Practical cryosurgery—an introduction for small-animal Clinicians*

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ABSTRACT

Cryosurgical equipment has been produced which is suitable for use in general veterinary practice and which need not be excessively expensive. A knowledge of the underlying principles of cryosurgery is essential if the advantages of this technique are to be gained in full. There is reason to expect an expansion in the list of conditions for which cryosurgical treatment will be preferred to conventional methods.

INTRODUCTION

The underlying principle of cryosurgery, the subjection of living tissues to freezing, is by no means a new idea: Arnott in 1851 used this method in the management of human breast and skin tumours. However, only during the last 15 years have great advances been made in the understanding of cellular responses to freezing and the movement of cold within tissues. These advances have been made possible by the developments in cryogenic technology which have provided the clinician with a controlled and accurate means of destroying living tissue.

Modern cryosurgery began in 1961 when Cooper & Lee developed a cryogenic system using liquid nitrogen as the refrigerant and producing a probe tip temperature of $-190^\circ$C; this apparatus was used to produce a localized area of necrosis in the thalamus in the treatment of Parkinsonism. There followed at first a trickle and then a stream of publications which have pointed to the potential value of cryosurgery in many fields of human surgical practice.
The convenience of cryosurgery has proved attractive to dermatologists and large series of cases of cutaneous lesions, including malignancies, have responded well to freezing (Torre, 1970, 1971).

In ophthalmic surgery cryoprobes are used to freeze, manipulate and extract cataractous lenses (Bellows, 1965); they have also been used to promote reattachment of detached retinæ (Lincoff & McLean, 1965).

Useful applications of freezing have been reported in ear, nose and throat surgery, including the management of malignancies of the pharynx and larynx (Holden & McKelvie, 1972). Cryotonsillectomy has been satisfactorily performed by Hill (1968). Oral tumours and facial lesions have been successfully ablated by freezing with little residual scarring (Leopard & Poswillo, 1974). Cryosurgery may be preferable to cautery in the treatment of epistaxis and nasal polypi (Brain, 1974).

In general surgery, liquid nitrogen systems have been used in the treatment of benign hypertrophy and neoplasia of the prostate (Jordan et al., 1967) as well as for recurrent carcinoma of the rectum (Gage, 1968). Cryotherapy in the treatment of haemorrhoids produced less post-operative discomfort than conventional techniques and stricture formation did not occur (Lloyd Williams, Haq & Elem, 1973).

There have so far been few reports in the veterinary literature on the results of cryosurgery. Borthwick (1971), Robins & Lane (1973), and Lane (1973) have described encouraging results using this technique in the treatment of peri-anal fistulation. Borthwick (1970) has also reported the favourable response of a range of tumours to cryosurgery.

The purpose of this present contribution is to summarize the responses of living tissues to freezing; to describe some of the instrumentation at present available and to suggest some points of technique which may assist the veterinary cryosurgeon. The advantages of cryosurgery over more conventional methods of treatment will be presented, as well as some of the limitations encountered by the author. An indication will be given of the general fields of clinical application where this technique has been found to be suitable.

EFFECTS OF FREEZING ON TISSUES AND ORGANS

To the surgeon the most important effect of freezing is cryonecrosis, but the property of cryoadhesion is useful in the manipulation of delicate structures such as the cataractous lens, or damaged peripheral nerve where the use of forceps may be inappropriate. Metal becomes adherent to tissue below \(-15^\circ C\), yet at very low temperatures the tendency for the frozen mass to fragment prevents good adhesion. The vapour barrier which forms between tissue and liquid nitrogen, e.g. where spray systems are used, also prevents adhesion taking place.

Although tissue becomes frozen at \(-2.2^\circ C\), the temperature must fall to below \(-20^\circ C\) for cell death to occur (Fraser & Gill, 1967). Once the cryoprobe has
been applied and freezing begun a tissue ice-ball will form (Fig. 1), the size of which will depend upon the following factors:

(1) The temperature reached by the probe; this, in turn, will depend on the refrigerant used.

(2) The duration of application. For tissue destruction, 1–5 minutes' freezing is required, depending on the site and nature of the lesion. Repeated freezing and thawing cycles or 'overkilling', increase the size and rate of formation of the ice-ball (Gill, Fraser & Carter, 1968), analogous to successively larger stones being dropped at the same point in a pond causing wider and wider ripples.

Fig. 1. An ice-ball forming during the cryosurgical destruction of a tonsillar carcinoma. The plastic shield prevents the oral mucosa from adhering to the probe.

