# Cryosurgery
## in Office Dermatology.
## An Update

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**Abstract**

During the past decades, Cryosurgery gained in practicability for office dermatology. Low temperatures are produced by thermoelectric cooling, gas decompression, or evaporation of fluid coolants. ***Thermoelectric cooling*** uses the Peltier-effect. Advantage: independence of coolants, except electricity. Drawback: limited refrigerating range, up to 241-231 K, -32°, maximal -42°C. - ***Gas decompression*** uses the Joule-Thomson effect. Important are $CO_2$ and $N_2O$. *$CO_2$* is applied directly, as a snow produced by rapid decompression from the cylinder into a bag, pressed to pegs or moulded to a paste with acetone. Advantages: low prize, simple handling. Disadvantage: weight and volume of the devices. Temperature: 194,7 K = -78,5°C.- *$N_2O$* is used with closed or open ("liquid freezing") probes. Closed probes are suitable for lips, oral or genital skin. Advantage: less adherence to moist surfaces. Disadvantages: weight of gas cylinders. – New are small devices with 15 g gas cartridges, fit for a pocket. Supply and storage are simple. Temperature: 184,4 K, or -88,8°C.- ***Evaporating coolants:*** $N_2$ is used in closed probes and in spray devices. Closed probes allow to use pressure, to avoid contact of the coolant with tissues, and inhalation. Aseptic subsurface working is possible. Spray probes allow to treat crusty, keratotic, uneven surfaces without contact. Both techniques are effective, the devices portable. Disadvantage: expensive storage. Temperature: 77,4 K =. -196°C. - ***The tissue reaction*** begins with a "physical phase", followed by a "vascular", and a late "immunologic" phase. The reaction is modified by minimal temperature, duration and rapidity of freezing or thawing, anatomical situation, tissue sensitivity. ***Aims and results*****:** Destruction requires rapid freezing and slow thawing. Two cycles are necessary. Selective destruction of tissue components is possible, using their different sensitivity. For example, pigment cells are very vulnerable, the reason for long lasting depigmentation. This is negligible in Caucasians, troublesome sometimes in tanned or pigmented patients. Cryothrombosis is helpful in the treatment of angiomas. Destruction of vascular and cellular components initiates the tissue remodeling in keloids, hypertrophic scars, granulomas. In skin tuberculosis, immunologic mechanisms following partial destruction may contribute to accelerated healing. In chronic lupus erythematodes, immune complexes are removed from the junction. In actinic keratoses or Bowen´s disease, ablation of the epidermis is the main principle. A broad range of indications requires a variety of therapeutic modalities.

Cryosurgery includes the medical applications of freezing techniques to destruction, ablation or renewal of pathologic tissues or tissue components[1-11]. Low temperatures are produced by several different means: thermoelectric cooling, gas decompression, and evaporation of fluid coolants.

**Cooling Techniques**

***Thermoelectric cooling*** uses the Peltier-effect: Consumption of energy within connections of two metals with different "thermoelectric powers" at various temperatures in electric circuits. The main advantage of semiconductor cooling elements in closed metal probes is their independence of gas or other coolant logistics, except electricity. The main drawback is the very limited refrigerating range, up to 241-231 K, respective -32° to -42°C.

***Gas decompression*** cools down by the Joule-Thomson effect. Two gases are practically important: Carbon dioxide (CO2) and nitrous oxide (N2O) [4-11].

***$CO_2$*** is applied directly, without probes. CO2-snow is produced by rapid decompression of the gas from the cylinder into a leather bag. The snow is pressed to pegs or moulded to a soft paste with a small amount of acetone, handled by a stick pad, applied directly onto the lesion. Main advantages are the relatively low prize and simple handling of CO2. Main disadvantage is the weight and volume of the devices necessary immediately beside the patient. The minimal attainable temperature is 194,7 K respective -78,5°C.

