

CRYOSURGERY WITH SPECIAL REFERENCE TO THE
CONTROL OF ORO-FACIAL PAIN AND ORAL LESIONS

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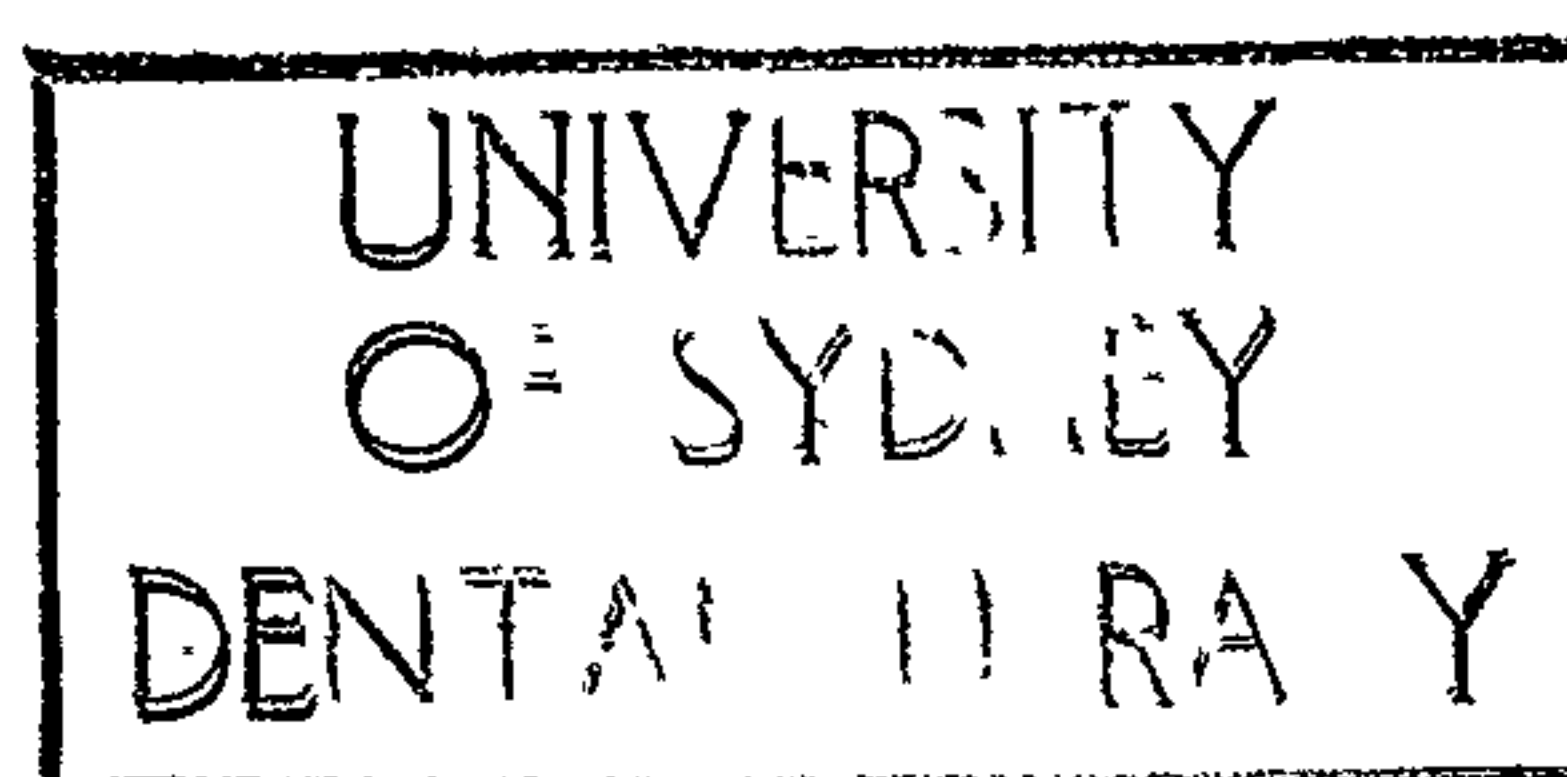
A TREATISE SUBMITTED IN PARTIAL REQUIREMENT FOR THE
DEGREE OF MASTER OF DENTAL SURGERY

Department of Oral Surgery

Faculty of Dentistry

The University of Sydney

1986



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		Page
<u>Chapter 1</u>	Introduction	1
<u>Chapter 2</u>	History of Cryosurgery	3
	- Oral Surgical Aspects of Cryosurgery	10
	- Periodontics and Stomatology	12
	- Facial Neuralgia	12
	- Cryosurgery in Ophthalmology	14
	- Summary	16
<u>Chapter 3</u>	The Cryo-Lesion (Effects of extreme cold on living cells)	17
	- Introduction	17
	- Theories of the Effects of Extreme Cold on Living Cells	17
	- Controlling Factors	50
	- Cell Survival	66
<u>Chapter 4</u>	The Scope of Cryosurgery (Lesions treatable by cryosurgery)	73
	- Susceptibility to Treatment by Cryosurgery	73
	- Lesions Related to Oral Surgery	76
	- Other Surgical Applications of Cryosurgery	86
	- Basic Cryosurgery Technique	89
	- The Clinical Tissue Response to Cryosurgery	90

<u>Chapter 5</u>	Instrumentation and Cryogenics	92
	- Spray Systems	93
	- Probe Systems	96
	- Solid and Slushed Cryogen and Liquid Cryogen Application	102
	- Poured Cryogen	103
	- Alternate Cryogenics	103
	- Accessory Equipment	104
	- Conclusion	106
 <u>Chapter 6</u>	 Advantages, Disadvantages, Complications and Limitations of Cryosurgery	 107
	- Advantages	107
	- Disadvantages, Complications and Limitations	115
	- Disadvantages Especially Related to Oro-facial Pain Control	122
 <u>Chapter 7</u>	 Oro-facial Pain	 123
	- The Definition of Pain	123
	- Theories of the Cause of Pain	124
	- Neurology and Anatomy of Oro-facial Pain	125
	- Types of Oro-facial Pain	130
	- Trigeminal Neuralgia and Similar Conditions	141
	- Post-herpetic Neuralgia	147
 <u>Chapter 8</u>	 Cryosurgery for Oro-facial Pain	 149
	- Cryosurgery for General Conditions Producing Oro-facial Pain	149
	- Paroxysmal Trigeminal Neuralgia	152
	- Non-cryosurgical Treatment	152
	- Cryosurgical Treatment	154

	- Paroxysmal Glossopharyngeal Neuralgia	162
	- Post-herpetic Neuralgia	163
	- Causalgia	165
<u>Chapter 9</u>	Case Reports	167
	- Trigeminal Neuralgia (T.N.)	171
	- Haemangiomata	188
	- Fibro-epithelial Polyp	190
	- Sublingual Keratosis	192
	- Chronic Ulcer	193
	- Comments	194
<u>Chapter 10</u>	Discussion and Conclusion	195
<u>Bibliography</u>		202

ILLUSTRATIONS

	<u>Page</u>
1. Hollow instruments devised by Fay and Henny, 1938.	7
2. The cooling system through which 95% alcohol was circulated by Rowbotham, Haigh and Leslie, 1959.	7
3. Freon cryosurgical system designed by Ries and Tytus, 1960.	9
4. Cryosurgical probes, designed by Ries and Tytus, through which Freon was circulated.	9
5. An insulated cryosurgical cannula for liquid nitrogen. Used for basal ganglia surgery by Cooper and Lee, 1961.	9
6. Development of cryosurgery for cancer to 1976.	11
7. Freezing of erythrocytes.	26
8. Intracellular and extracellular ice in frozen fish muscle.	30
9. Blood-vessels following freezing.	45
10. Blood-vessels before and after freezing.	46
11. Leukoplakia of labial aspect of maxillary ridge, in a seventy one year old female.	77
12. The same lesion as in Illustration 11, three days after cryosurgery. Typical sloughing lesion present.	77
13. The lesion as in Illustration 11, six weeks following cryosurgery. The lesion was treated with a nitrous oxide cryoprobe for two freezes of thirty seconds each at three sites.	78
14. Haemangioma of tongue in a sixteen year old female.	80
15. The same lesion as in Illustration 14, four days after cryosurgery. Surgery site exhibits typical slough.	80
16. The same lesion as in Illustration 14, two weeks post-surgical. The cryosurgical regimen was two freezes of sixty seconds, using a nitrous oxide cryoprobe.	81

17.	Haemangioma of the upper lip. The lesion had recurred three times after diathermy and local excision.	82
18.	The same lesion as in Illustration 17 after curative cryosurgery.	82
19.	Squamous carcinoma of tongue in eighty year old male.	84
20.	Same tongue as in Illustration 19 after cryosurgery. No local or metastatic spread observed three years post-operatively.	84
21.	Adenoid cystic carcinoma of elderly male. Maxillectomy or radiotherapy were contraindicated.	85
22.	Same tumour as in Illustration 21, five years after palliative cryosurgery. Full denture worn with complete comfort.	85
23.	W.S.L. Nitrospray Unit. As used at the United Dental Hospital, Sydney.	95
24.	T.T. 32-Physicians Products, Inc. Unit.	95
25.	Zacarian C - 21-Frigitronics, Inc. Unit.	97
26.	CE 8-Frigitronics, Inc. Unit.	97
27.	Details of CE 8-Frigitronics, Inc. Unit.	98
28.	Probes and spray attachments used with the CE 8-Frigitronics, Inc. Unit.	98
29.	Neoprene cones used to limit cryogen spray.	105
30.	Walsh Pressure Rings, used to limit sprayed cryogen.	105
31.	Cross section of normal myelinated nerve fibre. The dense myelin sheath surrounds the axon.	146
32.	Proliferative degenerative changes in a myelinated nerve fibre in a patient with trigeminal neuralgia.	146
33.	Case 19. Haemangioma of the right maxillary labial sulcus with cryoprobe ready for application.	189
34.	The same case as in Illustration 33, three months following cryosurgery.	189
35.	Case 20. Haemangioma of left maxillary gingiva.	191
36.	The same case as in Illustration 35, four weeks after the first sectional freeze and two weeks after the second sectional freeze.	191

CHAPTER 1

Introduction

The terms cryosurgery and cryotherapy are commonly used to convey the same meaning. This common usage is not strictly correct as cyrosurgery implies the destruction of tissue, whereas cryotherapy may well be of a non-destructive nature. Cryosurgery has been described as "surgical procedures in which tissue is destroyed by freezing", whilst cryotherapy was described as "the use of cold or freezing as a therapeutic measure", (Butterworths Medical Dictionary 1978, p.437). These descriptions are somewhat inadequate since cryosurgery in reality utilizes extremely low temperatures and it is in this context that the words cryosurgery and cryotherapy will be used in this treatise.

It has been stated that a method of surgery which offers the effective destruction of unwanted tissue, with anaesthetic properties, haemostasis and controlled limitation, along with remarkable wound healing, may well be close to realization in cryogenic surgery (Zacarian 1973, p.xiii). This statement has been shown to be at least partly correct in the ensuing years.

The aim of this treatise is to study the ways in which this technology can be used in the practice of oral surgery. The way in which freezing destroys tissue will be evaluated and the effects of cryosurgery on various types of tissues will be reported. The degree of susceptibility of various lesions to this mode of treatment will be discussed, as will techniques, advantages and disadvantages of cryosurgery.

Oro-facial pain, with its unique aspects and connotations, is to be looked at in general terms and thereafter special emphasis placed on intractable facial pain, such as is experienced in trigeminal neuralgia. The role of cryosurgery in the treatment of neuralgic conditions is increasing, with some clinics already having several hundred cases in their records. Pain control is being achieved either by the intense cold of cryotherapy alone, or by its use along with other forms of treatment, (e.g. Carbamazapine therapy). Several case reports will be presented towards the end of this treatise.

Some applications of cryosurgery are comparatively new, as can be seen from the following historical section and it is important that workers in oral surgery gain an understanding of what this modality of treatment can provide. While much has been achieved in the past few years, it appears that there is an exciting future in the surgical use of intense cold. In this regard two aspects may prove to be of special importance: first improved techniques, as in the case of pain control; and second the very interesting consideration of cryo-immunology, the study of which is virtually at the beginning stage. The concept of cryo-immunology is that the cryosurgical destruction of a lesion may promote an immune response sufficient to prevent the formation of similar lesions elsewhere in the body.

A final summary will attempt to correlate the material presented in this treatise, to give the reader a better grasp of the ways in which he or she may be able to utilize, or recommend the use of, cryosurgery.

CHAPTER 2

History of Cryosurgery

The evolution of cryosurgery is interesting and since there has been knowledge of the effects of cold on cells for hundreds of years, it seems strange that this modality has taken so long to become used therapeutically.

Since the days of Hippocrates (c.460-375 B.C.) man has known of the therapeutic effects of sub-zero temperatures for the treatment of sprains, the reduction of swelling, the alleviation of pain at operation in pre-anaesthetic times, plus other medical disorders (Zacarian, 1977, p.xiii). In the seventeenth century Robert Boyle found that cells could be killed by freezing (Jolly, 1976). Another century was to pass until in 1777 the anatomist John Hunter noted that after freezing there was local tissue necrosis, vascular stasis and that excellent healing of the tissues resulted (Barnard, 1980).

In a fine article, Neel (1980) stated that in 1851 James Arnott was the first to advocate the use of cold in the treatment of cancer and that he (Arnott) had treated a woman, in 1849, for carcinoma of the cervix, by means of powdered ice and sodium chloride mixture, introduced through a gutta-percha speculum. An interesting side issue is that James Arnott's older brother, Neil, was the inventor of the slow combustion stove and also physician to Queen Victoria. James Arnott, under his brother's influence, entered his cold applicator at the Great Exhibition in Hyde Park, London in 1851, where he became a prize medalist. At about the same time Dr M.H.

cryotherapy (Jolly, 1976), but it must be remembered that James Arnott in 1851 and Dr M.H. Collis at about the same time had been treating cancer patients with intense cold. This apparent discrepancy of opinion is probably explained by different interpretations of meaning placed on the word "successful".

In the early twentieth century cryotherapy took an interesting turn away from liquid refrigerants, when Dr William Allen Pusey reported the use of carbon dioxide snow for the treatment of vascular naevi, warts, calluses, senile keratoses, and other conditions. He presented and illustrated one remarkable case of a huge pigmented naevus on a girl's face before and after treatment and made very interesting comments on depigmentation by freezing (Pusey, 1907). He also noted bullae formation as a complication at freezes of 10-50 second duration.

At this point some twenty years passed without much information being presented on liquid cyrogens, until in 1929 Irvine and Turnacliff began reporting on liquid oxygen use in dermatology, (Irvine and Turnacliff, 1929). These two clinicians presented a review of the literature and accounts of some seventy five of their own cases, covering an impressive list of dermatological lesions, including plantar and palmar warts, ivy-dermatitis, herpes zoster, moles, vascular naevi and tinea. These conditions were treated with liquid oxygen on swabs. In a very enthusiastic conclusion they observed, among other things, that the use of liquid oxygen caused much less pain than carbon dioxide snow.

Fay and Henny (1938) described and illustrated the first closed

circuit apparatus, which consisted of four hollow instruments through which various cold solutions could be run and returned, cooling the cryoprobe in the process. These instruments (Fig. 2-1) were designed to go into and around cancerous lesions.

Fay and Henny also gave an account of five cases treated and in particular described prompt pain loss and reduction in size of the cancerous lesions following refrigeration. This important step into closed circuit apparatus provided the impetus for construction of more refined cryosurgery units. Fay also reported in 1939 the use of ice water or brine circulating through hollow apparatus inserted in cancer masses, with similar results of pain loss and tumour mass reduction (Smith and Fay, 1939). Fay continued enthusiastically investigating the effects of cold on cancer and in 1940 published a description of total body refrigeration, by means of cracked ice. In this manner and under general anaesthesia, over one hundred patients with malignancies were treated, of whom approximately fifteen per cent died during or shortly after treatment, whilst nearly all the remainder gained pain relief (Fay, 1940).

By 1959 closed circuit equipment had been greatly improved and a specifically made canula was being used to treat cerebral neoplasms, utilizing the circulation of 95% alcohol, by means of a pump and cooling chamber (Fig. 2-2), the coolant being solidified carbon dioxide and acetone (Rowbotham et al, 1959). A working temperature of -20°C was thus provided at the canula and these authors cited three cases treated, noting that the procedure did not endanger the patient's life. At approximately the same time, Ries and Tytus were experimenting with closed canula circuits (Fig. 2-3) using acetone

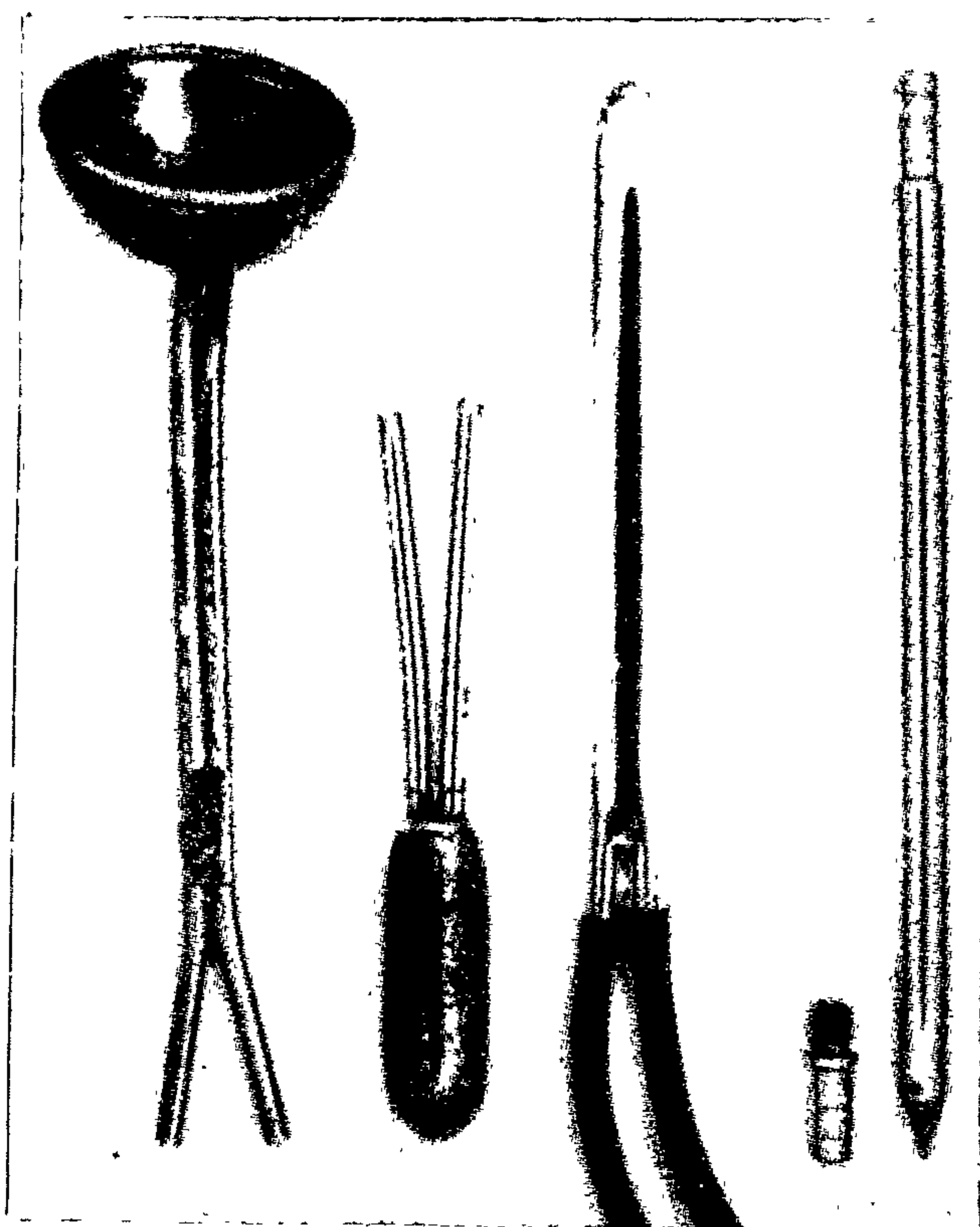


Fig.2-1. Hollow instruments devised by Fay and Henny, 1938, through which various cold solutions could be run. (From H.B. Neel, Laryngoscope, 1980. Courtesy of the Editor.)