(3) Tissue osmolarity. At slow rates of cooling, dehydration of cells and ingress of electrolytes occur until toxic levels are reached and cell death follows.

(4) Heat exchange within tissue. The ice-ball will increase in size until an equilibrium is reached between the heat gained from the surrounding tissues from local blood vessels, and the heat lost to the probe.

The precise mechanisms which bring about cell death after freezing are not fully understood. During slow sustained cooling, ice-crystal formation is first seen in the extra-cellular fluid. As extra-cellular water is taken up in this process, there follows a relative increase in ionic concentration in the extra-cellular compartment. In the face of this, intra-cellular water moves out of the cell and extra-cellular ions move in. Lethal intra-cellular hyperosmolarity is the end result.
Where cooling is rapid, intra-cellular ice-crystals form from the outset with the production of immediate physical damage. An intermediate or ‘escape’ rate of cooling exists where neither electrolyte damage nor intra-cellular ice formation is sufficient to cause cell death.

In terms of the clinical ice-ball, the ‘escape’ zone is a subliminal layer of cells within the frozen mass and whatever the nature of the lesion being treated, these potentially surviving elements are undesirable. Repeating the freeze-thaw cycle or, alternatively, overlapping of the cryolesions helps to avoid this.

The local vascular damage which follows cryosurgery enhances the overall destructive effect. The capillaries and venules become plugged by microthrombi and lead to infarction within and around the cryolesion. Only the larger vessels on the arterial side remain functional.

After cryosurgery, swelling and mild hyperthermia become apparent within 2–3 hours. This oedematous swelling can last for up to 4 days and by this time areas of superficial necrosis are becoming obvious with marked discoloration. In most sites such as mucous membranes or the peri-anal area, this necrotic tissue will appear yellow, whilst on dry skin a dark eschar is seen. The slough separates more quickly from mucous membranes than from skin, the normal time ranging from 7–20 days. After separation there is a clean granulating surface covered, to a greater or lesser extent, by new epithelium.

The incidence of secondary infection and haemorrhage is remarkably low at any stage following treatment, even in contaminated fields such as the perineum (Lane & Burch, 1974).

The result of cryosurgery is the unselective but controlled destruction of living tissues whether they consist of diseased or normal cellular elements. Thus, where bone is included in the ice-ball, the osteocytes are eliminated whilst the mineral matrix remains unchanged. Regeneration takes place by osteoblasts infiltrating from the periphery. Similarly, larger blood vessels, due to their collagenous structure as well as their inbuilt heat source, are only slightly affected by cryosurgery.

Nerve fibres are destroyed by cryosurgery and treated areas remain relatively anaesthetic for several weeks. Complete return of sensation usually follows, and normal functioning of even quite large peripheral nerves can be expected.

**INSTRUMENTATION AND TECHNIQUE**

**APPARATUS**

The most simple means of lowering tissue temperatures is to apply a pre-cooled instrument such as a copper rod or cotton wool swab after immersion in liquid nitrogen. Direct application of a refrigerant such as dry carbon dioxide snow to the area may also be employed. However, neither of these techniques offers a means of controlling the area of cryonecrosis.
Phase-change cryoprobes harness the loss of latent heat when a change of phase, usually liquid to gas, takes place. This may occur either within the probe tip or, as a result of the fine spray of the liquid refrigerant, on the tissue surface. Liquid nitrogen, the most powerful cooling agent, can be used in either of these systems and working tip temperatures approaching the boiling point of $-198°C$ can be obtained. However, liquid nitrogen is difficult to handle and to store; systems designed to utilize it are expensive. A further disadvantage of spray probes is that the liquid boils as it approaches the tissue surface; a vapour barrier is created which prevents cryo-adhesion.

![Fig. 2. A high-pressure non-electric Joule-Thompson cryosurgical unit. A: pin-index adaptor, B: pressure gauge, C: foot-switch, D: cryoprobe.](image)

The Joule-Thompson effect is utilized in Amoils cryoprobes. Pressurized gas is forced through a fine nozzle within the probe and this produces sudden cooling of the adjacent metal tip. Using this effect, working temperatures of $-70°C$ and $-50°C$ are claimed for nitrous oxide and carbon dioxide respectively. Many Joule-Thompson probes incorporate a defrosting heating element which accelerates detachment from the ice-ball, and so saves time, especially where larger lesions requiring multiple applications are being treated. More recently a non-electric system has been introduced (Spembley NCS 40—Vestric Ltd) (Fig. 2) which has the added advantage of portability. Interchangeable tip configurations (Fig. 3) are available for some equipment so that the contact shape of the probe can be changed to suit the procedure being conducted.
Lack of patient co-operation usually necessitates general anaesthesia for larger cryosurgical procedures. However, for interferences such as the treatment of small skin tumours or minor follow-up therapy, sedation alone may be adequate.