***$N_2O$*** is used as well in probes with closed therapeutic surface as in open probes ("liquid freezing"). Closed probes are suitable especially for lesions of the lips, the oral mucosa, or genital skin. They have a lower risk of inconvenient adherence to moist surfaces as probes with liquid nitrogen, even if applied with pressure[4,7,10]. Disadvantages are, as with CO2, weight and mass of the devices, especially the gas cylinders. – Therapy of lesions with small extent, however, is also possible with little open ("Liquid freezing"[12]) or closed probes ("Cryoalfa-Kontakt®"), and small 16g gas cartridges, comparable to the 12g cartridges used in cream siphons. Formerly, we simply used siphon cartridges, but they were not clean enough and particles blocked the probes. New special cartridges with filters contain sterile gas (Cryoswiss, Basel, Switzerland). Supply and storage of the tiny cartridges are simple. The complete device is fit for a shirt pocket, for the visiting Dermatologist far from the office. A possible drawback is the price of relatively great amounts of cartridges. The minimal temperature attainable by expansion of $N_2O$ is184,4 K or -88,8°C.

*Other liquid gas coolants* with minor cooling effects are the freons® or frigens®, especially dichlorodifluoromethane, Freon 12, (-29,8°C) or Chlorodifluoromethane, Freon 22, (-40,8°C) and mixtures of liquid gases, as dimethylether, propan and isobutan, for example, in the Histofreezer®, (-55°C). With regard to some substances, users must take into consideration environmental toxicity or inflammability.

***Evaporating liquid coolants*** represent an ancient principle (Moist compresses, for example)-.

***N2*** is the only important substance of this type and the most important cryogenic substance at all [4-11]. In cryosurgery, we use liquid nitrogen ($N_2$) in closed probes as well as in open spray devices. Closed probes allow, for example, to use pressure, to treat precisely a small lesion, to avoid contact of the coolant with the tissue, to avoid inhalation or damage by coolant missing the target. Aseptic subsurface working is possible. Spray probes, however, allow to treat lesions with crusty, keratotic, uneven surfaces without contact between probe and lesion. The ideal spray distance is ca. 1cm. Both techniques are the most important ones in Cryosurgery because of their effectiveness, relatively small portable devices, safe and simple handling. The main disadvantage, however, is the expensive supply and storage of this coolant. The minimal temperature attainable with liquid nitrogen is 77,4 K respective -196°C.

**Mechanisms and Reactions**

***Physical stage*:** The tissue reaction begins with direct cell destruction by rapid intracellular growth of ice crystals. Slow freezing causes at first extracellular, later and less intracellular crystal growth (so-called "heterogeneous nucleation"). Sudden (>100°C/min) freezing causes instant intracellular as well as extracellular crystal growth ("homogeneous nucleation"). Rapid intracellular crystal growth, however, is essential for cell destruction. Immediately after freezing and thawing, thermic conduction is more homogeneous. So, rapid deep freezing, slow thawing and a repeated freeze-thaw cyclus is the most effective way to tissue destruction[2,3,13,14].

***Vascular stage:*** Cryogelatio of fluid within the small vessels, additional damage to endothelial cells and cryothrombosis induce spreading necrosis for another 48 hours following the first "physical stage"[2,3].

***Immunologic stage*:** Delayed effects, caused by the release of internal components of destroyed cells, which become now apparent to the cells of the immune system, are interesting especially in tumour therapy, as for example in the therapy of metastatic melanoma [15-17].

***Additional factors:*** Important are the minimal temperature, duration of freezing, rapidity of freezing or thawing, but also anatomical site, different sensitivity of different tissues and tissue components [1,4,7-10]. Fibrous tissue, for example, is very resistant. Melanocytes are very sensitive (lethal temperatures between 4 and 7°C), Melanoma cells also, but some carcinomas and sarcomas survive more than -60 or -70°C. Therefore, only devices with the possibility of rapid (<100°C/min) cooling down to defined temperatures below at least more than -70°C are suitable for tumour cryosurgery.