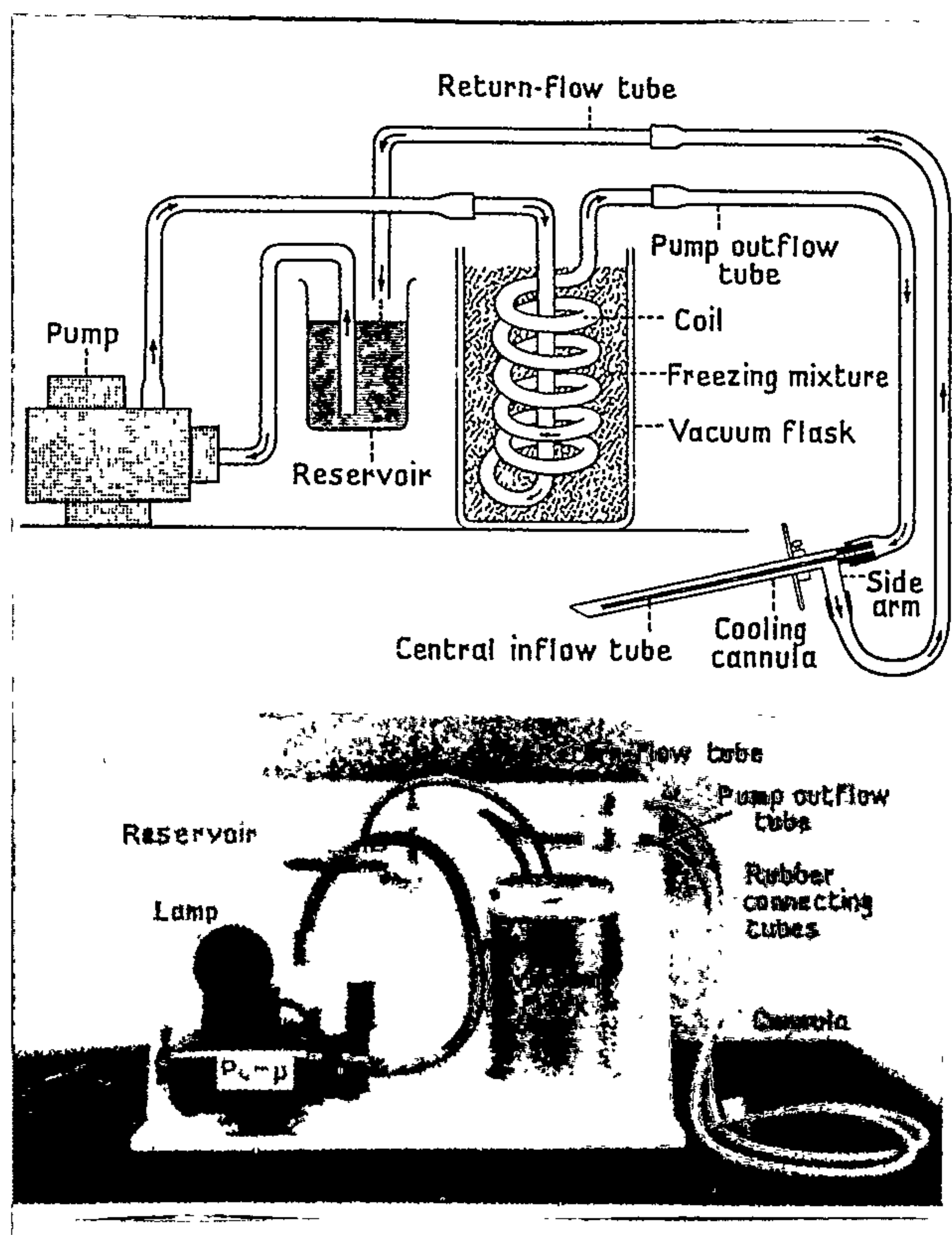


Fig.2-2. The cooling system through which 95% alcohol was circulated by Rowbotham, Haigh and Leslie, 1959. (From H.B. Neel, Laryngoscope, 1980. Courtesy of the Editor.)

and carbon dioxide snow and later freon as refrigerants (Neel, 1980). The freon produced a probe tip temperature of -40°C . They also carried out preliminary experiments with liquid nitrogen in a closed circuit, gaining probe tip temperatures of -190°C .

Cooper and Lee in 1961 described the first closed system liquid nitrogen apparatus for clinical use (Fig. 2-4). Their probe was a canula of stainless steel for the production of deep cerebral freezing, to control involuntary motor movements (Cooper and Lee, 1961). This equipment allowed for the production of, first, a reversible nerve block to test the reaction, and second, a cryo-lesion for permanent effect.

One major advance in the clinical utilization of cryosurgery came in 1962 with the remarkable report by Dr Irving S. Cooper of very successful treatment of Parkinson's Disease and other involuntary movement disorders, by means of selective freezing of basal ganglia using a liquid nitrogen canula (Cooper, 1962). This report covers some 2,210 cases over a ten year period and exhibited a ninety per cent success rate. During 1962-63 Cooper and Stellar (1963) carried on with cryosurgery to basal ganglia and cryosurgery began to play a significant role in neurosurgery.

Cooper and Stellar described the biological effects of freezing and referred to 1,000 cases of cryosurgery for involuntary motor movements in which the fatality rate at operation was one per cent. They went on to comment on twelve cases of similar treatment for brain tumours, and concluded that the method is simple, rapid, controllable and safe.

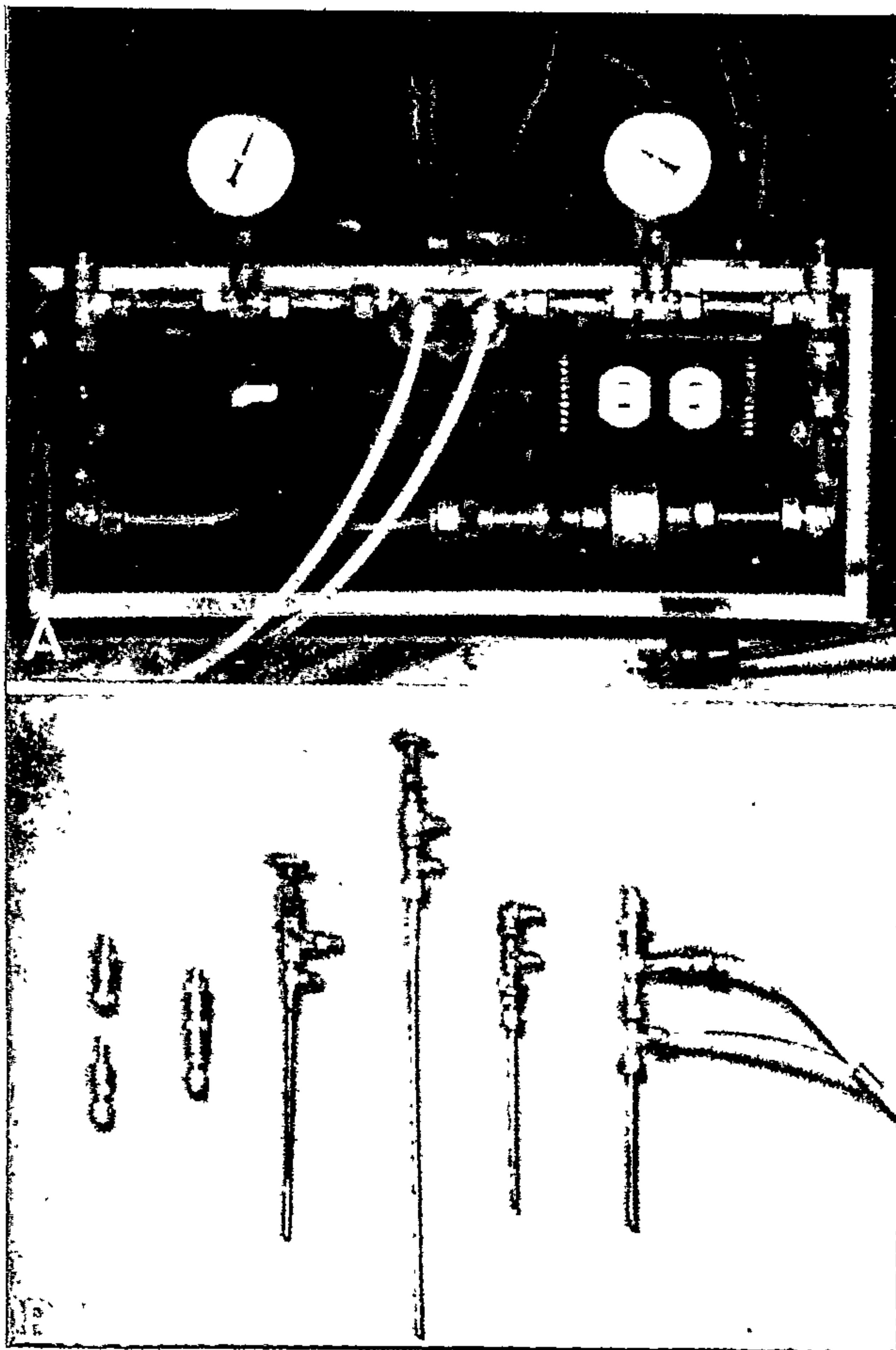


Fig.2-3.

A. Freon cryosurgical system designed by Ries and Tytus, 1960.

B. Cryosurgical probes, designed by Ries and Tytus, through which Freon was circulated.

(From H.B. Neel, Laryngoscope, 1980. Courtesy of the Editor.)

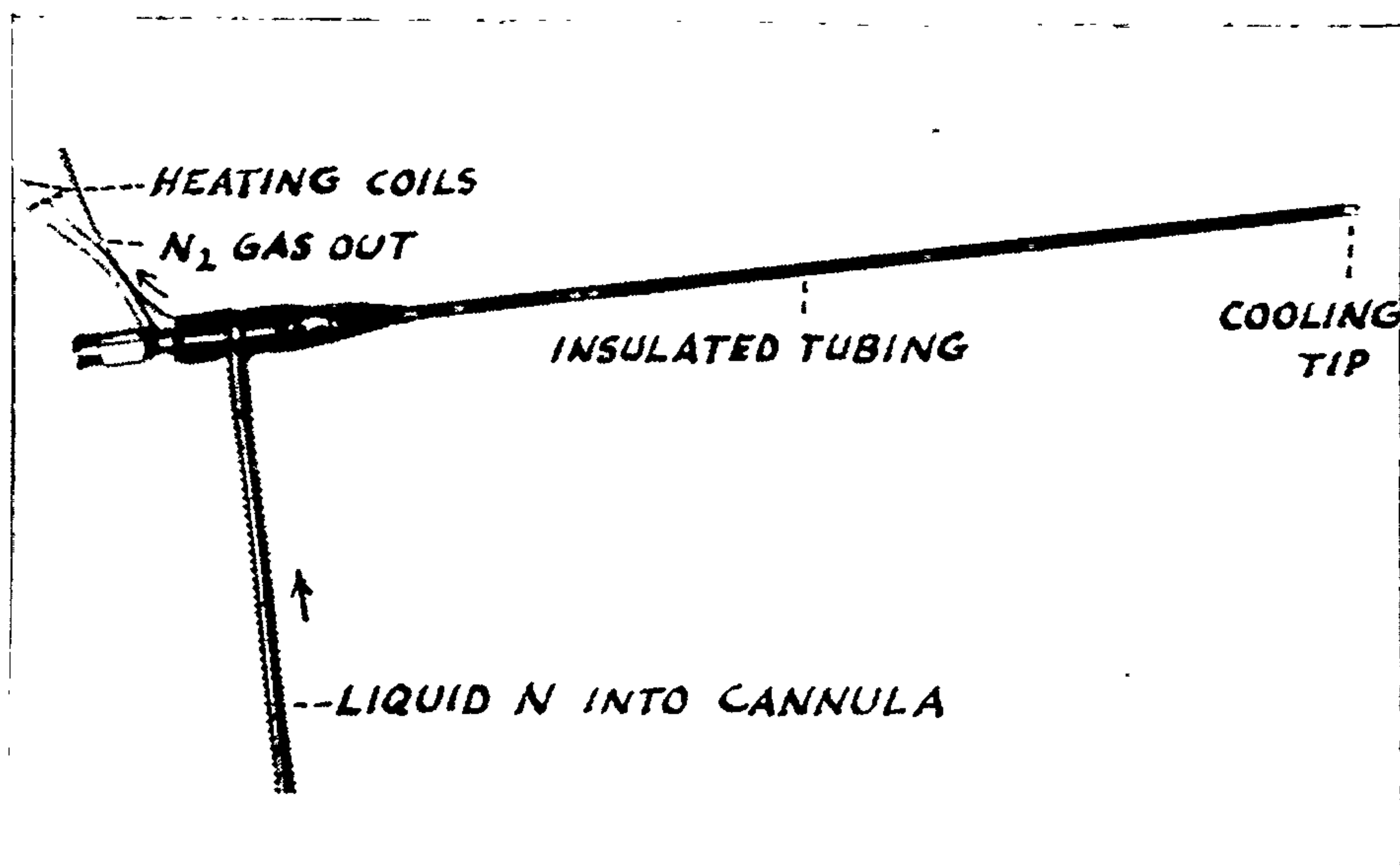


Fig.2-4. An insulated cryosurgical cannula for liquid nitrogen. Used for basal ganglia surgery by Cooper and Lee, 1961. (From H.B. Neel, Laryngoscope, 1980. Courtesy of the Editor.)

Following this period there has been a general increase in acceptance of cryosurgery for various procedures and corresponding advances in the apparatus available. One important step forward came in 1976, with the design by Neel and Sanderson (Fig. 2-5) of a 55 cm long cyroprobe, with several detachable tips, for endoscopic cryosurgery of the trachea and bronchi. In its use they noted several advantages over the traditional electrocoagulation methods, particularly in that structure and function of tissues were retained, with regrowth of normal mucosa (Neel, 1980).

Oral Surgical Aspects of Cryosurgery

From an oral surgery standpoint, cryosurgery really began to be seriously considered in the early 1960's. From 1962 an American army colonel, in Texas, William J. Amaral and his co-workers were using liquid nitrogen, on swabs, to treat cases of palatal inflammatory papillary hyperplasia (i.e. denture hyperplasia) and they later published a five-year study of their work (Amaral et al, 1968).

In the mid 1960s an outline of five cases of treatment by cryosurgery of benign and malignant lesions of the lip and oral cavity was presented (Gage et al, 1965). These treatments utilized liquid nitrogen, in blunt and pointed probes, producing a reported temperature of "always lower than -80°C ". The authors of this article noted that cryosurgery was useful for palliation and that it also preserved structural continuity of tissues. A further report, by three of these writers, deals with cryosurgery to haemangiomata, palatal mixed tumours, epithelial hyperplasia and leukoplakia. They concluded, among other things, that this treatment allows bone

TABLE I.
Historical Development of Cryotherapy of Cancer.

Investigator	Year	Cooling Agent	Apparatus	Site
Arnott ⁵	1857	Ice-saline	Hollow irrigating tubes Pig's bladder Metal balls	Vagina ("womb") Breast
White ⁷	1899	Liquid air	Spray, swabs, glass or brass globes	Skin
Pusey ⁸	1907	Carbon dioxide snow	Direct application	Skin
Fay and Henny ¹¹	1938	Ice-saline	Hollow instruments (closed)	Vagina, breast, brain
Fay ¹³	1940	Ice	Direct application	Total body cooling
Rowbotham, et al. ¹⁷	1959	Alcohol (95%) cooled with car- bon dioxide; ice-acetone mixture	Closed cannula	Brain
Ries and Tytus ¹⁸	1960	Freon	Closed cannula	Brain
Tytus and Ries ¹⁹	1961	Freon	Closed cannula	Pituitary, liver
Cooper and Lee ²⁰	1961	Liquid nitrogen	Insulated probes	Brain
Neel and Sanderson	1976	Liquid nitrogen	Long insulated probe, interchangeable tips	Trachea, bronchus, lung

Fig.2-5. Development of cryosurgery for cancer to 1976. (From H.B. Neel, Laryngoscope, 1980. Courtesy of the Editor.)

preservation, where other forms of treatment may necessitate bone loss (Emmings et al, 1967).

Periodontics and Stomatology

There have been a few attempts to carry out periodontal surgery by means of cryotherapy and Whittaker cited examples of investigations into the elimination of periodontal pockets, removal of gingival hyperplasia and treatment of aphthous ulcers and herpetic lesions (Whittaker, 1972). It would not appear, however, that there has been any widespread acceptance of cryosurgery in the field of periodontics.

Facial Neuralgia

"When a peripheral nerve is frozen, both the nerve axon and nerve sheath are devitalized" (Leopard and Poswillo, 1974). The nerve sheath structure however remains intact, allowing for regeneration of nerve fibres. These factors explain the relative absence of pain after cryotherapy and led to the realization that intense pain from facial neuralgias could be eradicated, or at least minimized, by the application of intense cold, using modern apparatus.

In 1945 Denny-Brown and his co-researchers presented a long, detailed account of experiments using carbon dioxide snow and spray applied to animal nerves. They cooled and froze nerves, noting that the effect on peripheral nerves was proportional to the intensity and duration of exposure to cold. They also illustrated, by means of several photomicrographs, nerves damaged by cold and subsequent regeneration

of nerve fibrils (Denny-Brown et al, 1945).

As long ago as 1899, White concluded that facial neuralgias could be treated by freezing (*vide supra*), but it is only in the last few years that cryosurgery has begun to displace more traditional forms of treatment in these conditions. Some clinics now have hundreds of cases under control (Nally, 1984, B).

It was not until the early 1970's that clinicians began seriously to apply cryosurgery directly to facial nerves in order to relieve the severe symptoms of facial neuralgias. Poswillo, in discussing the effects of cryosurgery on oral tissues, made note of the cellular damage to nerve tissues. Commenting on the distribution of the fifth and seventh cranial nerves, he stated (p.75) that, "it is likely that the application of a freezing probe to oro-facial structures will have an effect on the function of these peripheral nerves". In regard to this statement, since freezing of a peripheral nerve leads to devitalization of the axon and sheath, as reported earlier, one could reasonably expect that the freezing of oro-facial tissues in proximity to the facial or trigeminal nerve branches could indeed produce a diminution in function of those branches. It seems probable that at about this period Poswillo began to think in terms of direct attack on facial neuralgia by means of cryosurgery (Poswillo, 1973, p.69-101). He continued working in this field and concluded that in the treatment of trigeminal neuralgia "cryo nerve blockade offers unique features hitherto unobtainable by other methods of pain relief" (Poswillo, 1978). In this article mention is made of treatment of facial neuralgia, painful scar tissue and causalgia along with the observation that the treatment can easily be

repeated if necessary.

Also in 1978, Barnard et al, reporting on nerve blockade to twenty-one patients using nitrous oxide apparatus, outlined details of supra-orbital, supra-trochlear, infra-orbital, mental and lingual nerve blockade. They stated that although cryosurgery had been used to destroy brain tissue, its use to block peripheral nerves had not been previously developed (Barnard et al, 1978).

Later Barnard and co-workers in 1981 gave an account of eighty-five cryogenic nerve blocks for patients with chronic facial pain and concluded that the method gave better relief to patients with non-herpetic neuralgias than to those with post-herpetic neuralgia (Barnard et al, 1981).

Today, some ten years after a rather tentative beginning, cryosurgery for facial pain control is gaining wider acceptance and is the first method of treatment in a number of clinics.

Cryosurgery in Ophthalmology

Although cryotherapy has been used in many surgical fields, it has found one of its widest uses in ophthalmology. The literature contains an abundance of references to the application of cryosurgery in this area, mainly for repair of retinal detachment, cataract removal and the treatment of glaucoma.

According to Lincoff and McLean (1965), the repair of retinal detachment by freezing was attempted in 1933 by Bietti and also by

Deutschmann in the same year, both clinicians using carbon dioxide apparatus. Bietti went on to treat glaucoma by cryotherapy in 1950. Lincoff and McLean themselves in 1962 began experimenting with the use of cryosurgery for the repair of retinal detachments, in order to obviate the use of diathermy, which had marked disadvantages. They reported in 1965 on 110 cases of treatment for retinal detachment and in only three cases was there failure to obtain re-attachment of the retina.

Also in 1965, Bellows reported on 165 cataract removals with cryotherapy apparatus and detailed changes made in apparatus to render it more efficient and safe. He also outlined the technique for the removal of lenses affected by cataract, along with some complications encountered. He noted, in a three year follow up, no untoward effect on the eye from the use of cryosurgery (Bellows, 1965). Since this time, cryotherapy has found world-wide acceptance in a variety of ophthalmic surgical procedures.

In 1975 Holden edited a book on various clinical applications of cryosurgery, including ophthalmology. This work gave an impressive list of ophthalmological procedures, including tumour destruction, which can be carried out with the use of a cryoprobe and included some very well presented photographs of cases under treatment. The text of that book states that the use of freezing is "one of the most rewarding developments in the field of ophthalmology in recent years" (Amoils, 1975, p.35).

Summary

Cryosurgery is a relatively new science and in relation to oral surgery has only been seriously considered for the past twenty years. In respect of oro-facial pain control, the direct treatment dates back only a little over ten years. We can expect a considerable increase in the use of cryotherapy in oral surgery along with a much better understanding of the basic principles and techniques relative to this form of treatment.

