cryogen in dermatology. It is versatile, easily delivered via open spray or contact probes, and satisfies nearly all ideal criteria.[2] While N_2O and argon occupy specialized niches and CO_2 has historical roles.

Liquid nitrogen (LN_2) is the most widely used cryogen in cryosurgery.

Physical and Biological Properties

- *Temperature*: LN_2 has a boiling point of approximately −196°C (77 K) at atmospheric pressure.[3] This enables it to create a massive thermal gradient when applied to skin.

- *Expansion ratio:* Nitrogen expands at a ratio of 1:694 when transitioning from liquid to gas at 20°C. This high expansion ratio can generate tremendous force if the liquid is vaporized in an enclosed space without proper pressure relief.[4]
- *Inert nature:* It is a colorless, odorless, tasteless, and chemically inert substance. It does not produce toxic fumes during vaporization, though it can act as an asphyxiant in poorly ventilated areas by displacing oxygen.[4]
- *Tissue destruction:* It can achieve a temperature of –20°C to –30°C required for benign lesions and –50°C for treating malignancies.[2,5] LN_2 is uniquely capable of reaching temperatures between –25°C and –50°C within just 30 seconds.[6] A key reason why colder endpoints matter is that lethal injury correlates with temperatures where intracellular ice formation becomes likely, along with osmotic and membrane injury during freezing and thawing. An intracellular ice is almost always lethal to cells. Heterogeneous nucleation (ice formation assisted by membranes or impurities) can occur at –15°C.[1,7] To reach this threshold, rapid cooling (typically 50–100°C/min) is desirable to trap water inside the cell before it can osmotically dehydrate into the extracellular space. LN_2 spray provides this "flash freeze" effect, inducing the rapid freeze-thaw cycles that kill cancer cells most effectively.[8,9]

Alternative cryogens like nitrous oxide (N_2O) or solidified carbon dioxide (CO_2) cannot achieve the same depth and intensity of cold. These agents often fail to reach the surely lethal isotherms required for invasive pathologies and are generally reserved for benign lesions.[6] Rapid cooling with LN_2 induces a significant release of inflammatory mediators and preserves antigens on dead malignant cells to trigger a host-immune response.[2]

Storage and Handling

Liquid nitrogen is typically obtained through supplier delivery into insulated storage containers, commonly Dewar-based systems **(Fig. 1)**. They are heavily insulated, and vacuum-jacketed metal containers. These tanks range in size from 4 to 50 L and can store the cryogen for up to 2 months, but the holding time varies with container design, insulation integrity, and frequency of opening. LN_2 is continuously lost by boil-off (evaporation) even in well-insulated vessels.[6]

From the container LN_2 is filled into handheld cryoguns (300–500 mL), which provides usable cryogen for a day **(Fig. 2)**.

In clinical supply chains, medical grade nitrogen is generally tied to pharmacopeial/medical gas specifications and documented quality systems, including defined impurity limits and traceability. Official medical standards for cryogens are set by compendia such as the United States Pharmacopeia (USP), which provides monographs ensuring the identity, strength, and purity of medical substances. A critical requirement for cryosurgical nitrogen is that it should be moisture-free. The presence of water vapor or impurities in the gas supply can lead to equipment clogs, tip blockages, and internal corrosion.[10]



FIG. 1: Dewar.

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FIG. 2: Cryogun.

OTHER CRYOGENS

Closed-system Agents

Although liquid nitrogen spray is the standard for many cutaneous indications, closed-system cryosurgery is important when it comes to controlled contact cooling or if freezing needs to be delivered through slender probes. These systems typically operate through the Joule–Thomson effect, where high-pressure gas is expanded through a restricted orifice to produce rapid cooling.[11]