**Side effects and precautionary measures**

A precautionary necessity is, of course, to cover eyes (plastic shields, no metal!) and ears, nasal and oral cavity (closed probes!), and teeth against aberrant spray or liquid [5,7,8]. To avoid long lasting pains, skin covering very superficial nerves (finger sides!) must be lifted by hand.

***Depigmentation*** following cryosurgery is a result of the extreme cryosensitivity of melanocytes. In uncovered areas of tanned or pigmented patients, this is an important disadvantage. Repigmentation of large areas often requires several years! On the other hand, this is often irrelevant in small lesions, and some typical indications for cryosurgery, such as scars or keloids, by themselves are de- and hyperpigmented. Pigmented nevi in pigmented skin often require perseverant repeated careful treatments [7].

**Indications and appropriate techniques**

Cryosurgery in practice has not to cover the whole spectrum of techniques possible in specialized clinical centres. Cryomethods are very helpful at low costs, however, in many superficial, small, multiple and recurrent lesions [7-11,18-22]. A broad range of indications requires a great variety of special, sometimes multiple therapeutic modalities [19-20]. Some important indications are listed with references in the following paragraphs.

Superficial, epidermal or junctional diseases are treated by Cryoablation, that means blistering. Spray freezing or liquid freezing for keratotic epidermal or closed probes for oral or genital lesions are suitable [6].

***Precanceroses***, or in situ cancerous lesions of the epidermis, as actinic keratoses, Bowen´s disease, bowenoid papulosis: spray or liquid freezing, $N_2O$ or $NO_2$, 10 sec, single or repeated freeze-thaw cyclus. The effectiveness is evident [23-30].

Actinic cheilitis (cheilitis abrasiva praecancerosa) and precancerous leukoplakia: closed probe with $N_2O$ (not so adherent to moist surfaces as $N_2$ probes), repeated cyclus. Spray freezing is possible. In this case, however, very accurate covering of the teeth and nostrils is necessary to avoid dental damage or inhalation [7].

***Papillomas*** and epidermal nevi: The naevus verrucosus often affords repeated spray treatment with repeated freeze thaw cycles. Seborrheic keratoses are treated by a single freeze-thaw cyclus with N2spray or liquid freezing [6,7]. Viral papillomas, including condylomata acuminata and common warts, are mostly treated by two spray cycles with regard to complete cell destruction [31-33].

***Carcinomas:*** Only $N_2$ devices and repeated cycles are used for malignant epithelial tumours. In tumours of some extent, it is necessary to check the extent of freezing, for example by sonography. Cryosurgery is established for multiple superficial basal cell carcinoma, as in basal cell nevus syndrome [6,7]. Successful treatment of other variants of BCC is possible especially in patients who are not fit for surgical treatment and often also anaesthesia [34-37]. Prickle cell carcinomas are very resistant, but by no means totally incurable by cryosurgery [37,38].

***Pigmented nevi:*** The sensitivity of pigment cells allows specific eradication of small nevi without scars by a mild cryotherapy. All cryogens are suitable, two freezing cycles are practical. For example, in a girl with keloid disposition and FAMM-syndrome, we treated more than 60 atypical as well as common nevi (without anaesthesia) in one session. 8 years later, a nevus-free and scar-free young woman visited us. In moles with larger extent, for example in congenital nevomelanocytic nevi, and far more in deep lesions like Ota-nevus, it is necessary to avoid unnecessary radical depigmentation. It is possible to repeat cryosurgical treatments until the aesthetic success is perfect (fig.2).