CHAPTER 3

The Cryo-Lesion (Effects of extreme cold on living cells).

Introduction

Any form of surgery requires a basic knowledge of principles and in the case of cryosurgery the most important aspect, prior to clinical applications, is a thorough understanding of the effects of extreme cold on cells.

The underlying principle of cryosurgery is the destruction of living tissue by means of intense cold. Unfortunately, the exact nature of the changes occurring during freezing which bring about cell death are not fully understood, but it seems apparent that several conditions acting in harmony contribute to that end.

Theories of the effects of extreme cold on living cells

The most generally accepted phenomena leading to cellular destruction following the freezing and thawing of tissues are:

1. Extracellular crystallization.
2. Intracellular crystallization.
3. Toxic concentration of electrolytes.
4. Mechanical injury.
5. Dehydration.
6. Denaturation of proteins.
7. Thermal shock.
8. Ischaemia and infarction.
9. Cryo-immunization.

During cryosurgery "cells are at first injured and later die from the effects of the freezing injury" (Fraser, 1975, p.3). The changes which are generally accepted as combining to produce this cell death will now be examined. While these elements of the freezing process are to be looked at separately, it must be emphasized that there is a strong inter-relationship between some of them and, in particular, the first five.

1. Extracellular crystallization

As will be seen this phenomenon is closely related to intracellular crystallization.

Fraser (1975, p.4) stated that "slow cooling (about $1^{\circ}\text{C}/\text{min}$) is accompanied by the formation of extracellular ice crystals, by a process of heterogenous nucleation," and that these crystals self propagate through the extracellular spaces but may not be injurious to the cell. He also said that with small highly-permeable cells, water was withdrawn from the cells and contributed to the growth of extracellular ice crystals.

In regard to rapid cooling Holden proposed that if temperatures of -40°C and lower could be achieved "before large extracellular crystals have time to form", there was a consequent formation of very small multiple intracellular crystals.

Zacarian (1977, p.15) likewise stated that a slow rate of cooling led to ice crystals forming between the cells. He added that the cryosurgery freezing rate would be classed as rapid, but since a

given tissue is not homogeneous and freezing temperatures are at various gradients, some layers of cells (i.e. those furthest from the cryoprobe) would reach freezing temperature more slowly. Zacarian (op.cit., p.15), like Holden, agreed that extracellular ice withdrew water from cells, contributing to cell dehydration. This he believed led to a toxic increase of electrolyte concentration within the cell, and that there was a final shrinkage and collapse of the cell membrane.

Zacarian also observed that some "bound water " (8-10 percent of the total) within the cell could not be frozen, regardless of the cooling rate. Zacarian was, therefore, expressing the opinion that the damaging action by extracellular ice was not direct but rather indirect, by means of increased concentration of electrolytes and shrinkage of the cell with consequent membrane collapse.

On the other hand, Neel (1980, p.12), in discussing the freezing of cell suspension preparations in vitro, stated that "from a strictly mechanical viewpoint intracellular and extracellular ice formation are accompanied by compression and shearing forces which will destroy cell membranes". Although this statement appears to contradict Holden in part, it does not seem unreasonable to accept that such compression and shearing forces could play a role in cell membrane destruction.

Neel went on to say that "the growth rate of ice crystals depends on the temperature of the medium and the rate at which the medium is cooled", and that at below -25°C small thermodynamically unstable crystals formed while more stable crystals formed at higher

temperatures. Therefore, according to Neel, rapid cooling of about 100°C/min limited crystal growth but led to the formation of unstable crystals. He stated that if cooling was slower than 100°C/min water was withdrawn from the cells and all ice would be extracellular. This critical rate of cooling is much different to Fraser's concept (i.e. 1°C/min) and it seems that Neel's statement regarding "all" ice being extracellular is open to some debate.

If cooling is faster, Neel stated that the water loss from the cells could not keep pace with the freezing process and intracellular ice forms (i.e. unstable crystals) and that this was usually lethal to the cells. He further stated that during thawing the crystals coalesced and grew by recrystallization and, if the thawing was slow enough, large damaging crystals formed. If the thaw was rapid, Neel maintained that the unstable crystals merely melted and no recrystallization occurred.

Mazur (1966, p.253) considered that "extracellular freezing is a prerequisite for injury", but that it did not seem to be lethal by itself. He supported this statement with examples of cell survival in experiments during which the suspending medium was frozen to -10°C.

Poswillo (1973) did not enter into any detailed discussion regarding extracellular crystallization, but did give passing mention to it. He placed more importance on intracellular crystallization, toxic levels of electrolytes and vascular stasis, as causes of cell death following cryosurgery.

In referring to the work of Mazur and Meryman (see later text), Litvan (1972) stated that "at slow cooling rates, crystal formation is restricted to extracellular spaces". He also stated that rapid cooling led to intracellular ice formation and that "cytolysis invariably ensues", but gave no specific figures to describe his notion of slow or rapid cooling. The author also proposed an hypothesis "based on the assumption that intracellular ice does not form in intact cells" and went on to assume that, where intracellular crystallization was observed, it followed cell destruction and did not precede and cause the destruction. It must be noted that this hypothesis is based on assumptions and was presented without supportive evidence.

Litvan further suggested that during freezing there was a gradual release of "bound" water (desorption) and subsequent excretion of free water from the cell leading to severe dehydration, which, he maintained, had been shown to occur even at -60°C . Litvan believed that rapid cooling lead to water leaving the cell faster than the cell membrane permeability would allow, and that this action caused membrane destruction. This suggestion has to be reconciled with his previous statement that rapid cooling leads to intracellular ice formation.

In a summary, Litvan agreed with the supposition that cell injury occurred by dehydration during slow cooling and by membrane rupture during rapid cooling although he did not present any objective proof to support his hypothesis.

While discussing the haemolysis of red cells, Lovelock suggested that

"the formation of ice crystals is not in itself damaging to red blood cells" and placed far more emphasis on the concentration of electrolytes in and around the cells as a cause of injury during freezing (Lovelock, 1953). He gave a critical temperature range of -3°C to -40°C as being lethal to the cells. One must remember that Lovelock's suggestions were made in 1953, before much of the work of Mazur, Neel, Meryman and other investigators.

Nei, likewise, writing on red cell haemolysis, referred to Lovelock as hypothesizing that the electrolyte concentration increase was induced by extracellular and intracellular ice formation and affected the cell membrane constituents which in turn produced an increased membrane permeability and haemolysis (Nei, 1970, p.131).

Nei also submitted (op.cit., 131) that, at the time of Lovelock's writing, the "salt injury theory" (i.e. electrolyte disturbance) was generally accepted as the cause of animal cell damage during freezing. This theory would mean that ice formation exerted an indirect effect on the cell membrane and not a direct one, and that the compression and shearing theory of Neel's was invalid. In the light of subsequent knowledge it is likely that both these mechanisms play a part in membrane injury.

Interestingly, Nei himself (1970, p.136) mentioned that some cells are haemolysed "possibly by compression of ice crystals", this statement being more in agreement with Neel's assumption. Nei again referred to ice crystals in his conclusion (op.cit., p.140) and said that compression by surrounding ice and tight packing of cells in unfrozen solution may provide mechanical stress leading to

haemolysis. Of course red blood cells in suspension may behave somewhat differently to cells in solid tissue.

Shea and Dickson (1966) acknowledged that "there is a continuing controversy as to the mechanism of tissue destruction with freezing and there are as yet a number of unresolved theories". These authors maintained that large disruptive extracellular ice crystals may not be lethal to cells, provided that the exposure to these crystals was of short duration (op.cit., p.144). No real evidence was presented by these authors in support of their opinion which is similar to that expressed by Fraser (1975).

In the same year as Shea and Dickson's article, Meryman (1966) produced an extremely detailed account of freezing phenomena, and said that the idea of "bound" water being unfreezable was "clearly disputable". He also maintained that the ice-like structure of water when frozen "probably has very little to do with the alterations directly responsible for freezing injury". This statement seems to set aside the idea of mechanical damage by ice crystals. Meryman concluded that if a low enough temperature could be reached then "it is conceivable that no bound water would remain" (op.cit., p.11). Meryman added that "at slow rates of cooling many, perhaps most tissues and probably all cell suspensions freeze extracellularly" (op.cit., p.41). He said that the extracellular crystallization led to a hypertonic state and thus to cell dehydration, with large ice crystals perhaps many times the size of the cells. Meryman further discussed Mazur's proposition that extracellular ice crystal growth continues as long as the movement of water from the cell can support that growth, but was evidently not convinced and wrote (op.cit.,

p.44) that no satisfactory explanation had been proposed for the fact that with slow freezing the ice formation was preferentially extracellular. Meryman added that the crystallization was undoubtedly heterogenous and that extracellular catalytic nuclei must be larger than intracellular nuclei and thus produce extracellular crystallization at a higher temperature.

In regard to mechanical injury to frozen cells, Meryman (1966, p.48) concluded that it was difficult to prove that extracellular ice directly injured cells but admitted that the theory was "wholly believable".

Summary

- (i) Majority opinion allows that extracellular ice crystals form during freezing, preferentially at slow rates of cooling.
- (ii) It is reasonable to theorize that some mechanical injury to cells may be caused by extracellular ice.
- (iii) Extracellular crystallization is intimately related to intracellular crystallization, dehydration of cells, shrinkage of cells, increase in electrolyte concentration and possibly other mechanisms which lead to cell death during freezing and thawing.

2. Intracellular crystallization

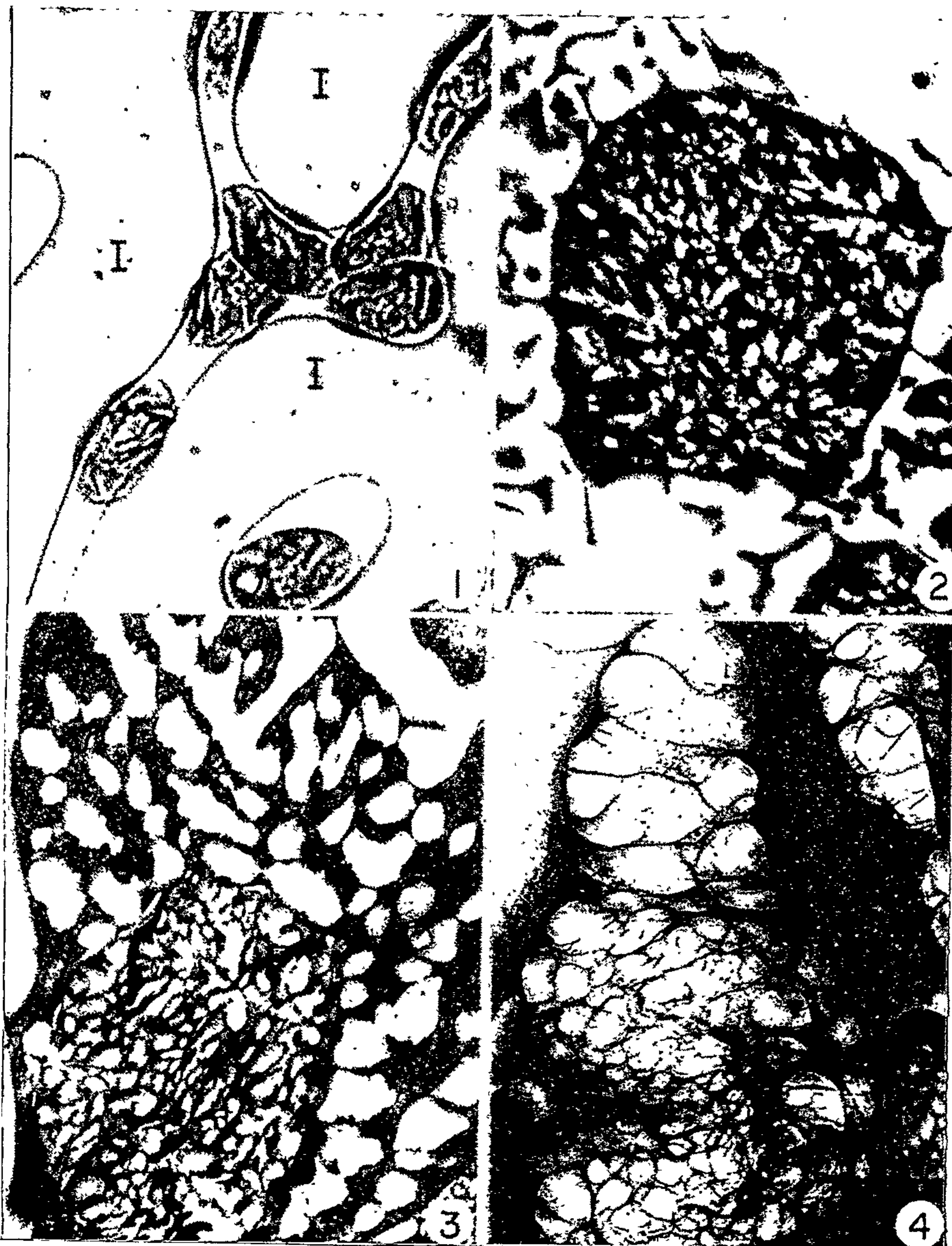
This phenomenon is now almost universally accepted as being one of

the prime mechanisms leading to tissue destruction following freezing and thawing. There remains, however, some debate as to just how these crystals form and in what manner they exert their lethal effect.

Following a lengthy discussion on the formation of extracellular and intracellular ice crystals, Meryman proposed, firstly, that slow cooling led to one or a few nuclei becoming "critical" and that ice then propagated through the extracellular space and that the cells may then be "seeded" by the extracellular ice. Secondly, that the ice may remain extracellular, or thirdly, that if the cell is relatively impermeable it may remain unchanged until "supercooling" leads to nucleation of individual cells (i.e. intracellular crystallization). He maintained that only if cooling is fast enough "to produce progressive supercooling despite crystal growth" can multiple intracellular crystals form (Meryman, 1966, p.48).

Mazur (1966, p.216) agreed with most others that "external water freezes before the cell contents" and added (op.cit., p.216) that the cell interior "always continues to remain unfrozen above -5°C and often above -10°C ". It was also contended by that author that ninety per cent of cell water becomes frozen at -20°C .

This, if correct, has great practical importance as, in order to induce intracellular crystallization, it would be necessary to freeze cells rapidly enough to reach -10°C to -20°C (at the actual cell site) before most intracellular water had diffused to form extracellular ice (Fig. 3-1).



Mode of action of freezing on red blood cells. (1): Effects of slow freezing at -5°C on blood; the photograph shows the cells (frog erythrocytes) confined in narrow channels between large masses of ice, labelled I. (2): Electron micrograph of a section through a red cell in bovine blood frozen rapidly at -150°C ; the micrograph illustrates the arborescent arrangement of the ice particles within the cell (the white specks represent cavities from which ice has been removed by freeze-substitution.) (3): Electron micrograph of a section through a frog erythrocyte frozen rapidly at -150°C , showing the difference in the size and the distribution of the ice particles (white specks) in the cytoplasm and the nucleus (the latter is at the lower left-hand side of the photograph.) (4): Electron micrograph of a replica of a frog erythrocyte frozen at -80° and recrystallized at -10°C . The spheroidal portion on the lower half of the photograph represents the main body of the erythrocyte which contains the nucleus; the upper portion represents one of the two narrow ends of the oval cell. Note that the two parts are filled with ice particles. (Magnifications: (1) $\times 655$; (2) $\times 14\,500$; (3) $\times 11\,900$; (4) $\times 6900$.) (From Rapatz and Luyet, 1960, 1961; and Rapatz, Nath and Luyet, 1963; by permission of *Biodynamica*.)

Fig.3-1. Freezing of erythrocytes. (From B.J. Luyet, *The Frozen Cell*, 1970. Edits. G.E.W. Wolstenholme and Maeve O'Connor. Courtesy of Churchill Livingstone, Edin. Publishers.)

Mazur continued (1966, p.219) that the remaining ten per cent of cellular water seemed definitely "bound" to cellular solids and that external ice probably nucleates (i.e. seeds) the cell contents, but that if a cell can lose water quickly enough (i.e. by slow enough cooling) "intracellular freezing is unlikely" (op.cit., p.228). That author then logically maintained that if water could not leave the cell rapidly enough, it became increasingly supercooled and more likely to freeze. In discussing yeast cell experiments, Mazur (op.cit., p.257) said that "internal ice crystals are chiefly responsible for the immediate low temperature injury" to the cells and that evidence showed that extracellular freezing and solute concentration seemed not to be important causal agents. He continued that conditions which produce internal ice do in fact kill a high proportion of cells and maintained that water, even without nucleating agents, cannot remain unfrozen below -40°C (op.cit., p.257). These statements are contrary to Lovelock's proposition but agree closely with Neel's views. As previously noted, all the mechanisms discussed by these authors may possibly contribute to cell death following freezing.

In re-asserting the strong correlation between intracellular ice formation and cell death, Mazur said that "the conclusion is that extensive mortality occurs only when internal ice is present" and that slow warming after freezing is more harmful to cells than rapid warming, which is almost identical to Neel's opinion. He also agreed with Neel that intracellular ice formed during rapid freezing and that events during slow warming killed cells, very possibly due to crystal growth and modification. Mazur maintained that when the rate of cooling was about $-100^{\circ}\text{C}/\text{min}$ intracellular ice formed in nearly

all cells and that this gave time for large stable crystals to form, which were lethal with slow or fast warming.

On this point Mazur seemed to disagree with Neel and other writers. At very high cooling rates (-10^4 °C/min) Mazur said that there was insufficient time for large crystals to form, so that slow warming was needed to produce large lethal crystals, by coalition of small crystals and that rapid warming merely melted the crystals causing no harm to the cells. This concept was more in line with Neel's and others' opinions.

Discussing the basis of cell damage by large ice crystals Mazur (1966, p.304) questioned whether intracellular ice damaged the membrane or whether the membrane was damaged first leading to secondary intracellular crystallization. This questioning was probably the basis for Litvan's (1972) assumption that intracellular ice does not form in intact cells. Mazur, however, continued (op.cit., p.305) on an important note, namely that since the warming rate is in fact a factor in cell survival then it follows that intracellular freezing "cannot have been a consequence of prior lethal injury". He concluded (op.cit., p.306) that only future experiments could absolutely prove that intracellular ice causes the irreversible membrane damage but that "it is clear that the formation of large intracellular ice crystals is lethal to most and perhaps all cells".

Love (1966) quoted several earlier investigators regarding cellular damage by ice during freezing, illustrating widely differing results and conclusions and then discussed his own experiments on fish muscle

(Fig. 3-2). He considered there to be three types of cell damage (op.cit., p.340), but the freezes under consideration were limited to between 0°C and -5°C for periods of from 20 min to 500 min. This work would thus hardly be applicable to cryosurgery in the modern sense.

Following experiments on ascites tumour cells, Shimada and Asahina (1975, p.209) stated that some animal cells survived freezing to -200°C but "invariably lost their viability during slow rewarming at temperatures below -30°C due to grain growth of intracellular ice crystals". In these experiments the cells mostly kept their initial shape and size (after rapid freezing to -27°C) but some showed contraction due to extracellular ice formation. It was reported that grain structures could be seen, which indicated intracellular ice crystals and that these crystals were always markedly smaller than the extracellular crystals. One interesting observation by these authors was that a cell with large intracellular crystals was often seen near a dehydrated cell and they stated (op.cit., p.212) that at faster freezing rates the intracellular ice grains became finer. They also said that slower freezing caused extracellular ice formation, which they expected caused dehydration of the cells. A further observation was that when cells were re-warmed to -17°C large intracellular ice crystals formed. Of importance were comments that under light microscopy the intracellular ice crystals were too small to see (i.e. the fine grain crystals), but the writers maintained (op.cit., p.214) that cells were invariably killed when visible ice crystals formed intracellularly.

Quoting their previous work on sarcoma cells, Shimada and Asahina



FIG. 16. Longitudinal section of cod muscle, showing both intracellular and extracellular ice in the same specimen. The effect was obtained by allowing partial cellular dehydration to occur by slow freezing, and then rapidly freezing to a low temperature, causing intracellular ice to form.

Fig.3-2. Intracellular and extracellular ice in frozen fish muscle. (From R.M. Love, Cryobiology, 1966. Edit. H.T. Meryman, Academic Press London Publishers.)

(op.cit., p.215) stated that intracellular crystals larger than 0.05 μm were invariably fatal to the frozen cell and that the cells were affected by the growth of the crystals and not by their initial size.

In a clear concise review article Shepherd and Dawber said (1982, p.323) that during cryosurgery the temperature changes were so rapid that intracellular ice formation was inevitable. As to the exact mechanism by which intracellular ice crystals caused death, they quoted Trump et al (1964) as postulating that damage to organelles and endoplasmic reticulum was possibly the lethal factor. Then quoting Meryman and Platt (1955) they suggested that the larger the intracellular crystals the more damage that is done. These authors decided that the "majority of evidence supports the view that intracellular ice is lethal" and also that "the destructive effects of slow thawing are well known".