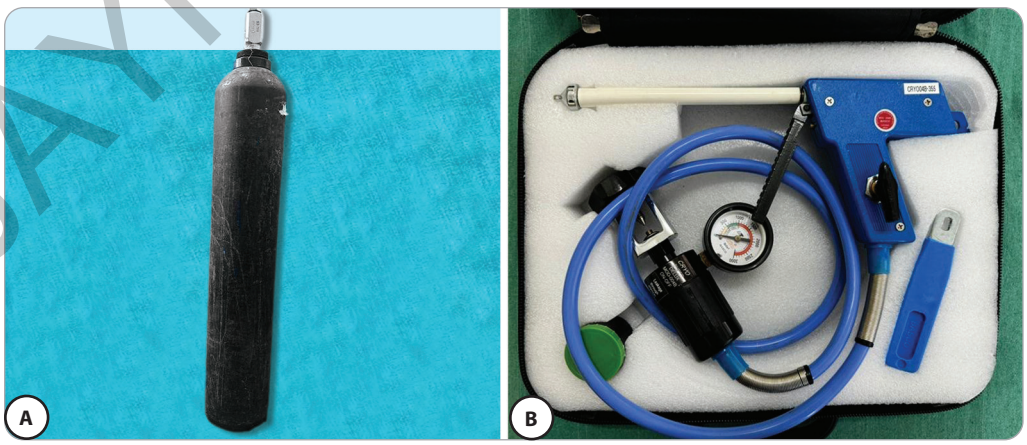
Nitrous Oxide

Nitrous oxide has been a mainstay in closed-system cryosurgery particularly for benign pathologies. It is a nonflammable gas with a boiling point of –88.5°C and –89.5°C.[12] N_2O is stored under pressure of 700 lb/in^2 (50 kg/cm^2). As it exits the restricted aperture, its pressure drops rapidly to approximately 20 lb/in^2 (1.4 kg/cm^2), inducing a cooling effect that lowers the probe tip temperature to a range of –40°C to –70°C **(Figs. 3A and B)**.[6,13]

Due to its lesser cryogenic effect compared to liquid nitrogen, N_2O is generally reserved for benign lesions. It is particularly favored for mucosal areas, such as the oral cavity or lips, because the probe tip thaws quickly once the gas flow stops, allowing for safe detachment without tearing delicate membranes. It also results in fewer side effects, such as intense pain or permanent pigmentary changes.[6] Even though closed systems reduce free cryogen spill, occupational exposure to N_2O can occur especially in a poorly ventilated settings, so good ventilation is important.

CryoPen

CryoPen is a single-use handheld device which utilizes N_2O contained within a preloaded internal cartridge (7.5 g/10 mL). The device is capable of achieving a rapid freeze within just 3 seconds with a tip temperature of –88.5°C. It can deliver approximately 15–20 freezing events per unit. The handheld design offers several clinical benefits over traditional



FIGS. 3A AND B: (A) Nitrous oxide cylinder and (B) nitrous oxide gun.

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apparatus such as more freedom of movement, no clogged or kinked capillary tubes and ease of use. This device includes a gas exhaust tube that can be connected to a scavenging system or if it is not available, a well-ventilated room is recommended. But, the available published data is an ophthalmic in vivo porcine model assessing cryopexy, dermatological studies are lacking. These studies effectively demonstrate the biological effects of cryopexy, such as the severe atrophy and thinning of target layers, and confirm the usability and effectiveness of the device **(Fig. 4)**.[14]

Argon Gas

Modern cryoablation systems, mainly in interventional oncology, commonly use high-pressure argon as the cooling gas.[11] It has a boiling point of –185.7°C to –186°C, which is nearly as cold as liquid nitrogen. Argon is the preferred agent for deep organ destruction (e.g., prostate and breast cancers). Liquid nitrogen is often impractical for use in the thin tubing or narrow needles required for these procedures because it tends to crystallize and obstruct its own flow.[9] But, requirement of specialized equipment, higher costs, and strict procedural safety protocols consistent with high-pressure gas systems remain as limitations for this method.

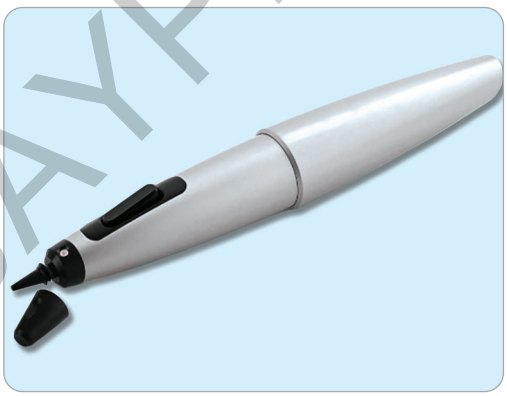

FIG. 4: CryoPen.