The operation site should be cleansed, but thorough preparation, as required for a sterile procedure, is not necessary unless the cryosurgery is to be combined with conventional sharp-knife surgery.

The cryoprobe should be applied to the site before freezing is begun, otherwise cryoadhesion makes accurate repositioning of the contact tip difficult. In order to produce good thermal conduction as well as adhesion when treating skin or hyperkeratotic lesions, a water-soluble lubricating jelly should be applied. Once freezing has begun and adhesion taken place, the lesion can be manipulated to
the wishes of the surgeon. The tissue ice-ball enlarges for about one minute and then remains constant. For most purposes freezing for two minutes is adequate to produce a zone of cryonecrosis which corresponds almost exactly to the visible and palpable ice-ball. The destruction of the escape zone cells mentioned previously is essential and thus the freeze-thaw cycle should be repeated at least once and for malignant lesions preferably three times. When dealing with large lesions a series of overlapping cryolesions are made, starting at the circumference and working towards the centre. Cryosurgery may therefore appear to be time-consuming and yet good results cannot be expected without patience.

After each freezing cycle is completed, it is important to permit the spontaneous detachment of the probe. Avulsion of the probe before defrosting is complete could lead to unnecessary haemorrhage which the cryoprobe will be quite ineffective in arresting. However, in dealing with hyperkeratotic warts, after freezing is complete the lesion can be snapped off without pain and with minimal post-operative sanguineous ooze. Where insufficient depth of freezing is obtained to destroy a tissue mass completely, a freezing and cutting technique is possible.

The degree of oedema which follows cryosurgery is variable and under most circumstances this is of little consequence as it disappears after 3–5 days. However, it should be noted that where cryosurgery is carried out in the pharynx, especially of brachycephalic dogs, even slight post-operative oedema may lead to severe respiratory embarrassment, or even to asphyxiation. Facilities for tracheotomy should therefore always be on hand for these patients.

Superficial dressing of lesions treated by cryosurgery is not necessary and experience shows that patients pay little or no attention to the site during the sloughing and healing stages. Owners should be briefed on the likely progress of conditions treated by this method; the sight of deeply discoloured necrosing tissue could otherwise prove unnecessarily alarming.

It is fortunate that the post-cryosurgical changes in pigmentation which result from freezing the deeper skin layers are of little cosmetic consequence and the freeze-brand-like white hair is acceptable to most owners.

ADVANTAGES AND LIMITATIONS OF CRYOSURGERY

The advantages of cryosurgery can be highlighted by indicating some of the shortcomings of the other methods available for the removal of unwanted tissue.

Sharp surgical excision usually requires general or local anaesthesia and, on recovery, pain may be present at the operation site or, at best, there will be irritation along a suture line. Serious haemorrhage can occur during an operation and reactionary haemorrhage, infection and wound dehiscence may follow. Handling of a malignant neoplasm during conventional surgery (including biopsy sampling) can precipitate the dissemination of metastases. Conventional surgery is not known to evoke any immunological benefit.

Diathermic cautery, including fulguration, is painful during and after the
procedure and, again, no immunological benefit is conferred. Excessive carbonization of tissue leads to poor healing of electro-incisions.

Radiation treatment can be dangerous to both patient and operator, particularly where special and expensive facilities for protection are not available. A wide range of side-effects has been described and for these reasons it is inadvisable to repeat treatment on those tumours which show a tendency to recur. The range of tumours which respond well to exposure to ionizing radiation is limited whilst immune responses are depressed.

A limited number of drugs are at present available for the chemotherapeutic control of tumours in animals. The therapeutic index of cytotoxic drugs is usually low and even with relatively non-toxic agents such as corticosteroids, long-term treatments may be accompanied by undesirable side effects.

Apart from being effective in destroying unwanted tissue, cryosurgery is above all else safe, and several factors contribute to this safety. As there are no adverse effects on the patient, nor on the operator, cryosurgery can be repeated as many times as necessary until the lesion has been totally ablated. Neoplastic cells which could migrate when otherwise handled are frozen in situ and thus during cryotherapy there is no danger of precipitating metastases. When cryosurgery is used correctly, haemorrhage is minimal and tissue responses are slight; reactionary haemorrhage and secondary infection at the treated site are not subsequent features (Lane & Burch, 1974). Healing of a cryolesion is not as rapid as first-intention healing of a surgical incision; however the possibility of dehiscence does not apply and scarring is not marked. As a result of the relative painlessness of cryosurgical procedures, there is not always a need to resort to general or local anaesthesia.