Summary

- (i) The vast majority of opinion suggests that intracellular ice formation is a very important, perhaps the critical factor, in cell death during cryosurgery.
- (ii) There appears to be little doubt that intracellular crystallization is maximized by rapid freezing and slow thawing.

3. Toxic Concentration of Electrolytes

(Intracellular and Extracellular)

Lovelock (1953), as previously noted, proposed that the concentration of electrolytes both extracellularly and intra-cellularly appeared to be "most important in causing damage on freezing". He suggested that his experiments showed that ice formation was not the lethal mechanism for cell damage and that a sodium chloride concentration of 0.8M and over was the important level. He experimented using red blood cells in suspension and note must be taken that Lovelock's opinions were expressed over 30 years ago.

In reviewing past literature Shepherd and Dawber (1982, p.323) said that extracellular ice formation lead to osmotic changes and consequent passage of electrolytes out of the cell, thus producing decreased cell volume and membrane disruption. These writers quoted Luyet, Rapatz and Gahenio (1963), and said that when a certain concentration was reached, some normally intracellular components passed out of the cell and that this caused "irreversible damage" to the cell.

These authors seemed to conclude that it was the passage of intracellular electrolytes across the cell membrane which caused damage during freezing, rather than the absolute electrolyte concentration itself.

Neel (1980, p.12), referring to in vitro cooling of erythrocytes, said that moderate concentrations of sodium chloride made cells sensitive to thermal and mechanical shock but that higher

concentrations killed the cells. He was of the opinion that chemically this appeared to be due to denaturation of lipid-protein complexes in the cell membrane but that a consequent pH change led to molecular damage and changes in the rates of biochemical reactions.

In relation to these biochemical reactions it is interesting to note that Melnick found, in experiments on some 350 tissue samples, that slow freezing often resulted in diminished or absent histochemical enzyme activity, but strangely, following rapid freezing enzyme activity could be "almost invariably demonstrated" (Melnick, 1968, p.73). It is difficult to reconcile these two somewhat diverse opinions.

Meryman (1970, p.52) referred to Lovelock's theory that cellular damage commenced at 0.8M concentration of sodium chloride and stated that the only real quarrel with this was that no such biochemical injury had been demonstrated. He went on to say that similar effects were produced if other osmotically active agents were substituted for sodium chloride (e.g. sugar). Meryman then described experiments "primarily at room temperature" on red cells suspended in concentrated solutes to simulate those concentrations produced by freezing. He found that decreasing concentrations of solute in suspension led to cell shrinkage, but at a certain concentration (about 1300 m-osmolal) there was a cellular "volume increase" which he said implied extracellular solutes entering the cell. He stated that at about these concentrations there was a steady increase in intracellular sodium and a loss of potassium at a rate sufficient to deplete the cell in 60-90 mins. Importantly, he noted that haemolysis did not occur to "leaky" cells until a return was made to

isotonic conditions "as would occur with thawing" following freezing. He and his co-workers were not convinced by Lovelock's theory and concluded (1970, p.62) that the freezing injury in erythrocytes and probably most cells is not due to an absolute solute concentration and is more related to dehydration to a "critical cell size" (please see section on dehydration for further details of this theory).

While presenting a basically clinical paper Gill et al (1968, p.412) did refer to ultrastructural damage (such as alterations to mitochondria) to cells during freezing and observed that these changes were consistent with osmotic influences, pH changes and hypometabolism. This would in turn be consistent with an increase in electrolyte concentration.

Seim (1980) commenting on the mechanisms of cold induced cell death proposed that an increased concentration of electrolytes could -

- (i) modify the structure of macromolecules;
- (ii) remove lipids from cell membranes; and
- (iii) cause large pH changes, all of which could cause irreparable cell damage.

Summary

- (i) There seems no specific evidence to show that increased electrolyte concentrations during cryosurgery produces an insult to the cell sufficient to prove lethal.
- (ii) On the other hand, it is wholly believable that this electrolyte concentration increase could be one of several

mechanisms which contribute to cell mortality during freezing and subsequent thawing.

4. Mechanical Injury

Lovelock (1953, p.424) said that his experiments showed that a secondary consequence of a sodium chloride concentration of 0.8M and over was a "sensitivity to thermal and mechanical shock" in the cells. He further stated that mechanical "shock" was likely to play a small part in cell damage in the early part of freezing when cells are being distorted by ice formation.

As previously referred to, Neel (1980, p.12) was of the opinion that compression and shearing forces would destroy cell membranes during intracellular and extracellular crystallization.

It can be readily seen that Lovelock and Neel were at least partially in agreement as regards mechanical injury to cells during freezing.

As also previously mentioned in the section on extracellular crystallization, Litvan (1972) suggested that the cell membrane was damaged during rapid freezing by water leaving the cell at a rate faster than the permeability would allow. Presumably his idea was that this flow of water was sufficient to literally tear the membrane apart, but no real evidence was produced to support this suggestion.

Meryman (1970, p.51), discussing cell injury by freezing, stated that extracellular ice "probably exerts no mechanical pressure on the cells and certainly does not puncture them". This statement is

notably different to the opinion of Neel referred to above. Meryman did however proceed to say that there were only rare exceptions when animal cells would survive intracellular freezing.

In discussing the mechanical injury to a cell membrane during freeze-thaw cycles, Farrant (1971, p.20) was of the opinion that the two main causes are, firstly, changes in concentration of extracellular solutes and, secondly, the formation of intracellular ice. He reviewed the work of Lovelock and Meryman (referred to elsewhere in this chapter) and concluded that "cellular uptake of solutes and damaging osmotic swelling on thawing", plus freezing of internal cell water (at rapid cooling rates) were the main causes of cell damage. Farrant did not go into detail as to just how the internal ice damaged the cell, but did say that cell shrinkage played a part in this particular destructive mechanism.

In discussing crystallization Seim (1980, p.756) agreed with Neel (1980) and with Mazur (1966) that the recrystallization of minute intracellular crystals to larger crystals following rapid freeze and slow thaw was the mechanism by which cells are damaged. It appears that Seim believed that these enlarged crystals damaged the cell membrane mechanically, as did Neel.

Summary

- (i) Mechanical injury to cells during freeze-thaw cycles is probably closely related to intracellular and perhaps extracellular ice formation.

- (ii) Other mechanisms such as movement of water or solutes across the cell membrane may induce mechanical damage during cryosurgery.
- (iii) Swelling of the cell during thawing may mechanically damage the cell membrane.

5. Dehydration

Following experiments on red blood cell suspensions, Meryman (1970, p.55) suggested that a possible cause of cell injury during freezing could be dehydration leading to a "minimum cell volume". He observed that as a cell shrinks a resistance against the shrinkage is encountered due to compression of cell contents and that when the minimum cell volume is reached, osmotic stresses across the cell membrane occur resulting in membrane damage. He added that normally extracellular solutes then enter the cell, due to the pressure gradient exceeding the tolerance of the membrane and that this leads to irreversible changes in membrane permeability.

This is an interesting concept and fits in very neatly with other theories of movement of solutes across the cell membrane as being the cause of cell damage during freezing.

A somewhat different approach was taken by Gill and Fraser (1968) who, in summarizing the different hypotheses for cell death following freezing, were of the opinion that cell dehydration could result in "denaturation of cell proteins or changes in the pH or ionic concentration of the intracellular milieu". These writers concluded

that these results of the dehydration could be lethal to the cell.

In relation to dehydration, Mazur (1968, p.39) agreed with Zacarian and others that it is the result of slow cooling and produces extracellular ice formation. Interestingly, Mazur stated (referring to experiments on yeast cells) that the low cell survival rate after slow freezing (10-40 per cent) might be due to dehydration (op.cit., p.38) on account of an increase in the concentration of electrolytes, a decrease in spatial separation of macromolecules and the removal of a "critical" amount of water. It will be seen later that Mazur's opinion was rather similar to that of Rinfret.

In a later article Mazur et al (1970, p.83) put forward a very similar proposition on dehydration, but were unable to say which of the above three phenomena should be regarded as the major cause of cell injury. They concluded that intracellular crystallization was the major cause of cell death following rapid freezing and it seems that they considered dehydration more important during slow freezing.

Rinfret (1968, p.19) made somewhat similar observations to those of Gill and Fraser, in that "water is the major component of living systems and functions therein". Presumably water is essential for the metabolic function of the cell and when changed to a solid the metabolic system can no longer function. He continued that modification of those functions can cause irreversible changes. Rinfret referred to water leaving the cell during freezing as "phase transition", and stated that "ordered" water was necessary for molecular and intermolecular activities and that its removal (e.g. from a cell membrane) leads to "catastrophic effects" and cell death.

This opinion appears to give a simple explanation as to how dehydration can lead to cellular death, as it can do to a complete living system.

Summary

- (i) Dehydration of cells seems to occur more predominantly at slower rates of cooling and is intimately connected to extracellular ice formation.
- (ii) There appears to be a critical amount of water which when lost by a cell leads to irreversible damage to the cell.
- (iii) At cooling rates associated with cryosurgery dehydration probably plays only a small part in cell death.

6. Denaturation of Proteins

Regarding cellular destruction, Levitt and Dear (1970) believed that cellular proteins are denatured during freezing by the weakening of hydrophobic bonds between the proteins. They observed that this denaturation is usually reversible but can be converted to an irreversible aggregation of proteins. They believed (op.cit., p.150) that extracellular ice dehydrated the protoplasm until the proteins came close enough to each other for bonds to form between them. The hydrophobic bond group according to Levitt and Dear are maximal in the cell membrane and therefore the membrane proteins are the most vulnerable to this irreversible aggregation. These authors maintained that the aggregation produced a rigidity within the

membrane which was not reversed and that extracellular ice produced a tension on the protoplast surface.

In a summary Levitt and Dear (1970, p.170) gave their opinion that "holes" are formed in the cell membrane by -

- (i) intracellular ice penetrating the membrane and
- (ii) tension on the membrane due to cell collapse during extracellular crystallization. These "holes", they believed, lead to an efflux of cell substance and cell death.

Karow and Webb (1965) put forward a theory that during slow freezing bound water lattices were formed which acted as exoskeletons to the cellular proteins and supported them, but that rapid freezing used up part of the bound water, thus leading to a weakening of the lattice structures. They were of the opinion that this phenomenon led to "physical derangement of the membranes and promotes their denaturation with subsequent breakdown".

Seim (1980, p.757) believed that freezing led to a loss of phospholipids which "renders the cell membrane permeable to ions so that it slowly swells and bursts". He stated that this could occur during the freeze or thaw stage.

In referring to the work of several investigators Gill and Fraser (1968) stated that there was mounting evidence to suggest that critical alterations to the phospholipid complexes of the cell membrane could occur during freeze-thaw cycles.

This statement is very similar to the summary of Seim, and it would

appear that the idea of some derangement or loss of phospholipid complexes in the cell membrane during freezing is gaining wide acceptance.

In an in-depth account of experiments on mouse liver tissue, Trump et al (1965) suggested that damage to intracellular membrane systems may be the primarily important mechanism in cell death following freezing and thawing. They added that after most types of freezing and thawing there were prominent changes seen in the plasma membrane. They dealt with changes observed in the mitochondria and the endoplasmic reticulum and commented (op.cit., p.163) that "alterations of intracellular membrane systems are more numerous and pronounced after more rapid rates of freezing". They further linked this fact to intracellular crystallization and went on to say, as do other writers, that "with few exceptions, very rapid freezing is lethal to mammalian cells". It was also suggested (op.cit., p.166) by these writers that changes in the plasma membrane following freezing and thawing may represent the limiting factor in cell survival.

Summary

- (i) There is wide agreement that freeze-thaw cycles do produce a damaging alteration to cellular proteins.
- (ii) There are several theories as to the nature of this damaging alteration, the most accepted of which is a loss of denaturation of phospholipid complexes.
- (iii) There appears to be almost universal acceptance that rapid

freezing causes the most damage to cellular proteins.

7. Thermal Shock

Neel (1980, p.10) wrote that "some cells can be damaged or destroyed simply by cooling at near 0°C in the absence of freezing and this is referred to as thermal shock". Neel considered that mammalian cells and most other cells are certainly damaged by a cooling rate of 10°C/min and that the thermal shock damage occurs in the cell membrane's lipoprotein.

Lovelock (1953) however concluded that thermal shock was not likely to be important in cell damage above a temperature of -10°C. He maintained that cells were made more sensitive to thermal shock at sodium chloride concentrations of 0.8M or more. These statements did not however appear to be well established by Lovelock's experiments.

In a further article one year later Lovelock (1954) again discussed electrolyte concentration and thermal shock and suggested that some cells in their normal state show a sensitivity to cooling and that thermal shock affects cells very rapidly. He regarded the cell temperature and the temperature change to which the cell was subjected as important factors and that a physical change in the cell membrane at low temperatures was probably the cause of the destructive effects. Lovelock stated that the important factor which sensitizes a cell to thermal shock is "the ratio of cholesterol, or possibly cholesterol lipoprotein complex to lecithin in the cell membrane", (i.e. the higher the ratio the more sensitivity).

It can be seen that Lovelock agreed with Neel that thermal shock affects the cell membrane.

Mazur (1966, p.214) was more orientated to the effects of temperature on physical, chemical and therefore biological processes and observed that enzymatically catalysed reactions in living cells are affected by a temperature fall which modifies cell function. Mazur also gave his opinion that rapid cooling was necessary to induce thermal shock. Thus it can be assumed that the cryosurgery cooling rate would suffice to produce some degree of thermal shock.

In giving a similar opinion to Mazur, Seim (1980) decided that at times a rapid temperature change could damage a cell before freezing occurred. He pointed out, interestingly, that this could account, in part, for cellular damage with rapid cooling, as opposed to slow cooling. Seim also cited a school of thought that cellular damage may be caused by "varying coefficients of expansion in membranes resulting from heat change in various components of the cell".

In 1942 Sano and Smith published details of experiments carried out on five different types of malignant tumour cells at temperatures between 37°C and 0°C. They concluded that there was a "definitely critical level around 22-24°C" which, if maintained long enough, led to lethal interference with the metabolism of neoplastic cells. Since this range of temperatures excludes ice formation and other allied mechanisms, it would seem reasonable to conclude that the cells were, at least in part, damaged by what we refer to as "thermal shock" and it is noted that Gill and Fraser referred to Sano and Smith's paper under that heading.

Summary

- (i) Thermal shock refers to a damaging effect to cells by pure temperature reduction and excludes freezing effects.
- (ii) Rapid cooling appears to produce more thermal shock.
- (iii) Thermal shock probably damages cells by affecting the cell membranes.

8. Ischaemia and Infarction

The effect of extreme cold on the regional circulation was investigated by Whittaker (1972) who reported freezing experiments on twenty five hamsters, injected post-operatively with a solution of carbon particles (Figs. 3-3 and 3-4). Whittaker provided excellent photomicrographs of the vascular network at various times after freezing (op.cit., p.447). He wrote that "normal blood flow is restored within a few minutes of operation, but the permeability of the vessels becomes marked within the succeeding thirty minutes", (i.e. both venules and capillaries) and that "stasis of the area becomes increasingly severe from two hours post-operatively". The arteries, Whittaker reported, remained patent but exhibited increased permeability. Whittaker added that "intracellular damage is visible shortly after removal of the freezing probe and becomes severe within one hour of operation". He believed that cellular damage was primary and that vascular stasis was secondary, acting by the second post-operative hour.

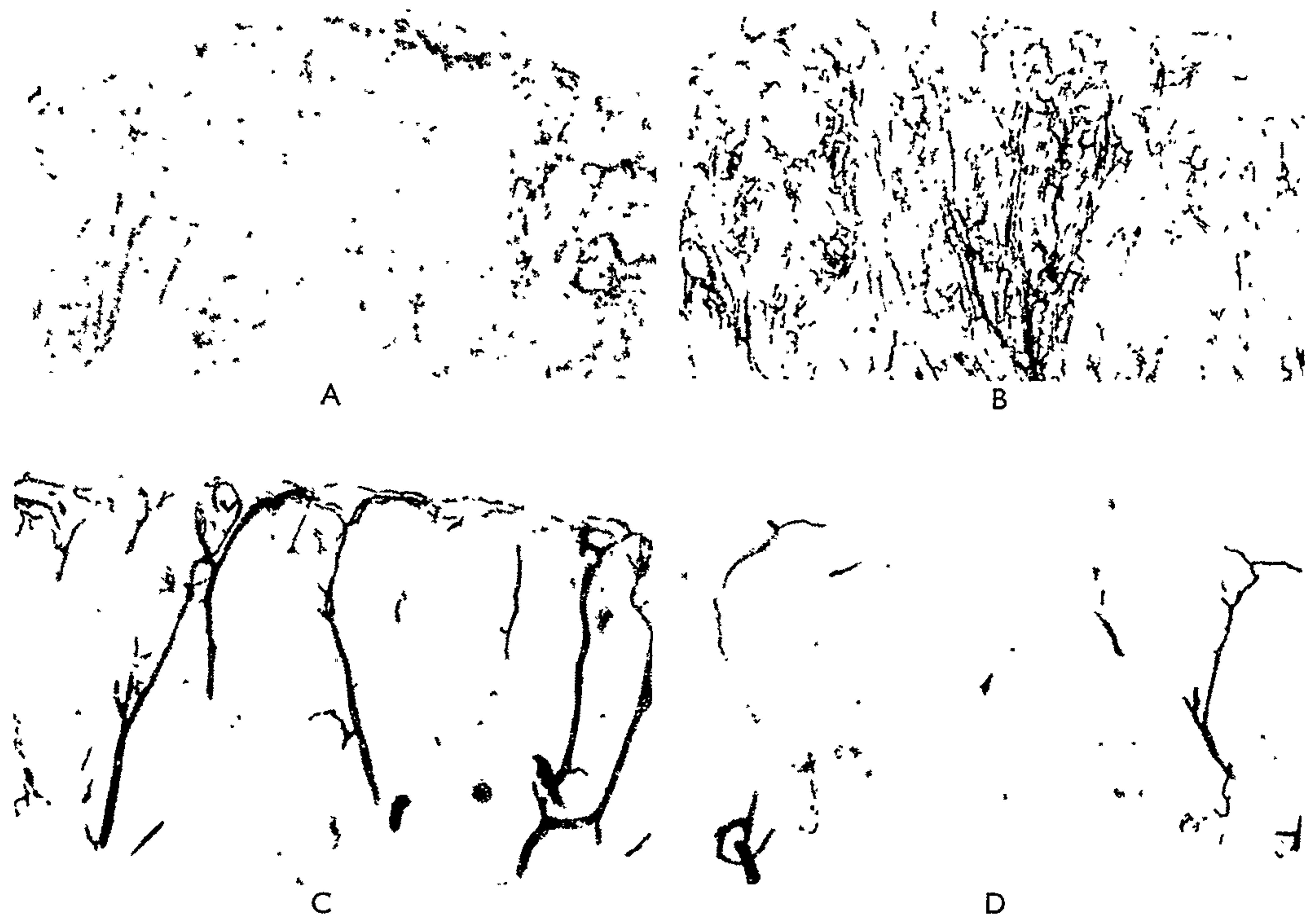


Fig. 2.—Carbon particles adhering to the walls of blood-vessels. Frozen sections. ($\times 100$.) A, Carbon injected 5 minutes after cryosurgery. Venules at the periphery of the frozen area are lightly labelled. B, Carbon injected 30 minutes after cryosurgery. There is heavy labelling of venules and capillaries. C, Carbon injected 2 hours postoperatively. A small number of venules are heavily labelled. D, Carbon injected 24 hours after cryosurgery. Stasis prevents the ingress of carbon to the majority of vessels.

Fig.3-3. Blood-vessels following freezing. (From D.K. Whittaker, *Dental Practitioner*, 1972. Courtesy of John Wright and Sons, Ltd., Publishers.)