***Melanomas*:** Normally, melanoma is treated by scalpel surgery. But in old or ill patients with large lesions or in problematic locations the extreme cold sensitivity of pigment cells is sometimes useful. Only N2 devices are used with regard to rapid freezing down to the basis, with individual freezing times and always with repeated freeze-thaw cycles. Lentigo maligna [39] is a junctional lesion, but with extents into the hair follicles. So it is necessary to treat it in the same way as invasive lesions. Combined modalities are, for example, excision of tumour nodes and cryosurgery of the surrounding large in situ-areas. A special indication are multiple recurrent cutaneous epidermotropic metastases. For example, a patient developed 2382 cutaneous metastases within 6 years, and we treated them all at once with an N2 device. In the first time appeared more and more nodules, later on only few, followed by 10 years without tumour manifestation. Within the $11^{th}$ year, we removed a single nodule by scalpel. After that, she remained disease free the following 7 years until she died in high age16. We suppose that immunologic mechanisms are important for some effects in Melanoma therapy [15-17, 40-41].

***Vascular tumours*** and malformations: Cryosurgery is established more than 3 decades as a standard therapy for capillary hemangiomas [42,43]. However, statistical evidence for the therapeutic effectivity with regard to the probability of spontaneous regression was not achieved before the year 2000 [44]. All cryogens are useful, one freeze-thaw-cyclus is enough. closed probes are necessary to achieve pressure and reduce the blood flow during freezing. The mechanisms underlying the induction of regression in angiomas are complicated [44]. All thin-walled angiectatic diseases are suitable for cryotherapy using cryothrombosis. In 220 venous lakes, for example, we saw only 11 recurrences. This method is at least as effective as the treatment with vascular lasers, but by far not so expensive.

***Malignant vascular tumours*** are also suited for this method. For example, small recurrences after radiation in a Patient suffering from multicentric endothelioma in hairy skin were treated by $N_2$ spray. He survived disease-free 7 years, - a very rare success in this diagnosis. Kaposi´s sarcoma with multiple, recurrent superficial tumours is a very special indication for this type of cryosurgery. No anaesthesia is necessary, and the treated efflorescences, especially early, small ones, vanish without impressive scars. Several clinics use the method [45].

***Granulomas and inflammatory diseases***: For leishmaniasis, cryosurgery alone and in combination with different drugs is established and effective [46,47]. In former years in Hornheide, we treated lesions of skin tuberculosis with single applications of $CO_2$ snow. Destruction as well as immunologic mechanisms and transient hyperemia may contribute to the effects. The time

necessary for healing with tuberculostatic therapy was shortened, but we did not manage to enter a controlled study. The same was with Granuloma anulare, Necrobiosis lipoidica etc.[7]. Single applications of $CO_2$ are useful also in cutaneous autoimmune diseases, as lupus erythematodes (CDLE). Maybe, the method works via local elimination of immune complexes [48]. Porokeratosis was also treated with success [49].

***Hypertrophic scars, keloids:*** Cryosurgery with $N_2$ spray alone or in combination with corticosteroid infiltration is therapeutic standard [50,51]. The working mechanisms are very complex [52]. The therapy needs a long time and multiple sessions with repeated 10 sec. N2 spray applications. The effectiveness is evident [53-56].

## Conclusions

Cryosurgery in office Dermatology offers a broad spectrum of effective and economic therapeutic possibilities for trained physicians. Therefore this group of methods deserves adequate attention in our discipline.

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**Figures**

Fig. 1 Keloids following acne and the result of combined treatment with spray freezing ($N_2$, 2x10 sec.) – 12 treatments with intervals of three weeks –1 year later.

Fig. 2 Naevus fuscocoeruleus ophthalmomaxillaris Ota and the aesthetic result of 18 partial treatments with $N_2$ (spray freezing, 1x5 sec) in intervals of 2-8 weeks – 3 years later

Fig. 3 Test area within a congenital nevomelanocytic nevus 2 months after spray freezing ($N^2$, 1x10 sec).

Fig. 4 Capillary hemangioma in an infant. Closed probes allow to use pressure and to protect the eye without covering.