An advantage of Joule–Thomson systems (particularly with argon) is the ability to integrate helium gas for controlled thawing. Helium has a negative Joule–Thomson coefficient at room temperature, means it heats up upon expansion resulting in active thawing. This provides precise control over the freeze-thaw cycle and allows for the rapid release of a probe tip from frozen tissue.[15]

Historical Agents

Carbon Dioxide

Dry ice or solidified carbon dioxide or CO_2 snow was first introduced to clinical practice in 1900s. It serves as a significant historical precursor to modern techniques.[16] Unlike liquid nitrogen, which boils, solidified CO_2 sublimes directly from a solid to gas at 1 atmosphere of pressure. It maintains a stable temperature of approximately –78.5°C to –79°C.[1] When liquid CO_2 is released from a pressurized cylinder into the air, it produces a fine snow that is easily compressed into solid shapes or sticks for clinical application. These solid sticks allow for direct contact cooling of various skin lesions, including warts and epitheliomas.[17] In practice, CO_2 can be applied using the dipstick method. This involves creating a slush by mixing the agent into a workable consistency or using it to cool a cotton bud. The bud is then applied firmly to the lesion until a halo of ice forms. While this method is cost-effective and requires no specialized spray equipment, it is less effective than liquid nitrogen.[18]

Liquid Oxygen

Liquid oxygen was utilized in dermatological practice between the 1920s and 1940s. However, its use has been strictly discontinued due to extreme hazards. Liquid oxygen is a pale blue liquid with a boiling point of –183°C.[19] It is a powerful oxidizer that can

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cause or intensely amplify fires. It will likely spontaneously explode if spilled on or mixed with any hydrocarbon.

PORTABLE AND OVER-THE-COUNTER HYDROCARBON MIXTURES

Dimethyl Ether–Propane

Dimethyl ether–propane (DMEP) mixtures are commonly used in portable/over-the-counter freezing devices for benign cutaneous lesions. These devices typically cool by evaporative cooling during rapid expansion of compressed solvents and are flammable. In a randomized controlled trial comparing DMEP spray (low freezing, –59°C) with LN_2 (intense freezing, –196°C) for benign cutaneous lesions, DMEP was evaluated as a less intense freezing modality.[20,21]

Hydrozid

Hydrozid is a cryosurgery device using norflurane. It is portable and aerosol-based. It consists of a 200 mL canister with a valve and spray head, weighing approximately 252 g, utilizing focused spot-freeze technique that help direct the spray precisely to the lesion while protecting the surrounding normal skin. The device is documented to deliver stable temperatures below –50°C to the treatment area. Norflurane is described as nontoxic, nonflammable, and has no propensity to cause ozone depletion in the atmosphere.

A phase IV clinical study conducted in four centers across India evaluated the device for superficial epidermal and dermal lesions such as wart, seborrheic keratosis, acrochordons, and molluscum contagiosum, lentigo, and actinic keratosis. The paper reports complete lesion disappearance in 47.4% of treated lesions and >50% diameter reduction in 79.38%, with pain typically mild to moderate and most pain resolving by 24 hours.[22] **Table 1** summarizes the comparison of different cryogens.

Global Warming Potential

Liquid nitrogen has near-zero *direct* global warming potential (GWP), but its lifecycle carbon footprint depends on the energy used for liquefaction. N_2O is recognized as a potent greenhouse gas. The widely used IPCC AR6 100-year GWP is 273. The industrial gas industry has established specific regulatory guides to address the environmental impacts of N_2O plants. Regulatory bodies increasingly recommend that clinicians work with suppliers to choose refrigerants with lower GWP or no ozone-depleting potential wherever possible.[23]

TABLE 1: Comparison of different cryogens.

Cryogen	*Boiling point*	*Mechanism*	*Probe tip temperature*	*Primary use*
Nitrous oxide	–89.5°C	Joule–Thomson	–40°C to –70°C	Benign lesions; oral mucosa
Argon gas	–186°C	Joule–Thomson	<–125°C to –180°C	Deep organ cryoablation
Carbon dioxide	–78.5°C (sublimes)	Contact	–78°C	Historical use, benign lesions, "slush" method
DMEP/ Hydrocarbon	–59°C	Evaporative	–59°C	OTC devices, very superficial benign lesions

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Transportation Regulations and Practical Safety (Liquid Nitrogen)

It is advised that LN_2 dewars should be moved in a service elevator when possible and passengers should not ride with the Dewar because of asphyxiation risk if a spill occurs in a confined space. Containers must always be carried on the open tray of a truck or utility vehicle. It should never be stored or transported in the closed cabin or trunk of a car. Vessels must be secured in an upright position and protected against tipping or movement during transit.