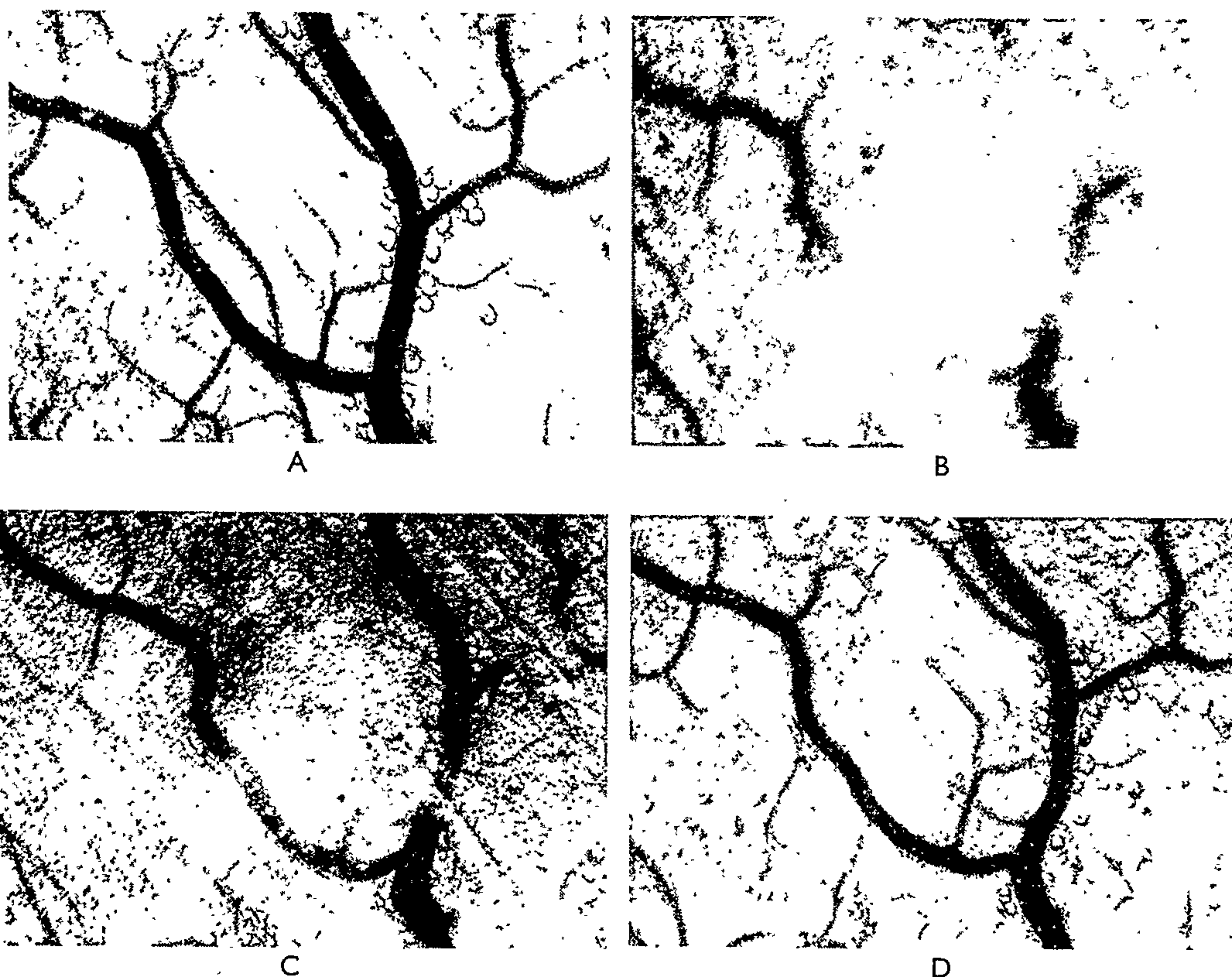


Fig. 6.—Time-lapse series of blood-vessels in an area of freezing. ($\times 200$.) A, Preoperative situation. B, Immediately after freezing. C, One minute postoperatively. D, Ten minutes after operation. Flow through the vessels has been restored.

Fig.3-4. Blood-vessels before and after freezing. (From D.K. Whittaker, Dental Practitioner, 1972. Courtesy of John Wright and Sons, Ltd., Publishers.)

In a later article Whittaker (1980, p.242) confirmed his previous findings.

Gill and Fraser (1968) also referred to vascular response to freezing and stated that "the histological features of a cryo-lesion closely parallel those of ischaemic infarction". These writers also concluded that "vascular stasis and capillary sludging are known consequences of freezing".

A clear distinction was pointed out by Neel between in vitro and in vivo freezing, since in vivo freezing is opposed by two heat sources, namely air and heat from the lesion itself, both of which are absent in the case of in vitro freezing. Neel held a strong opinion that vascular stasis was extremely important in the production of tissue death and stated (1980, p.13) that "the heat sink and the pathogenesis of tissue injury is largely dependent on vascular stasis, anoxaemia and ischaemic necrosis". Neel referred to the work of Zacarian and of Lenz separately and outlined their findings regarding blood flow and vascular damage upon thawing, noting that "venules are more susceptible to thermal injury than are arterioles."

In 1972 Lenz published a study of experiments carried out on 155 golden Syrian hamsters and stated that during freezing the vessels were scarcely visible due to ice formation but also stated that -

- (i) rupture of vessels was seen fifty hours after freezing,
- (ii) vascular permeability increased on thawing, and
- (iii) complete stasis was observed during the thaw period,

but the blood flow was re-established as the tissue was warmed. Lenz also observed that cryonecrosis occurred in 38 per cent of cases at

50 hours post-operatively and 100 per cent of cases at 100 hours post-operatively.

In an article devoted to the effects of cold on the microcirculation, Zacarian and his co-workers stated (1970, p.27) that sustained impairment of the microcirculation produces inevitable tissue death. These authors, like Whittaker, found that tissue death following freezing was due firstly to direct cellular insult and secondly to "vascular stasis which leads to anoxemia and ischaemic necrosis". Their experiments showed "definite vascular stasis", and they concluded that cryogenic temperatures have little effect on large vessels but that "microvessels are extremely cryosensitive". These investigators described their experiments on thirty six hamsters using single and double freezes at temperatures between 0°C and -100°C, and reported that freezing completely obscured the vascular network and that during the thaw the circulation was entirely arrested. As the temperature returned to normal they observed,

- (i) that the circulation returned, but slower than normal,
- (ii) momentary constriction of arterioles and venules (not capillaries),
- (iii) showers of emboli in larger microvessels, and that some capillaries could not be seen.

They observed sustained vasodilation for up to 45 minutes and that venules and arterioles never regained their original calibre. A huge increase in vascular permeability was observed, especially in the venules, within minutes after the freeze and vascular stasis began 5 minutes post-freeze and was complete in 30 minutes. Zacarian and his

colleagues (op.cit., p.37) that "the hallmark of tissue damage is the alteration and arrest of the microcirculation". These experiments showed that capillaries were least damaged by freezing, but were affected by virtue of their bridging position between the arterioles and venules.

One very interesting point emerged from these investigations in that little difference in microcirculation damage was noted between single and double freezes, nor at temperatures between -30°C and -100°C .

Summary

- (i) Ischaemia and infarction are probably very important mechanisms in the lethal effect of freezing on tissue.
- (ii) In the microcirculation venules are more affected by freezing than are arterioles. Capillaries are least affected directly.
- (iii) Complete vascular stasis probably occurs at between half an hour and two hours after freezing.

9. Cryo-immunization

It is not proposed to enter into a long discussion on this topic in this treatise as the relevant research work has not progressed to any conclusive stage. However, some reference to experiments carried out by Shulman and his co-workers (1968) does seem worthy of note. In describing freezing experiments on rabbits Shulman stated (p.83) "it is clear that a strong and definite antibody response can be

obtained". Shulman also gave two interesting theories as to the possible mechanisms of this reaction, namely:

- (i) the antigenic substance may be slightly modified by freezing which allows it to behave like a sufficiently foreign substance for the antibody forming cells to react to it; or
- (ii) the antigenic materials are not altered, but due to massive cell membrane destruction the antigen is simply liberated into the blood stream in huge quantities which leads to antibody formation.

The whole of this subject may prove to be of enormous value, particularly in the field of cancer control, but the research and practical application of this mechanism are for future consideration.

Controlling factors

1. Rate of freezing and thawing

In discussing the controversy about the mechanisms of destruction during freezing, Shea and Dickson (1966, p.144) said that, regardless of the exact mechanisms of cell death, rapid freezing producing ice crystals seemed to be uniformly fatal to cells, except epithelium cells, some tumour cells and erythrocytes.

This statement seems to be an oversimplification and does not, for example, differentiate between different types of ice crystals, although it could be assumed that these authors were referring to intracellular crystals.

Seim (1980) stated subsequently that the more rapid the freeze the greater degree and depth of tissue necrosis. He also stated that the

slower the thaw the more cellular destruction was observed. These observations are very similar to majority opinion, as previously examined in the sections of this treatise dealing with crystallization.

Mazur (1968, p.43), referring to the reviews of Smith (1961), said that "cells are more likely to be killed when cooling is rapid ($>100^{\circ}\text{C}/\text{min}$) than when it is slow ($1^{\circ}-5^{\circ}\text{C}/\text{min}$)", and that the "cells are more likely to be killed when warming is slow ($1^{\circ}-10^{\circ}\text{C}/\text{min}$) than when it is rapid ($>100^{\circ}\text{C}/\text{min}$)". He went on to give a concise but impressive table which was compiled by Billingham and Medawar (1952) in support of these propositions.

It can be seen that Mazur's views correlate well with those of Shea and Dickson in regard to the value of rapid freezing and slow thawing.

Mazur (1968, p.44) attributed these phenomena basically to the formation of intracellular ice, but tempered his opinion by saying that "it seems quite certain, however, that intracellular freezing is not the only cause of cell injury". He suggested that solute concentration and dehydration of the cell were important factors also.

Mazur, referring to the distance from the cooling source and surrounding heat sources, gave details of experiments carried out on starch solutions, which showed the cooling "rate" (from 0°C to -30°C) to be ten times as great at 1 cm distance than at 4 cm distance (namely $10^{\circ}\text{C}/\text{min}$ compared with $1^{\circ}\text{C}/\text{min}$). These experiments utilized

a cold plate at -72°C as the source of cooling.

One could assume that some similar effect would be produced in tissues cooled by a cryosurgical probe.

Mazur decided that a thaw of between 10 to 30 minutes was desirable in order to maximize the lethal effect to cells and that this time allowed cells not already killed by the freezing to be injured by increased electrolyte concentration.

Poswillo (1973) agreed that freezing rapidly enough to produce intracellular ice crystals was one of the major factors in producing cell death. He did not give an absolute mathematically optimal rate of freezing or thawing, as Mazur did, but did say that the cooling rate should be between that rapid rate which produces intracellular ice but almost no shrinkage, and a slower rate producing a greatly reduced amount of intracellular ice but a great degree of shrinkage.

As to the rate of thawing Poswillo quoted Smith (1961), previously referred to in this section, and agreed that slow thawing was more damaging to cells than was rapid thawing.

Zacarian (1977, p.10) observed that the rate (and depth) of freezing could be altered to some extent by the cryogen used and said that, for example, liquid nitrogen will give a faster freeze than nitrous oxide and that the "velocity of freezing and depth of the ice front far exceeds that of nitrous oxide at the same interval of time".

Zacarian interestingly noted (1977, p.10) that, while the thaw period

was somewhat out of the operator's control, "the thawing period is usually one and a half times the duration of the freezing time".

Zacarian further considered that a complete thaw was "extremely important" and rejected opinions on half-thaw being of value on the basis that evidence pointed to the likelihood of maximal cell damage occurring at between -10°C and 0°C .

2. Absolute temperature

Seim (1980) wrote that generally the lower the probe temperature the larger the cryo-lesion due to higher temperature gradients leading to more peripheral tissue being cooled. As will be seen later this opinion is very similar to that of Zacarian.

Walder and his co-workers (1968) carried out one hundred freezing experiments on the brains of sixty-eight cats. They used probe temperatures of -10°C to -180°C cooling for 5 minutes and stated (op.cit., p.135) that "the size of the cryogenic lesion can indeed be predicted within limits". A graph (op.cit., p.134) given by these authors showed an almost uniform increase in cryo-lesion size from about 3mm diameter at -10°C to as high as 18mm diameter at -180°C .

As with cooling and thawing rates Poswillo (1973) did not go into absolute figures for optimal temperatures for cryodestruction of cells. He did however subscribe to the belief (op.cit., p.69) that "there is probably a critical temperature zone at which the concentration of toxic solutes is maximal, inflicting irreparable damage".

Zacarian (1977, p.16) discussed eutectic temperatures (i.e. the lowest temperature at which a solution remains liquid) and reported that various tissues have different electrolyte levels from which he concluded that a temperature, at cellular level, of at least -20°C was needed to assure that the "hypothermia will be effectual and lethal".

This opinion followed Zacarian's previous statement (1973, p.9) that both cryobiologists and clinicians alike had well established that a temperature of between -20°C and -30°C was required to produce cryonecrosis. Here Zacarian strongly emphasized the fact that in the case of malignancies liquid nitrogen, due to its lower temperature and therefore deeper penetration, was the only cryogen with the capacity to induce an ice front deep enough for successful treatment of these lesions.

It is interesting to note that Mazur (1968, p.49), writing on the maximizing of cryosurgical effects, agreed that a temperature of -20°C was required to produce the desired cell death.

In relation to the size of the cryo-lesion produced during cryosurgery, Fraser (1975, p.7) listed probe temperature as one of the most important factors which relate directly to the cryo-lesion's extent. While allowing that body tissues, except possibly bone, "are constant in their thermal properties" Fraser interestingly stated that a 1°C fall in ambient temperature can produce a five per cent increase in the dimensions of a cryo ice ball.

3. Freeze-thaw cycles

Seim (1980) stated that it was "generally accepted that at least two applications of temperatures ranging from -15 to -20°C will result in adequate cellular destruction and tissue necrosis". There is however no specification in this statement as to whether the given temperatures are at probe or cellular level and no mention is made of freeze or thaw durations.

Seim believed that multiple freeze injury appeared to be due to "increased thermal conductivity" and observed that repetitive freezes lead to slower thaw, presumably due to lower tissue temperature and disruption of microcirculation. These factors combined to produce a greater degree of cold insult to the tissue in the opinion of Seim.

Poswillo (1973) cited the work of Gill et al (1968), previously referred to, and stated that in regard to freeze-thaw cycles the volume of tissue affected was increased by repeated freezing, reaching a maximum after five to seven applications.

He, like Seim, attributed this effect to an increase in the thermal conductivity produced within the tissues by the repeated freezes.

Zacarian (1977, p.10) gave great importance to freeze-thaw cycles and in relation to thaw stated that "cryobiologists consider this phase to be even more lethal than the freezing cycle". He said that rapid thawing led to more cellular survival in plant and animal cells and went on to agree with other writers that slow thawing led to recrystallization of ice, particularly intracellularly, which he

considered to be more lethal to cells.

Zacarian gave experimental evidence to support his opinion regarding a full thaw by means of figures obtained during experiments on HeLa cells. He observed a ten per cent higher kill rate with complete thaw in comparison to "half thaw" as advocated by some investigators.

Mazur, (1968, p.50) writing on methods to maximize the lethal effects of cryo-surgery (1968, p.50), stated that the effect of freezing was probably increased by multiple freeze-thaw cycles at below -20°C .

In giving an account of five years experience in the use of cryosurgery in the treatment of benign and malignant tumours, Cahan (1968, p.388) set out three conditions under which successful cryonecrosis could be obtained and the third of these conditions was "repetition of the cycle of freezing and thawing of the same area two or more times". Cahan gave several examples of a two freeze-thaw technique including an unusual one where liquid nitrogen was poured in to fill the bony cavity left after removal of a giant cell tumour of bone.

Cahan argued in favour of multiple freeze-thaw cycles (1968, p.403) in that after the first freeze many capillaries are thrombosed and so less temperature resistance is experienced with subsequent freezes.

Fraser (1975, p.8) was also firmly of the opinion that a multiple freeze regimen could increase the attainable size of a cryo ice ball and attributed this fact to the increased thermal conductivity in the tissues produced by the multiple freezes. He reported that 80-90 per

cent of the maximum freeze effect could be obtained in about 15 minutes of application of a cryoprobe, but that subsequent applications "alter this performance significantly". He went on to state that the "maximum effect is obtained after the fifth to seventh application".

4. Depth of freeze

The depth to which a cryoprobe can freeze tissue assumes great importance, especially in cancer therapy, and indeed in any situation where a considerable thickness of tissue is to be treated.

In discussing tissue temperature and density, Seim (1980) observed that vascularity affects the speed and extent of freezing and highly vascular tissues took longer to freeze and thawed more quickly. To offset this disadvantage Seim suggested the use of pressure on the probe, the injection of epinephrine and ligation of vessels (rarely possible).

Seim stated that higher water content (as he maintained existed in neoplastic tissue) facilitated freezing.

In relation to vaso-constrictors, Neel (1980, p.37) agreed that the injection of epinephrine around the area to be treated led to more rapid freezing, greater depth of freezing and, very importantly, a lengthening of the thaw period to about three times that experienced when no epinephrine was employed.

Mazur (1968), in writing on "maximizing lethality in the target"

pointed out that the cryosurgeon should allow the ice ball to expand until all the target has been cooled to below -20°C and the ice has extended beyond the limits of the target. This obligation of course must apply in all dimensions including depth for complete eradication of unwanted tissue.

Poswillo (1973), writing on the effects of local heat sources on cryosurgery, was of a very similar opinion to Seim in that a cryo-lesion is surrounded by a "very effective heat source in the form of the local vascular supply". He likewise mentioned the advantageous use of pressure on local blood vessels and the use of chemical vasoconstrictors to maximise the cryodestruction of tissue.

Describing an in vivo experiment on canine skin using a liquid nitrogen spray, Zacarian (1973, p.12) gave figures of temperatures recorded at one and two minutes after commencement of freezing and at depths of 2mm and 5mm. He pointed out first that after one minute the surface ice continued to extend during the second minute but the ice front below (i.e. deep) advanced much more slowly and, secondly and very importantly, that at 2 minutes the temperatures at both 2mm and 5mm depths were much colder. Zacarian stated (op.cit., p.12) that "we must be cognizant to relate time temperature and depth parameters in the freezing experience".

Later in 1977, Zacarian went into more detail on the importance of establishing the depth of the cryo-lesion and reported (p.5) that his experiments had shown that tissue in close proximity to the cryoprobe can be frozen at rates some 10 to 100 times as rapidly as those tissues 2mm and 5mm deep in the cryo-lesion. He also reported that

the depth of cryo-lesion below the cryoprobe approximated the distance between the edge of the cryoprobe and the extent of ice on the surface. Zacarian also emphasized the absolute need for the use of thermocouples imbedded in the tissue to monitor temperatures at depth when dealing with cancer destruction by cryosurgery.

5. Thermal conductivity of tissues

As previously noted, Poswillo (1973) was of the opinion that repeated freezes led to an increase in the thermal conductivity of tissue and enhanced the damage inflicted by cryosurgery.

This principle is a generally accepted fact in the field of cryosurgery and forms one of the criteria for clinical treatment.

In his excellent article on the "engineering aspects of cryosurgery" Garamy (1968, p.112) reported that the response of living tissues to cryosurgical temperatures was of paramount importance and that water, being the main ingredient of living cells, influences the tissue response to the largest extent. Writing on the thermal conductivity of ice, Garamy showed that there was a 28 per cent increase in thermal conductivity of ice as the temperature was reduced from 0°C to -170°C. This is of great importance as very low cryosurgical temperatures will thus allow a far greater heat transfer throughout the tissue mass.

It was noted in the section on depth of freezing that Seim (1980) had stated that a higher water content of tissue facilitates freezing. This statement would basically agree with Garamy's findings.

It has also been seen in the section of freeze-thaw cycles that Fraser (1975, p.8) agreed with Poswillo that multiple freezing increased the thermal conductivity of tissue so that as a consequence a larger mass of tissue was capable of being frozen than was the case with a single freeze.

Neel (1980) also agreed that multiple freezes did lead to an increase in the size of a cryo-lesion due to a consequent increase in the thermal conductivity of the tissues, but argued that the alteration in conductivity was due to a change in the basic cellular structures and progressive interruption of the blood supply. It can be seen that this concept is slightly different, but not completely so, to the ideas of Garamy.

Fraser and Gill (1967, p.774) also agreed that multiple freezes increased the thermal conductivity of tissue which increased the rate of freezing with each subsequent freeze and also allowed a larger cryo-lesion to be formed.

6. Applicators, probe size, etc.

In regard to instrumentation, Seim (1980) was of the opinion that the greater the probe size (i.e. diameter) then the greater the volume of the cryo-lesion able to be produced. This author went on to state that the probe size "should approach as nearly as possible the size of the lesion" to be treated. These opinions would seem to be very reasonable and generally acceptable to cryosurgeons.

Poswillo (1973, p.82) decided that the ice ball should be

"approximately 0.5 cm larger than the boundaries of the lesion to be destroyed". He allowed that this may at times not be possible with a single application of the probe and stated that when this was so the lesion should be mapped so that several applications produced an ice ball to cover the whole lesion. He pointed out that the lesion should be treated from the periphery first and the centre last and placed great importance on the careful selection of a suitable probe as regards size and shape.