Cryosurgery is precise in two ways. Firstly, as a result of cryoadhesion, tissues can be manipulated with great control. Secondly, cryonecrosis is accurate: the line between total cell destruction and total tissue survival is very sharp. The temperature throughout a tissue ice-ball is almost consistent so that, within the limitations already described, the mass of tissue destroyed will correspond to the size of the ice-ball and this can be easily assessed by the surgeon.

There is evidence that cell death by freezing is accompanied by antigen formation, probably through the liberation of lipoprotein complexes from cell membranes (Shulman, Yantorno & Bronson, 1967). Apart from rises in circulating antibody titres following the cryodestruction of tumours, increased lymphocyte activity has been demonstrated (Holden, 1972).

The author has encountered limitations where cryosurgery has been used in the management of very large tumour masses. The size of the tissue ice-ball is such that even with large probe tips using nitrous oxide, the maximum depth of freezing is only 1 cm from the surface. This may be increased by incising into the frozen mass, allowing thawing to occur and then introducing the tip into the incision. Alternatively, the ultra-freezing procedure may be repeated at intervals so that the lesion is reduced progressively; this may require repetition of general
anaesthesia. However, as with other techniques, a favourable prognosis may depend on early presentation followed by prompt intervention.

With the exception of ablating small areas within the central nervous system in man, cryosurgery is only applied where there exists a suitable route by which dead cellular material can be discharged. At present cryosurgery is thought to be unsuitable for the treatment of internal lesions.

Fraser & Gill (1967) have suggested that the susceptibility of tumours to the effects of freezing is variable; mesenchymal cells appear to be more resistant to cold than epithelial cells. Anaplastic neoplasms are also less responsive to cryotherapy. In practical terms, less susceptible neoplasms should be subjected to more severe cryosurgery by extending the duration of freezing, and by repeating the freeze-thaw cycle at least three times.

APPLICATIONS OF CRYOSURGERY

It is beyond the scope of this paper to describe in detail those conditions where cryosurgery has been found to be useful in small animal practice. The following list and comments will serve to indicate those diseases of the dog and cat where this technique is likely to be the treatment of choice:

- Anal adenoma
- Anal furunculosis
- Benign skin tumours such as fibromata and papillomata
- Biopsy of malignant neoplasms
- Granulation tissue
- Inter- and supra-digital cysts
- Lendectomy
- Malignant skin tumours
- Oral and pharyngeal tumours
- Oral ulceration
- Tonsillectomy including tonsillar carcinomata
- Tumours of the eyelids

Apart from the absence of secondary infection already referred to, cryosurgical interferences in the peri-anal region are characterized by the lack of stricture formation. Lane & Burch (1974) propose a composite treatment for anal furunculosis in the dog, consisting of anal sac ablation, débridement and cryosurgery. Results with the first forty cases managed in this way showed that in terms of complete resolutions, freedom from undesirable post-operative complications and the incidence of recurrence, this was superior to the other methods reported to date.

Old dogs and cats, which may be poor-risk anaesthetic patients, are frequently afflicted with disfiguring benign skin tumours. These can be removed using cryosurgery and, when required, restraint may be facilitated by promazine hydrochloride alone.
Biopsy specimens obtained by excision of frozen tissues may be transported in dry ice and treated as for frozen sections, or allowed to thaw and then fixed in formal saline. In either case the quality of the specimen is adequate for histological examination (Leopard & Poswillo, 1974).

Granulation tissue, whether it be the result of excessive reaction during wound healing, or the response to persistent mechanical irritation such as a lick granuloma, may be eliminated by ultra-freezing.

The successful results which follow the cryosurgical treatment of intractable inter- and supra-digital cysts probably stem from the ablation of the follicular elements which are thought to initiate and perpetuate the condition.

Intra-capsular extraction of the cataractous lens may be facilitated by the use of a cryoprobe. Following adhesion to the probe tip, the lens can be manipulated whilst the zonular attachments are broken down.

Cryotonsillectomy may be performed without risk of haemorrhage and in those few cases of tonsillar carcinoma where spread to the local lymph nodes has not already taken place, successful destruction may be achieved by cryosurgery. Experience to date suggests that the use of cryosurgery may improve the otherwise hopeless prognosis for some oral and pharyngeal tumours.

Basal cell carcinomata and sebaceous gland adenomata can be removed from the eyelids with little scarring and therefore no distortion of the lid margins.

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