The most catastrophic risk in handling cryogens is the rapid expansion ratio of LN_2, which is approximately 1:694 at 20°C. Every cryogenic system and segment of piping must have its own pressure relief mechanism to prevent an explosion if the liquid is trapped and warms up. The extreme cold of LN_2 can condense moisture from the air, forming ice plugs in vent lines. If a vent is obstructed by ice, the resulting pressure build-up can cause a container to fail catastrophically.

CRYO-DAYS

Because LN_2 is continuously lost by boil-off/evaporation, losses in standard vacuum vessels typically ranging from 2 to 5% per day depending on insulation quality, and frequency of opening or transfer. Wastage can be reduced by batching cryotherapy sessions (cryo-days) and minimizing the number of Dewar openings and transfers.[24]

CRYOGENIC FLUID HAZARDS

Skin contact with cryogenic liquids or uninsulated materials at cryogenic temperatures induces rapid localized damage known as cryogenic burns. Direct contact initially causes a feeling of numbness and intense cold. Pain typically manifests only once the tissue begins to thaw significantly.

Contact with super-cooled materials can instantly freeze the moisture on the skin surface, causing the skin to stick to the cold material. If the operator attempts to pull away, the frozen bridge can cause the flesh to tear.

Personal Protective Equipment Standards

Personal Protective Equipment (PPE) is mandatory whenever handling cryogenic materials to mitigate the risks of splashing and accidental contact. Selection of PPE is based on the volume of cryogen and the task.

Nonporous cryogenic gloves: Gloves must be made of nonporous material. Woven mesh or standard heat-resistant gloves, are prohibited because they can trap and pool liquid cryogen against the skin, resulting in a deeper and more severe burn than a simple splash. Gloves should be loose-fitting to ensure they can be quickly discarded if liquid nitrogen accidentally enters the cuff.

Face shields and eye protection: Face shield is required for moderate-to-large volume transfers to avoid splash injury. It will provide front and side coverage to protect the head. Safety glasses or goggles must be worn underneath along with it. The shield should have a sloped top surface to direct splashes away from the head and prevent liquid from getting behind the shield from above.

Aprons and body protection: Heavy-duty aprons are recommended when pouring large quantities of cryogen or when retrieving samples from bulk storage dewars. Operators must wear long-sleeved shirts or laboratory coats and cuffless trousers. Pants with cuffs can trap liquid nitrogen in the fold against the skin. Shoes must be closed-toe and made of nonperforated materials like leather.[24]

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CONCLUSION

Liquid nitrogen remains the cryogen of choice in modern dermatology due to its unique combination of thermodynamic efficiency, clinical versatility, and cost-effectiveness. While alternative agents such as N_2O and argon have established essential roles in closed-system Joule–Thomson probes for benign or internal pathologies. Nowadays, portable systems such as CryoPen, which is a N_2O-based device and hydrozid has emerged as an office-friendly devices.

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Shashikumar BM is a dermatologist, academician, author, and teacher with extensive experience in clinical and procedural dermatology. His areas of interest include cryotherapy, dermatosurgery, trichology, and clinical dermatology. He is the co-editor of the IADVL Textbook and has contributed significantly to dermatology education, research, and academic publishing. He was also among the editors of one of the first Indian textbooks dedicated to tattoos and tattoo-related dermatological conditions.



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R Raghunatha Reddy is a respected dermatologist, teacher, and clinician with rich experience in dermatology and procedural interventions. His areas of expertise include cryotherapy, dermatosurgery, and clinical dermatology. He has actively contributed to postgraduate training, scientific publications, and academic activities. He was also among the editors of one of the earliest Indian textbooks on tattoos and their dermatological implications.



Jagadish P is a distinguished clinical dermatologist with extensive experience in the diagnosis and management of a wide spectrum of dermatological disorders. Known for his strong clinical acumen and patient-centered approach, he has built a reputation for excellence in clinical dermatology and evidence-based practice. His vast clinical experience and practical insights have enriched this textbook, bringing valuable real-world perspectives to the understanding and application of cryotherapy in dermatology.

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