Neel (1980), in discussing in vivo freezing, likewise placed importance on the probe tip in the formation of a satisfactory cryo-lesion. He maintained that the important factors were refrigerant temperature and the rate of flow, the conductivity capacity of the probe tip, the shape and area of the tip and the duration of application. He stated that the cryo-lesion took the shape of a sphere or segment of a sphere around the probe tip. Neel stated (op.cit, p.16) that liquid nitrogen is vastly superior "for cancer treatment mainly due to its low boiling point of -196°C ". He also mentioned the need for a variety of shapes and sizes of probe tips and stated that open spray techniques were more difficult to control but on the other hand are able to freeze larger regions more rapidly.

In giving details of freezing experiments carried out on rats' livers, Fraser and Gill (1967), using liquid nitrogen as a refrigerant, reported that maximum local freezing occurred within four minutes. It was reported also that the probe, if placed in liquids at room temperature or on the surface of the rat's liver, took only 20-30 seconds to reach -190°C , whereas if placed deep in the rat's liver it took several minutes to reach -190°C .

These investigations concluded (op.cit., p.775) that one way of approaching bulk tumours was by increasing the probe size, thus indicating that the larger the probe the larger the cryo-lesion produced.

Gage (1968), like many others, was convinced that the probe size, to a great degree, determined the size and extent of the cryo-lesion produced during cryosurgery. This fact appears to be generally accepted in conjunction with the factors of probe temperature, freeze duration and the effect of blood supply within the tissues.

7. Duration of freezing and thawing

Seim (1980) stated that a freeze of -20°C or below, for one minute or longer, led to virtually all living tissue undergoing necrosis.

Seim continued that the longer the freeze then the larger the ice ball and consequently the larger the area of necrosis. There is however a limit to this process due to an equilibrium being eventually reached between heat loss from the tissues to the cryoprobe and heat gain by the tissue from vascularity and the air (see previous text).

Poswillo (1973, p.83) rightly stated that the freeze duration was dependent on many factors and went on to state that "most benign lesions can be controlled with two freezes of 1.5 minutes duration at one intervention". In timing the 1.5 minutes duration Poswillo commenced after the ice ball had reached its required size and shape.

During tumour control experiments on mice and monkeys, Neel (1980) measured the duration of freezing as being the time needed for the ice ball extension to reach 5mm beyond the tumour margin.

It is interesting to note that Neel gave figures (op.cit., p.32) to show that this 5mm extension beyond the tumour margin, using a probe temperature of -170°C , took 79 seconds using three cycles as opposed to 144 seconds for one cycle and 115 seconds for two cycles (this was with a probe area of 80mm^2). With a probe of 20mm^2 area the figures were 206 seconds (1 cycle), 156 seconds (2 cycles) and 130 seconds (3 cycles).

Fraser, (1975, p.7) regarded the duration of freezing as being one of the most important factors in the size and growth of a cryo-lesion and listed the probe size and absolute probe temperature as the other main factors. In clinical terms this would mean that a freeze of too short a duration may produce an inadequate size of ice ball to encompass a lesion completely.

In regard to absolute freeze duration figures Holden (1975), in a chapter on head and neck tumours, gave an opinion (p.87) that for lesions in the posterior part of the oral cavity a closed nitrous oxide apparatus was preferable utilizing a freeze duration of four to five minutes. Then, quoting Miller (1974) in regard to the use of an open nitrogen spray for oral lesions, Holden gave an application time of five to seven minutes and stated that then "repetition is not absolutely necessary". This statement would be open to serious debate and would be a contrary opinion to those expressed by Cahan, Zacarian and Mazur who are among the great majority of writers who

place prime importance on multiple freeze-thaw cycles.

When writing on cryosurgery to the naso-pharynx (op.cit., p.89), Holden again advocated the use of a closed nitrous oxide system and this time a freeze duration of three to four minutes. For treatment of maxillary neoplasms following radical excision, either a nitrogen spray or closed system nitrous oxide application was recommended by Holden (op.cit., p.90) who stated that the freeze duration "must exceed three minutes and be repeated". It can be seen that this statement is partly contradictory to Holden's previously expressed opinion in relation to cryosurgery for oral lesions.

In discussing cryosurgery for cancer, Gage (1968, p.376), like Zacarian, advocated the use of a nitrogen closed system and stated that the amount of tissue frozen was dependent on, along with probe size and temperature, the duration of exposure. This author did not, at this point, give express times of freezing but stated that "when freezing had reached the desired extent, flow of liquid nitrogen was cut off". It can be seen that this method of calculating duration of the freeze was similar to that of Neel's (see previous text).

Zacarian was especially concerned with the effect of freezing duration in relation to the duration of thawing and, as previously stated, believed (1977, p.10) that the complete thawing time, which he concluded to be more lethal than freezing, was approximately one and one half times the duration of freezing. There are obviously mathematical limits to this equation; however, Zacarian was writing in the context of normally accepted cryosurgical timing.

Later, in his chapter on the cryo-lesion, Zacarian (p.24) cited a practical example of cryosurgery to a malignant growth on a patient's back and outlined his technique of marking an outline 1cm outside the visible limits of the lesion and then employing a double freeze-thaw cycle of, firstly, a two and one half minute freeze, followed by a three and one half minute thaw and, secondly, a two minute freeze and four minute thaw. This regimen produced a completely healed wound in 2 months but further details of progress of the patient were not given. In this report it can be seen that the thaw times do not exactly agree with Zacarian's previously expressed opinion regarding the thaw period, being approximately one and one half times the duration of freezing.

Summary of controlling factors

- (i) It seems, regardless of the exact nature of cell injury by freezing and thawing, that rapid freeze and slow thaw are, in combination, maximally lethal to the cells.
- (ii) The absolute temperature of the cryoprobe directly affects the size of the cryo-lesion produced and this factor is inter-dependent on the probe size and duration of freezing.
- (iii) There seems universal agreement that multiple freeze-thaw cycles are more lethal to tissue than a single freeze-thaw cycle. Thermal conductivity of tissue appears to be increased by repetitive freezing.
- (iv) A temperature, at cellular level, of -20°C or lower should be

obtained to allow for tissue destruction.

- (v) The duration of the freeze and thaw does not appear to be universally agreed; however, it can be said that the freeze duration must at least allow for the whole tissue lesion, plus a margin, to be completely frozen and the thaw time must allow for a complete thaw.
- (vi) Pressure on the cryoprobe and the use of a vaso-constrictor increase the velocity of freezing, the depth of freezing and the length of the thaw period.

Cell Survival

Since cryosurgery is concerned with the destruction of selected tissue by the use of intense cold, the question as to whether some cells within that tissue are able to survive the freezing conditions produced is paramount.

In relation to the survival of malignant cells following cryosurgery for cancer, Gage (1968, p.386) considered that this position was "most likely due to failure to freeze the entire cancer". Gage did however allow the possibility of some tumour cells actually surviving the freezing, but submitted that this was almost impossible considering the great care which is required to preserve tumour cells by freezing. He argued that, even if some individual cells could survive during cryosurgery, the hypoxia caused by vascular stasis would suffice to destroy the frozen tissue as a whole. Gage maintained there was no evidence to support the belief that tumour

cells could survive freezing and categorically stated that "freezing is non-selective, all frozen cells die and the extent of necrosis is predictable". This statement is surely an over-simplification and is difficult to accept in the light of the experimental findings of other workers (see later text).

A prolific contributor to the literature on experimental cryobiology, Mazur (1966), described freezing experiments on yeast cells and stated that up to sixty per cent of these cells could survive temperatures below -30°C if cooling was slow and, surprisingly, they could likewise survive if the freezing rate was "exceedingly rapid" (op.cit., p.253). Mazur also contended that about eighty per cent of the cells could survive a temperature of -10°C and, further, the rate of survival was "not related to the proportion of the suspending medium that is frozen". Mazur observed (op.cit., p.254) that even at a temperature of -75°C a survival rate of fifty per cent could be obtained if the cooling velocity was slow enough (i.e. $1-10^{\circ}\text{C}/\text{min}$) or again surprisingly when extremely rapid cooling and warming were employed (i.e. in the region of 10^4 $^{\circ}\text{C}/\text{min}$). Mazur concluded (op.cit., p.257) that conditions producing intracellular crystallization kill a high proportion of cells and at a cooling rate of $50-300^{\circ}\text{C} / \text{min}$ cell survival is much less than that observed at a cooling rate of $1-10^{\circ}\text{C}/\text{min}$. A further observation by Mazur was that the rate of cell survival was some eight times as high at a temperature of -10°C than it was at -20°C . This must be seen as a most significant difference in a temperature change of only 10°C and is vitally important in cryosurgery and especially in cancer surgery. Following on in this discussion Mazur stated that between one and sixty per cent of cells can survive cooling rates which induce

intracellular ice formation if the subsequent warming is rapid.

Writing again later on cell survival Mazur et al (1970) said that cryobiologists, when aiming at maximum cell survival, mostly utilized a cooling rate of $1^{\circ}\text{C}/\text{min}$ and a final temperature of -78°C or -196°C together with warming velocities of several hundred degrees per minute. Mazur and his co-workers maintained that this regimen was not optimal and cell survival was low after both rapid and slow cooling, but was maximal at some intermediate rate. They concluded that the cooling and warming velocities which produce optimal cell survival can differ by a factor of at least two thousand for different cell types (op.cit., p.82). These investigators attributed cell death following slow freezing to "solution effects" (i.e. electrolyte concentration) and following rapid freezing to intracellular ice formation as Mazur had done in 1966. Partly in agreement with Gage these writers stated that "regardless of the cooling and warming rate, most nucleated mammalian cells fail to survive freezing in the absence of a protective additive" and quoted Meryman (1966) on this point.

Meryman himself, discussing cell survival in a lengthy review of biological freezing, stated (1966, p.64) that only a penetrating additive was able to give any protection to nucleated mammalian cells. Meryman maintained these additives allowed the cells to tolerate slow freezing but that regardless of the use of additives, nucleated cells rarely tolerated rapid freezing.

One very important observation (1966, p.83) by Mazur and his co-investigators was that those cells cooled more rapidly than the

optimal rate for survival were generally more sensitive to slow warming than those cells cooled more slowly than the optimal rate for survival. This situation is obviously of great importance to the cryosurgeon especially if some cells are not in fact destroyed by the initial freeze.

One opinion on cell survival within the cryosurgical ice ball came from Farrant (1971, p.34) who assumed that a small number of cells survive the freezing. It must be noted that this was an assumption and this statement is virtually contradictory to that made by Gage (see previous text). Farrant held that there was an optimal cooling rate which gave maximal cell survival even though the survival rate was very low and in this he was at least partly in agreement with Mazur.

Describing three zones within the ice ball in relation to the proximity to the cryoprobe, Farrant expressed the opinion that the intermediate zone encompassed the optimal cell survival rate of cooling. Farrant argued that within this zone some cells would not be damaged by either intracellular crystallization or high solute concentration since the cooling rate was intermediate, thus preventing both of these phenomena from affecting the cell. He continued by saying that when the temperature in this zone became low enough further cellular damage was prevented and this situation was "the basis for preserving cells for long periods at low temperatures".

Certainly cells can be preserved at low temperatures under suitable conditions but it seems arguable as to whether these conditions occur

within a cryo-lesion.

Farrant also stated that cooling in itself did not destroy cells but "determines the time of exposure to the different damaging conditions at different temperatures". This statement evidently gives no regard to thermal shock but apart from that appears basically correct.

In regard to the preservation of cells, Neel (1980, p.13) observed that a slow rate of freezing and a rapid rate of thawing were required to prevent cell damage. This opinion is essentially in agreement with Mazur's findings, and the labelling by Neel of a cooling rate of $1-5^{\circ}\text{C}/\text{min}$ as slow also agrees with Mazur's opinion (Neel, 1980). Neel went on to report (op.cit., p.15) the probability of cell survival being great in the vicinity of the advancing ice margin during cryosurgery, as temperatures in this area approximate 0°C .

An interesting theory regarding the preservation of tumour tissue was put forward by Gye and his co-workers (1949). These investigators noted that numerous authors had reported tumour tissue was able to be preserved for at least one year at temperatures between -10°C and -79°C and still maintain its ability to produce fresh tumours when implanted experimentally. As a result of their experiments, Gye and his team concluded that freezing probably destroyed the cells but allowed a cell-free tumour producing agent (possibly a virus) to remain vital. They admitted they could give no conclusive proof of total cell destruction, but stated that at the same time they could find no evidence of cell survival either, (Gye, et al., 1949).

A reference to Gye and his associates was made by Billingham (1954) in a discussion on tissue preservation by freezing and drying. Billingham also described the experiments of various other workers in the field of tissue preservation, particularly sarcoma cell preservation, and noted that their reports on cell survival following freezing and drying experiments were inconclusive. Billingham himself concluded that slow freezing was of paramount importance if tissue was to be stored and advocated the use of a storage medium containing glycerol.

Zacarian (1977, p.4) expressed the opinion that the survival or demise of cells during cryosurgery was closely related to the cooling velocity. He went on to state that the cooling velocities generally utilized in cryosurgery, as judged by the lethal effect on malignant tumours, are optimal for tissue destruction, but no matter how rapid the cooling rate may be, there are always some cells, both normal and malignant, which survive. This statement is far less ambiguous when taken in context with Zacarian's other lengthy dissertation on the lethal effects of the vascular stasis following cryosurgery, on which he placed great importance in the final destruction of tissue.

Summary

- (i) Cell survival following freezing is significantly higher when slow cooling and rapid thawing are employed.
- (ii) There appears to be an optimal cooling rate somewhere between rapid and slow which allows for maximum cell survival following freezing.

- (iii) Following cryosurgery any cells which do survive are probably destroyed by the hypoxia produced by the subsequent vascular stasis.
- (iv) Cell survival appears to be far greater at temperatures above -20°C than at temperatures below -20°C .

CHAPTER 4

The Scope of Cryosurgery

(Lesions treatable by cryosurgery)

The scope of cryosurgery has become very wide in a short period and will no doubt expand further in the future. Some reference has been made in earlier chapters to different applications of this mode of treatment, and now the overall field of cryosurgery will be examined more closely.

Cryosurgery is currently being used by, among others, dermatologists, ophthalmologists, cancer surgeons, E.N.T. surgeons, and head and neck surgeons, with certain lesions being more susceptible to its effect than others.

While there is as yet no universal agreement as to the exact regimens to be employed in treating lesions with cryosurgery, some plans of treatment will be suggested as guidelines in the case of lesions related to the field of oral surgery.

Susceptibility to Treatment by Cryosurgery

It has been stated by Gill et al. (1970, A, p.439) that "from the accrued evidence, we have come to believe all tissue frozen in situ will die". This uncompromising statement must surely be open to debate and the reader is referred to the material presented previously in this treatise in the chapter on the cryo-lesion and the effects of extreme cold on cells.

It is interesting to note that Neel (1980, p.6) made a brief observation regarding fibroblasts when discussing previous experiments on neoplastic cells, noting that "normal human fibroblasts" were much less affected than were neoplastic cells at temperatures of 22°C to 24°C. While these temperatures are well above those experienced during cryosurgery there is some indication of a resistance to cold on the part of fibroblasts.

Gage et al (1965, p.1650) in discussing cancer-therapy, however, believed that "freezing is not selective and all frozen cells die". These authors observed that cryosurgery produced "local necrosis only" and that no effect, of course, was produced on any malignant cells in lymphatics not included in the cryo-lesion.

A brief review of cryosurgery in dermatology was presented by Zacarian (1967) who observed that, to his knowledge, cryosurgery was the best treatment for keratoses and verrucae. He also stated that verruca vulgaris and plantaris were the most susceptible to cryosurgery, but that periungual and mosaic warts were less responsive. At that stage Zacarian had, for two and a half years, been treating "all patients seen with carcinoma of the skin" by means of cryosurgery.

The difficult problem of tattoo removal was assessed by Dvir and Hirshowitz (1980), who discussed the traditional methods of removal and described cryosurgery as a "simple method" of treatment. These writers described four cases, classing their results as three good and one fair, and noting that the dark blue tattoos were the most resistant to cryosurgery. Illustrations in this article showed

results which are probably best described as mixed.

As early as 1962 Allington and Allington (1962) gave an acceptable account of the use of solid carbon dioxide and of liquid nitrogen in treating various lesions. In this outline of cryosurgery the authors also gave their opinions of the response of different lesions to freezing. They reported that small keloids "may be improved by freezing with liquid nitrogen" and that "more recent hypertrophic scars or keloids respond better than older lesions". They also observed that the response of older scars was slow and multiple freezes were required to gain improvement. Referring to treatment of haemangiomas, these investigators decided that "deep and extensive cavernous haemangiomas" did not respond as well as the shallower more vascular varieties and "port wine" haemangiomas were resistant to cryosurgical treatment. With modern equipment this last observation would now be, at least, debatable. With some reservations, Allington and Allington in addition listed as susceptible to cryosurgery such lesions as warts, seborrheic keratoses, senile or actinic keratoses, leukoplakia, acne scars and pyogenic granuloma.

Recently Hirshowitz et al (1982) presented a paper on the treatment of keloid scars in which details were given of 58 patients, many of whom had previously been treated by means of intra-lesional triamcinalone and surgery. In these treatments the authors employed a double freeze-thaw cycle followed by intralesional injections of corticosteroids, this regimen being repeated, where necessary, when the cryo-lesion produced had completely healed. The results obtained from the 58 cases showed complete regression of the keloid in 41 cases, 8 improvements and in 9 cases there was regression but

subsequent recurrence. It is noted that as many as 12 treatments were needed to obtain total scar regression.

It seems reasonable to conclude that lesions of high fibrous character such as old scars are resistant to cryosurgery, as are tattoos. There appears to be also a difficulty in using cryosurgery on bulky lesions, such as deep cavernous haemangiomas and cancers; however, debulking in these cases may be of distinct advantage.

Lesions Related to Oral Surgery

Gage (1980) devoted a complete chapter to oral disease commencing with the statement that "oral disease, including certain inflammatory lesions, precancerous conditions and benign and malignant tumours, is suitable for treatment by cryosurgery". As will be seen later, there are some exceptions to this statement, which was made by Gage in a general manner and was not intended to be dogmatic. The author continued that cryosurgery in the oral cavity carried almost no risk, caused little discomfort or haemorrhage, could easily be repeated and allowed the preservation of bone where other methods of treatment may call for the sacrifice of bone.

In regard to epithelial dysplasias, Gage offered the opinion that nitrous oxide apparatus is satisfactory when treating dysplastic or non-neoplastic lesions limited to the epithelium (Figs. 4-1, 4-2 and 4-3), but that liquid nitrogen apparatus is preferable for the treatment of carcinoma in situ. The regimen of treatment for these conditions, by spray or cryoprobe, was given by Gage as two freezes of one to two minutes separated by a spontaneous complete thaw. A



Fig.4-1. Leukoplakia of labial aspect of maxillary ridge, in a seventy one year old female.

Fig.4-2. The same lesion as in Fig. 4-1 three days after cryosurgery. Typical sloughing lesion present.



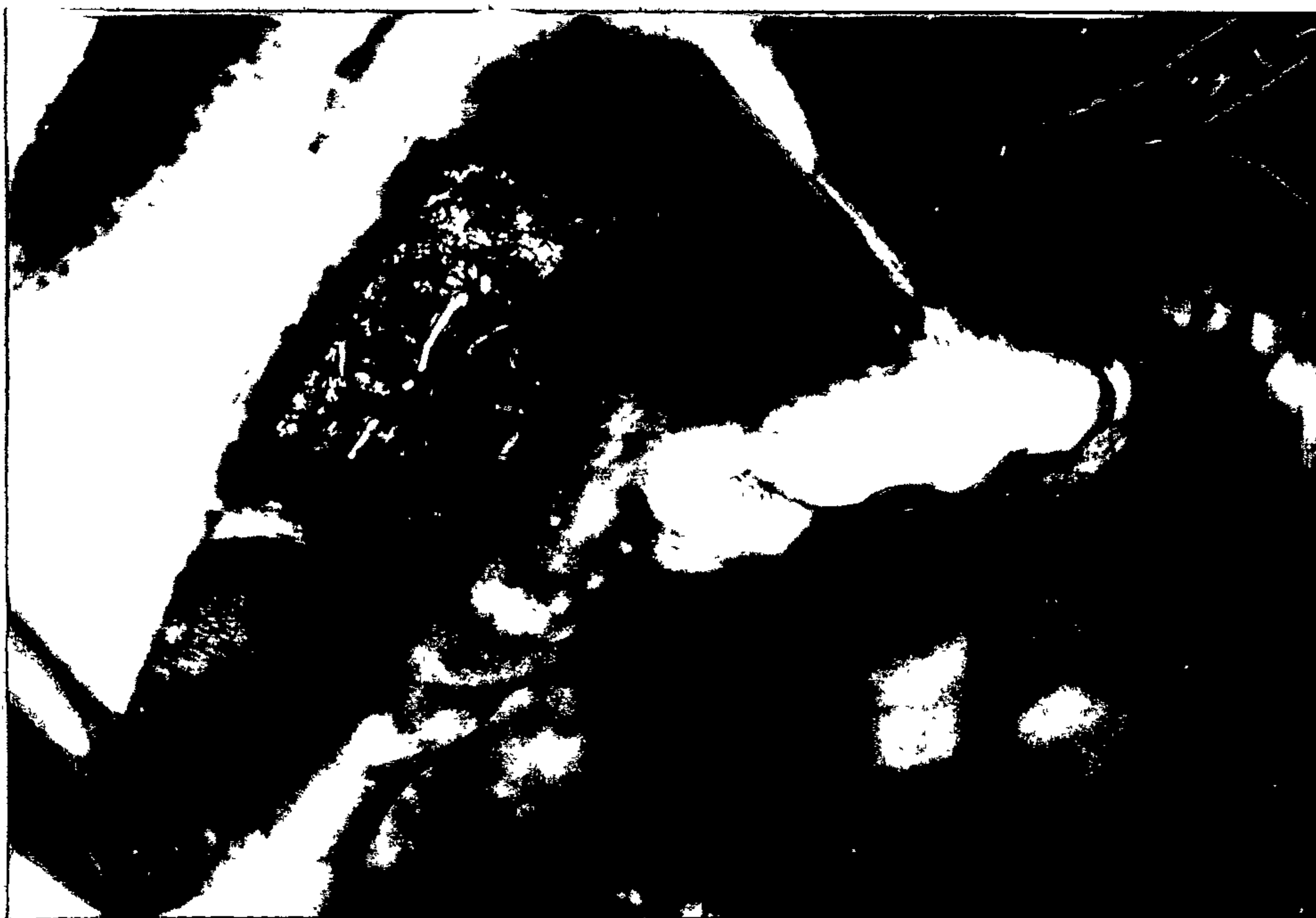


Fig.4-3. The same case as in Figs. 4-1 and 4-2, six weeks following cryosurgery. The lesion was treated with a nitrous oxide cryprobe for two freezes of thirty seconds each at three sites. (Illustrations in this series courtesy of Professor N.H.H. Smith, United Dental Hospital, Sydney.)

temperature of -40°C at the site was recommended.

The treatment of oral haemangiomata (Figs. 4-4, 4-5 and 4-6), by a cryoprobe pressed onto the lesion, was advocated by Gage, but no regimen of freeze-thaw cycles was given. On this point Poswillo (1978) proposed two one minute freezes separated by a five minute thaw and added that for vascular lesions of the skin near the mouth repeated freezes of ten to twenty seconds were preferable in order to avoid the problem of depigmentation (Figs. 4-7 and 4-8). Here monthly intervals between treatments were recommended until the lesion disappears.

Some bone tumours were listed by Gage as suitable for cryosurgery and the treatment of ameloblastoma by a combination of curettage and subsequent freezing was described. This combined treatment, in the opinion of Gage, "increases the possibility of cure because freezing destroys tumour in the bone which may be beyond the reach of curettage". Gage also believed that "cryosurgery is possibly the best method of management for most benign mandibular tumours" and gave as examples aneurysmal bone cysts and ossifying fibroma. He recommended repeated freeze-thaw cycles at temperatures of -50°C , or colder, for these cases.

In the case of oral cancer, Gage first wrote on palliation by cryotherapy as a means of debulking tumour and desensitizing nerve tissue. He advised that "large incurable cancers are usually not good choices and are better treated by radiotherapy". Poswillo agreed that "there will always be a place for palliative cryosurgery in oral malignancy" (Figs. 4-9, 4-10, 4-11 and 4-12).



Fig.4-4. Haemangioma of tongue in a sixteen year old female.

Fig.4-5. The same lesion as in Fig. 4-4, four days after cryosurgery. Surgery site exhibits typical slough.



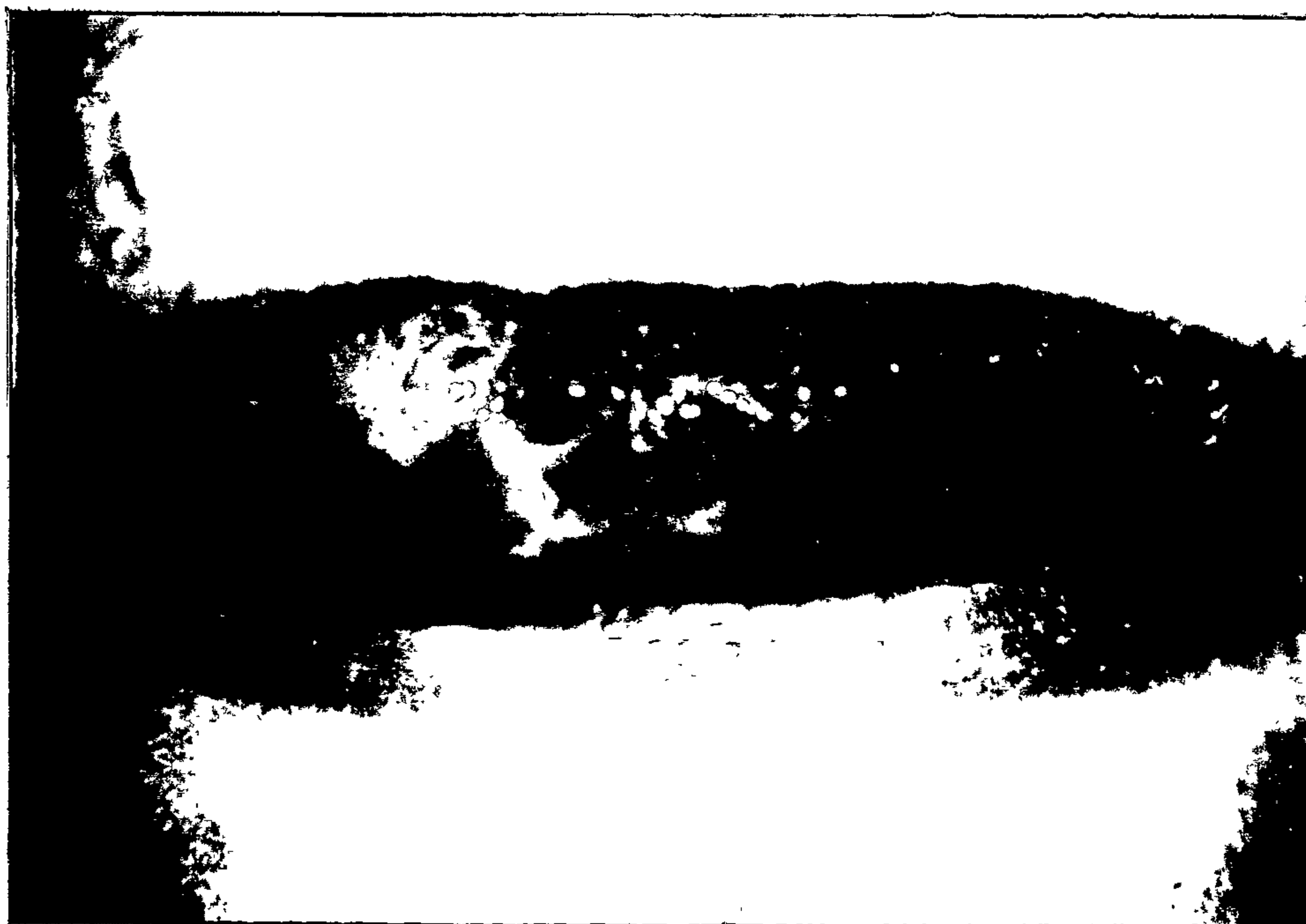


Fig.4-6. The same case as in Figs. 4-4 and 4-5 two weeks post-surgical. The cryosurgical regimen was two freezes of sixty seconds, using a nitrous oxide cryoprobe. (Illustrations in this series courtesy of Professor M. Jolly, United Dental Hospital, Sydney.)



Fig.4-7. Haemangioma of the upper lip. The lesion had recurred three times after diathermy and local excision. (From David Poswillo, Dental Update, 1978. Courtesy of the author.)

Fig.4-8. Same lesion after curative cryosurgery. (From David Poswillo, Dental Update, 1978. Courtesy of the author.)



Gage also discussed cryosurgery for persistent oral cancer after excision or radiotherapy, stating that in some cases residual tumour can be destroyed and pain relieved.

Finally, Gage wrote at length on the primary treatment of oral cancer by cryosurgery and here outlined the criteria of selection as being small to medium sized tumours, especially those near bone and in patients who are high risk cases for traditional surgery. The patients should not exhibit cervical lymphadenopathy or, alternatively, have radical neck dissection one month after cryosurgery to the primary lesion according to Gage. He also stated that cryosurgery was not suitable for patients with large tumours of the floor of the mouth or posterior portion of the tongue. A regimen of repeated freezes at temperatures of -50°C to -60°C was advised.

Poswillo felt that cryosurgery to malignant lesions, except for palliation, "should be confined to special cases, such as elderly, debilitated patients" where other methods of treatment are unsuitable.

Poswillo (1978) listed several other conditions which he regarded as particularly responsive to cryosurgery. Papillary hyperplasia of the palate he stated could be removed and a normal palatal mucosa produced in about four weeks. Mucous retention cysts could likewise be satisfactorily treated by cryotherapy. Oral leukoplakia, Poswillo observed, was commonly treated by two freezes of two minutes separated by a five minute thaw and here he believed that "cryosurgery has added an entirely new dimension to the definitive treatment of oral leukoplakia". With oral lichen planus, Poswillo



Fig.4-9. Squamous carcinoma of tongue in eighty year old male. (From David Poswillo, Dental Update, 1978. Courtesy of the author.)

Fig.4-10. Same tongue after cryosurgery. No local or metastatic spread observed three years post-operatively. (From David Poswillo, Dental Update, 1978. Courtesy of the author.)





Fig.4-11. Adenoid cystic carcinoma of elderly male. Maxillectomy or radiotherapy were contraindicated. (From David Poswillo, Dental Update, 1978. Courtesy of the author.)

Fig.4-12. Same tumour five years after palliative cryosurgery. Full denture worn with complete comfort. (From David Poswillo, Dental Update, 1978. Courtesy of the author.) The contrast in this reproduction reflects the quality of the original illustration.



maintained that cryosurgery was limited to palliation of painful ulcers and he was of a similar conviction in the case of aphthous ulceration. In relation to the relief of oro-facial pain, Poswillo was firmly of the belief that cryosurgery has a great deal to offer and referred to trigeminal neuralgia, painful scar tissue and types of causalgia as being suitable for treatment. This subject will be examined in detail later in this treatise. Lastly, Poswillo discussed the excisional biopsy, under cryotherapy, of such lesions as papillomata and incisional biopsy of conditions such as speckled leukoplakia.

An article devoted entirely to cryotherapy of oral leukoplakia was published by Al-Drouby (1983) giving details of a five year study. In this investigation areas of leukoplakia were frozen twice for two minutes separated by a thaw (unspecified). Some thicker lesions were frozen twice for three minutes. Of thirty cases only three failed to respond to cryotherapy and two of those may have been lichen planus and the third a lichenoid drug reaction.

Other Surgical Applications of Cryosurgery

It is not intended to give an elaborate account of general surgical uses of cryosurgery in this treatise, but merely to provide the reader with an outline of the scope to which this modality can be applied. Some of these applications have already been mentioned briefly in earlier parts of this paper.

Probably the widest use of cryosurgery is to be found in dermatology. Here Zacarian (1980, p.109) gave an account of treatment of benign,

precancerous and malignant lesions of the skin listing some twenty-seven different benign and precancerous lesions amenable to cryosurgery including haemangiomata, small keloids, sebaceous cysts, keratoses and xeroderma pigmentosa. He also provided details of cryosurgery to malignant lesions, basically basal cell carcinomata and squamous cell carcinomata.

Another area in which cryosurgery has found a prominent place is that of ophthalmology, as briefly referred to previously in this treatise. Bellows (1964) described the effects of a cryoprobe on the cornea and lens of the eye and went on to give details of cataract removal by cryosurgery. He also mentioned experiments on cryotherapy to herpetic lesions and treatment of the cornea following contact with strong alkalis. He put forward retinal detachment as a possible condition amenable to cryotherapy. In this field Amoils and Kaufmann (1972) later referred to retinal detachment repair by cryosurgical techniques and also to the treatment of haemorrhagic glaucoma. Amoils (1975, pp.35-65) discussed the above mentioned uses of cryotherapy in ophthalmology and in addition its utilization in intraocular tumour removal, ciliary body surgery, iris surgery and vitreous surgery.

In the field of neurosurgery the use of a cryoprobe has proved effective for thalamotomy for Parkinson's disease and hypophysectomy for such conditions as acromegaly and Cushing's disease. Rand (1980) reported various aspects of the treatment of these and allied conditions and stated that in approximately one thousand cases of Parkinson's disease, which he had treated, cryotherapy had produced "excellent to good results".

Cryosurgery has likewise established an identity in certain aspects of gynaecology. The main value of cryotherapy here appears to be in carcinoma control, haemorrhage control and palliation in advanced cancerous cases. Lash (1980) discussed these conditions in some detail and, among other material, listed eight distinct advantages of cryosurgery over cautery in treating these cases.

Perhaps of more interest to the oral surgeon is the range of procedures which can be carried out by cryosurgical methods in E.N.T. surgery. Ozenberger (1980) provided an excellent review of this topic. He reported that lesions in the external, middle and inner ear were treatable by cryosurgery as was anterior and posterior epistaxis, chronic rhinitis and nasal polyps. He also listed other nasal conditions amenable to cryosurgery and gave a well-balanced account of cryotonsillectomy. Of special interest was Ozenberger's observations of cryosurgery in the treatment of vascular headaches, where he referred to the work of Cook and of himself, reporting that his own patients had exhibited a success rate of over ninety per cent following cryosurgery. In this article Ozenberger refers to freezing of the sphenopalatine ganglion, the superficial temporal artery and the occipital artery. Cook (1973) himself reported on the results of cryosurgery in 322 patients "for various types of migraine", by freezing of the superficial temporal, occipital and spheno-palatine arteries, of which he said that the spheno-palatine artery seemed "to dominate the migraine picture in the majority of patients". In his article, Cook also described cryosurgery to the internal maxillary artery and the middle meningeal artery and warned that the superficial temporal and the internal maxillary arteries should be considered as one in migraine surgery and that therefore both should

be frozen at the one operation.

One extremely rewarding application of cryosurgery is to be found in anorectal surgery where its use obviates a considerable amount of pain and haemorrhage. The main conditions in this field conducive to the use of a cryoprobe are haemorrhoids, fissure in ano, venereal warts, carcinoma of perianus, anus and rectum, rectal and colonic polyps, lichen sclerosus et atrophicus, leukoplakia, dyskeratosis of the perianus and fistula with abscess. This elaborate list is compiled from a lengthy article by O'Connor (1980) who observed, among other things, that cryosurgery in such cases produced less pain and less morbidity than conventional excisional surgery.

Some forms of urologic surgery are also possible by means of a cryoprobe and Jordan et al (1980) gave details of cryogenic prostatectomy, reporting that this technique is now gaining wider acceptance. Reuter and Reuter (1980) in addition described cryosurgery to some bladder tumours as well as referring to prostatectomy.

Basic Cryosurgery Technique

A concise but thorough summary of the basic rules for cryosurgery was set out by Gage when discussing the treatment of oral disease.

The "important points" as laid down by Gage (1980) are:

1. "Use a cryogen suitable for the lesion.
2. Maintain good contact between the tissue and the cryoprobe.
3. Use the cryoprobe as cold as possible.

4. Freeze as quickly as possible.
5. Allow the tissue to thaw without assistance.
6. Maintain control of the freezing procedure with thermocouples.
7. Overlap frozen areas.
8. Repeat freezing after thawing.
9. Include a margin of normal tissue."

While it is possible to argue some minor points in regard to these rules as put forward by Gage, such as thermocouples not being essential in all cases, the underlying principles expounded must be regarded as very sound.

The Clinical Tissue Response to Cryosurgery

There are numerous similar descriptions of the clinical effect of freezing to be found in the literature and Leopard and Poswillo (1974) observed that "the clinical changes before and after freezing follow a predictable pattern". These authors stated that the visible ice ball enlarges for about one minute and then remains the same size. They reported that mild hyperaemia and swelling occur during the following two to three hours after thawing and that vesicle formation occasionally occurs "at an early stage" especially on the lips. By twenty-four hours post freezing they stated that a "dusky discoloration" occurs with increased swelling and after two or three days superficial necrosis occurs with a dark eschar on skin or a yellow-grey slough on mucosa. The slough or eschar separates in seven to twelve days on mucosa and in ten to twenty days on the skin, according to these writers, leaving a clean granulating surface, and healing is complete in about three weeks leaving no scar on mucosa.

They observed that skin frozen for more than thirty seconds heals with a thinned epidermis which takes several weeks to return to normal appearance.

CHAPTER 5

Instrumentation and Cryogens

Examples of the earlier types of cryosurgical equipment have been described in the historical section of this treatise and it is now proposed to consider only contemporary systems and cryogens. In this regard the main emphasis is to be placed on those systems with particular application to oral surgical procedures.

In considering the concept of a perfect cryosurgical unit, Lubritz stated that his idea of a "nearly ideal" system was that "it should be:

1. Capable of producing freezing to any depth sufficient to treat all skin lesions.
2. Simple to operate with adjustments that can provide varying control of the applied refrigerant.
3. Light and portable.
4. Uncomplicated to produce and manufacture and therefore inexpensive.
5. Able to provide long term storage of the unused refrigerant."

Lubritz (1977) added that "safety and freedom from malfunction" should be included in the list of desired properties. While Lubritz was referring to treatment of cutaneous lesions, the above criteria

should suffice for the cryosurgical treatment of lesions in general terms.

Cryogens can be used in several different ways to produce freezing conditions in tissues. The principal methods employed are closed circuit cryoprobes, sprays, solid or slushed cryogen, swabs soaked in cryogen and occasionally liquid cryogen poured directly onto tissues. In modern times the first two of these methods are by far the most commonly employed.

Torre (1977) provided a well illustrated and concise description of some cryosurgical units and methods as well as some accessory equipment.

Spray Systems

Those systems utilizing a spray of cryogen (usually liquid nitrogen) are based on the "Dewar" bulb principle in which one glass bulb is blown inside a second glass bulb, the two being separated by a vacuum and the surfaces silvered to increase insulation. Liquid nitrogen is poured into the inner bulb or reservoir which is then closed except for two outlets one of which is the spray, the system being operated by occluding the second opening thus allowing evaporating nitrogen to force liquid nitrogen from the spray outlet. Several spray units involving variations of this principle were described by Torre, some of which have stainless steel reservoirs. In these units pressure is produced either by a sphygmomanometer-type bulb, plus self-pressurizing by evaporation of cryogen or purely by self-pressurizing. Some of these units, in addition, employ a trigger

control to produce an instantaneous spray of cryogen.

One unit which has been used for several years at the United Dental Hospital of Sydney is the W.S.L. - Nitrospray (Fig. 5-1). This equipment employs a stainless steel Dewar bulb holding liquid nitrogen, is pressurized by evaporation plus bulb pump and allows instantaneous spray control by the occlusion of an opening to the Dewar.

An important point brought out by Torre was that some spray units incorporate a "heat exchanger" which converts part of the liquid nitrogen into a gas so that a gas-liquid spray is produced. This minimizes the tendency to drip and splatter which is observed in a pure liquid nitrogen droplet spray. In some units this "heat-exchanger" consists merely of a plastic tube leading to the spray nozzle, as in the T.T. 32 - Physicians Products, Inc. unit (Fig. 5-2), while in others, e.g. the Zacarian C-21 Frigitronics Inc. model (Fig. 5-3), a built-in coil "heat-exchanger" is incorporated inside the apparatus. Several of these units have only a short metal tube between the reservoir and the nozzle allowing for singlehanded use, while others with a long flexible tube leading to the nozzle require two hands to operate.

Depending on design these different spray units have holding time for liquid nitrogen of from one half-hour to over eight hours.

In relation to a spray technique, Gage (1980) observed that it was less controllable than a cryoprobe technique but that on the other hand a spray "takes advantage of the coldest temperature attainable



Fig.5-1. W.S.L. Nitrospray Unit. As used at the United Dental Hospital, Sydney.

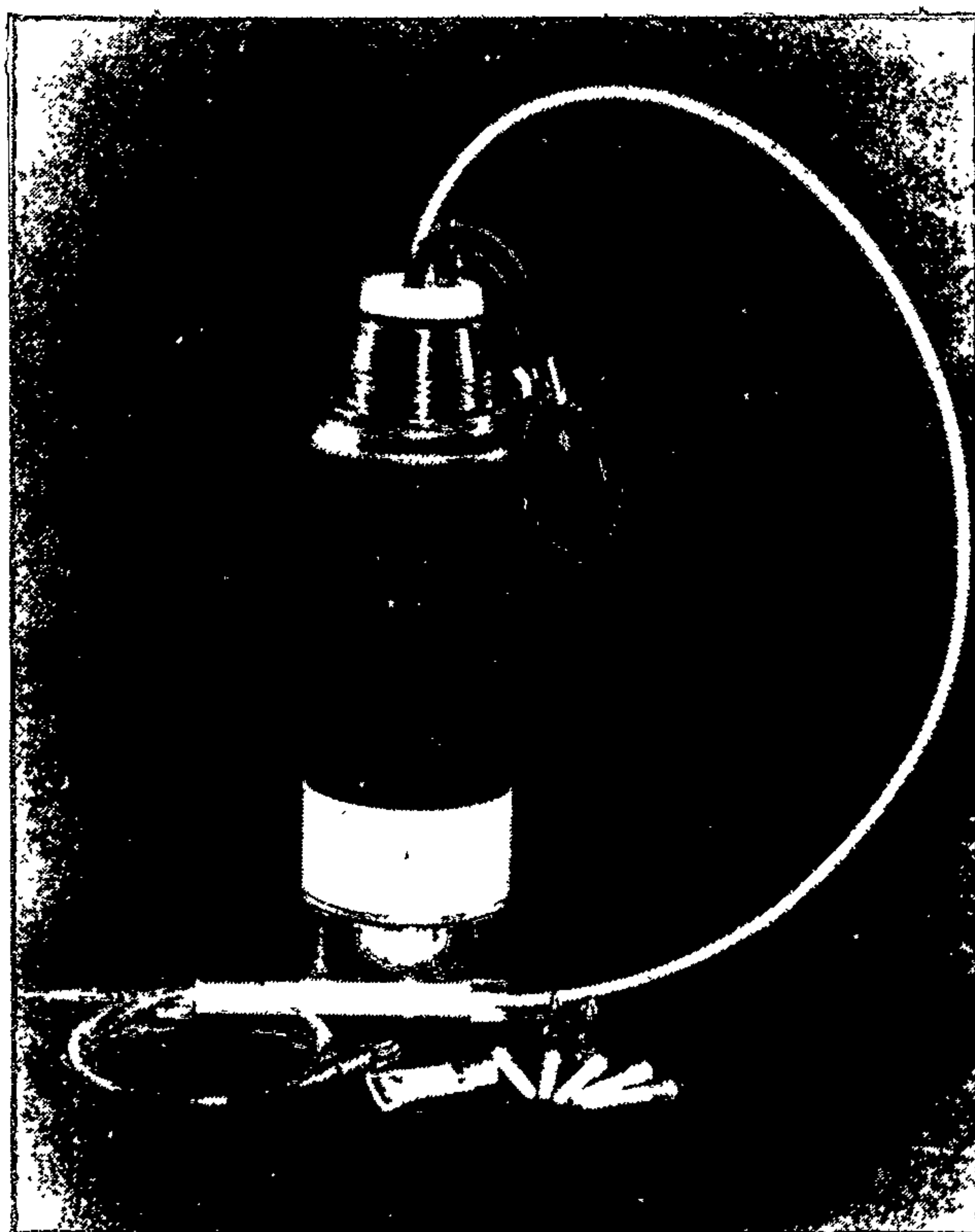


Fig.5-2. T.T. 32-Physicians Products, Inc. Unit. (From Zacarian, Cryosurgical Advances in Dermatology and Tumours of the Head and Neck, 1977. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois.)

with the agent" (i.e. the particular cryogen). That author also stated that a spray technique was not the method of choice for lesions in the posterior part of the oral cavity and, indeed, most oral lesions were better treated with a cryoprobe.

Neel (1980, p.16) agreed that "sprays are more difficult to control" than a cryoprobe, but argued that on the other hand "larger regions are more rapidly frozen" when a spray technique is employed.

An interesting reference to a spray technique, as opposed to a probe technique was made by Miller (1974) when discussing tumours of the head and neck. Miller stated that he and his colleagues had only used liquid nitrogen as a cryogen and had formerly confined their work to the use of a cryoprobe. However, he went on to say that "since we have found that direct liquid nitrogen spray is much more penetrating and much more destructive, it is used more and more in this fashion".

Wild (1975, p.23), however, gave only scant reference to open spray systems in general but did illustrate a portable liquid nitrogen unit. This apparatus was a Keeler Kryospray unit supplied with a variety of spray nozzles.

Probe Systems

One cryosurgical unit described by Torre was the Frigitronics CE 8, a large floor-standing unit (Figs. 5-4, 5-5 and 5-6) which can produce a liquid nitrogen spray or be used with cryoprobes. In this case Torre was of the opinion that when used to produce a spray this

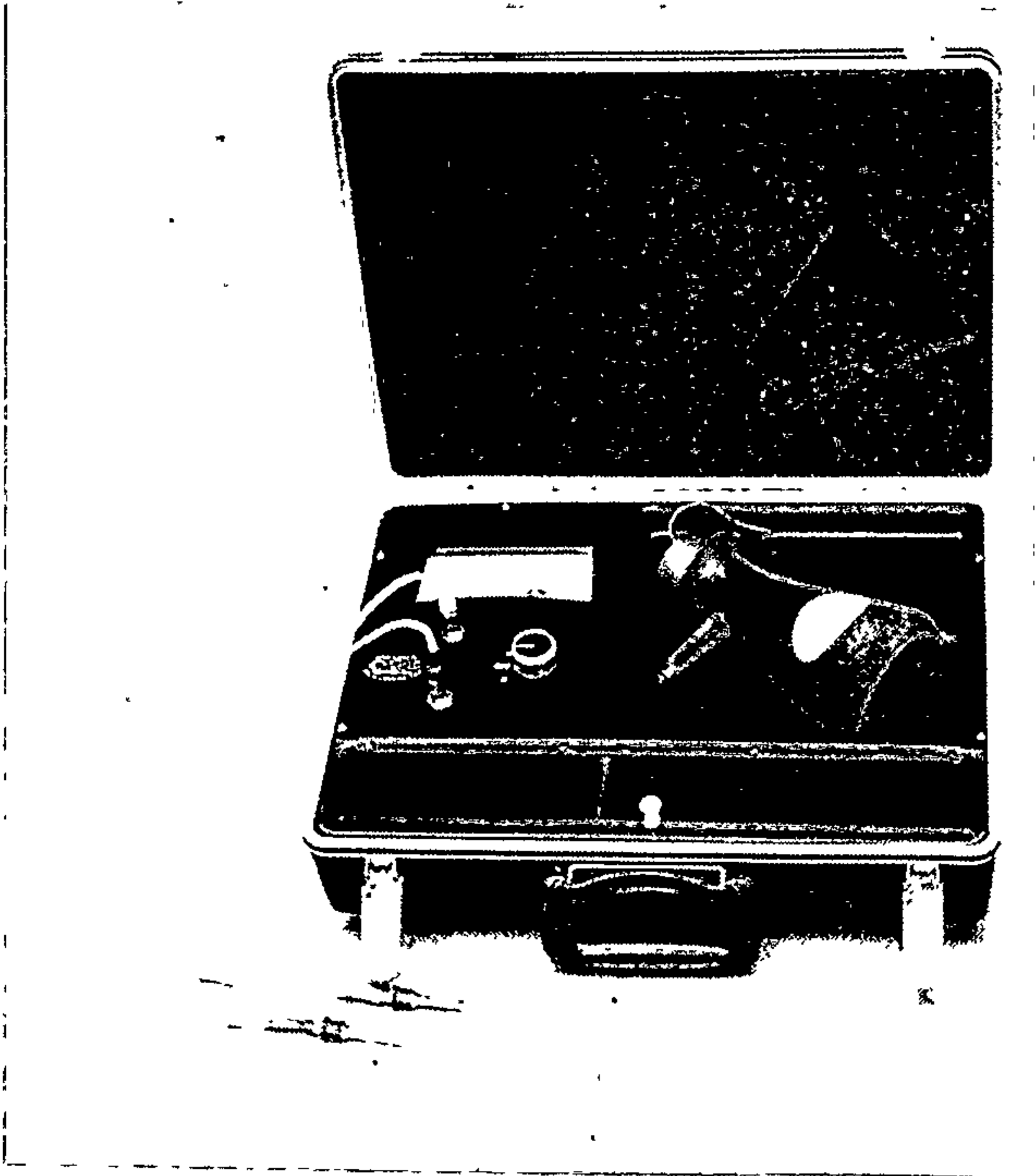


Fig.5-3. Zacarian C - 21-Frigitronics, Inc. Unit. (From Zacarian, Cryo-surgical Advances in Dermatology and Tumours of the Head and Neck, 1977. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois.)

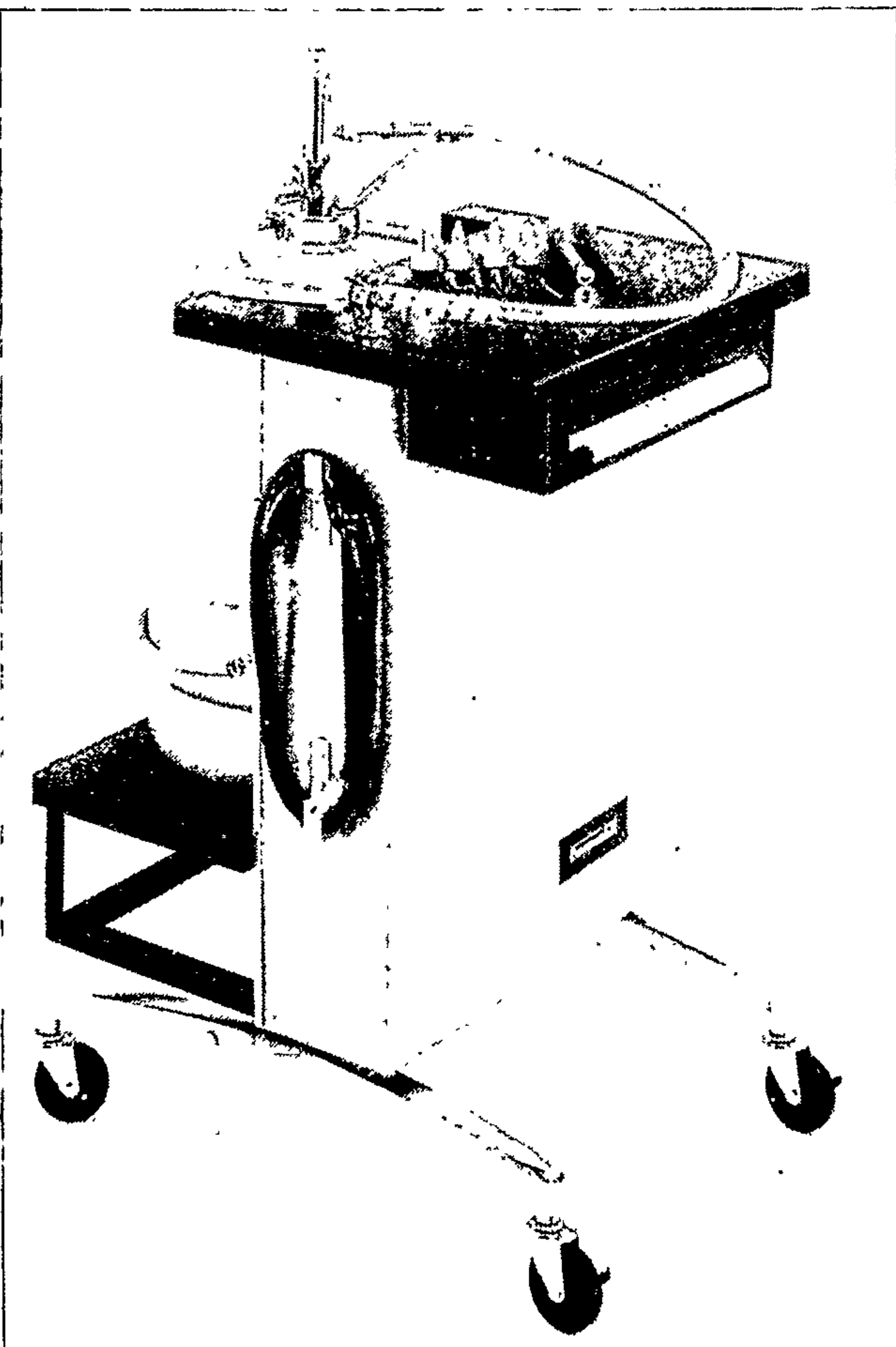


Fig.5-4. CE 8-Frigitronics, Inc. Unit. (From Zacarian, Cryo-surgical Advances in Dermatology and Tumours of the Head and Neck, 1977. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois.)

Figure 2-11. CE 8®—Frigitronics, Inc., 770 River Road, Shelton, CT 06484

a. Floor standing unit

b. Cryoprobes and intermittent spray tips

c. Luer-Lok adapter and spray tips

Type of unit—table or floor standing unit with handle connected to reservoir by flexible tube

Reservoir—17, 25, 31 liter steel or aluminum vacuum Dewar

Holding time—two to eight weeks

Pressurization—immersion heater

Intermittent spray control—levered “ethyl chloride” type nozzles (optional equipment)

Luer-Lok fittings—yes

Heat exchanger—plastic tube between reservoir and handle

Other equipment available—“Dermatology Kit” cryoprobes consist of 12.7 mm round tip, pointed tip and 3 and 5 mm flat; other size probes including a “door knob” type and insulated extension type also available; acne spray tip, pyrometer, and special wheeled carrier optional

Cost—approximately \$1000.00 for basic unit

From *J Cryosurgery*, 1:206, 1968.

Fig.5-5. Details of CE 8-Frigitronics Inc. Unit. (From Zacarian, Cryosurgical Advances in Dermatology and Tumours of the Head and Neck, 1977. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois.)

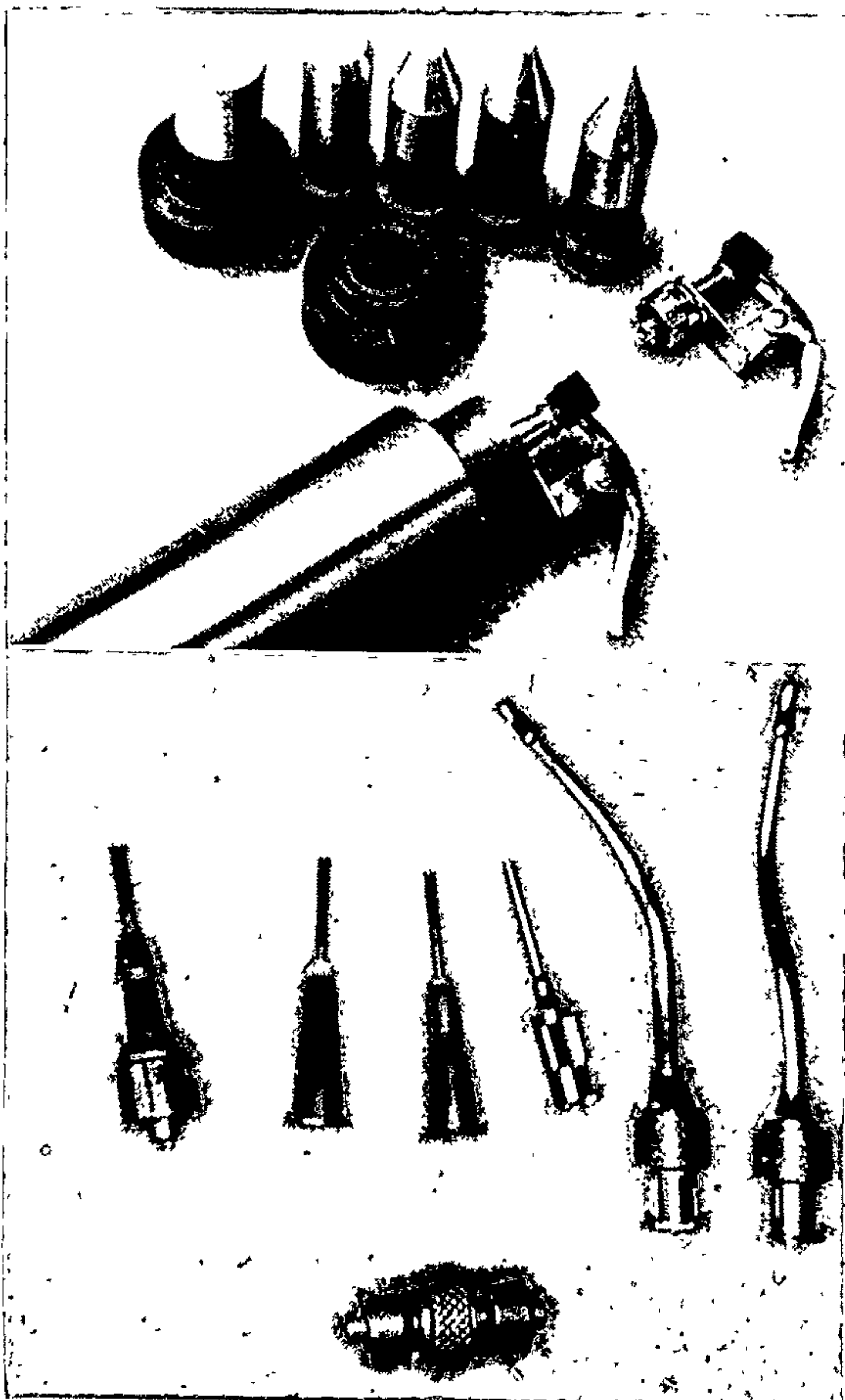


Fig.5-6. Probes and spray attachments used with the CE 8-Frigitronics Inc. Unit. (From Zacarian, Cryosurgical Advances in Dermatology and Tumours of the Head and Neck, 1977. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois.)

equipment was not as satisfactory as modern hand-held spray units. This unit stores liquid nitrogen for up to six weeks in 17, 25 or 31 litre reservoirs under 8-10 P.S.I. pressure (approximately 56-70 Pascals).

The many different cryoprobe units available operate on the principle of either circulating liquid nitrogen inside the probe or the expansion of a compressed gas through a small orifice, which is again situated inside the probe. This latter method employs the Joule-Thomson principle in that the rapid expansion of a compressed gas through a small orifice produces a dramatic fall in temperature. The gas used in this system is usually nitrous oxide.

Leopard and Poswillo (1974) stated that the closed system cryoprobe unit was "the instrument of choice" for oral lesions and went on to describe the apparatus they then used, namely the Amoils cryo-unit. No particular model number or name was specified. This equipment works on the Joule-Thomson principle and carries gas (usually nitrous oxide) at a pressure of 53 kg/cm^2 to the probe tip.

These authors maintained that a probe temperature of about -70°C was obtained with this unit. A foot switch operates the equipment and incorporated is an automatic defrost heater to the probe which is engaged upon release of the footswitch.

Chandler (1972), in reporting on treatment of malignant neoplasms of the head and neck, said that in the vast majority of cases he had used a Brymill cryoprobe unit, but that for some small lesions he had operated with the Linde-Cooper apparatus. Chandler also stated that

"in general closed-tip probes are favoured", although he did refer elsewhere in his article to apparatus which could deliver liquid nitrogen directly to the tissues.

The apparatus used by Holden and McKelvie (1972) for treatment of head and neck neoplasia was reported to be an Amoils Cryo-unit (1968) modified by McKelvie and Shaheen, with probes of two to eleven mm in diameter. This unit operated on nitrous oxide through a Joule-Thomson nozzle and was used with a working tip temperature of -40°C which reportedly produced an average 10mm ice ball. The equipment was used to treat various carcinomata of the head and neck and the results reported show rather mixed degrees of success, probably due, in part, to the use of nitrous oxide rather than nitrogen as a cryogen.

In discussing the requisites for successful cryosurgery for cancer, Neel et al (1971) reported the use of a cryoprobe (of unspecified make) utilizing liquid nitrogen as the refrigerant. They regarded this type of equipment as a "reliable cryosurgical system" following its development by Cooper in 1962. These researches used the liquid nitrogen probe in experiments on mice, working with a tip temperature of -180°C and produced very successful results in cancer control.

De Santo (1972) provided an account of the cryosurgical treatment of 44 patients with head and neck tumours over a two year period, where his choice of cryo unit was the self-pressurizing Brymill model SP5, plus a laryngoscopic unit, using liquid nitrogen as a cryogen. In these cases both open spray probes and closed system probes were used depending on the site and accessibility of the tumour.

Several types of cryoprobes were discussed by Wild (1975, pp.10-34) and that author supplied illustrations of probes suitable for a variety of surgical purposes. One illustration of three electrically defrosting probes was included, these probes being described as suitable for oral procedures.

For oral surgical work the unit preferred by Jolly (1976) was the Keeler T.C.C. 10, which employs nitrous oxide as the cryogen. This closed circuit cryoprobe equipment allows for quick tip defrosting, by a built-in heating coil, upon termination of the gas flow. The unit has proved very satisfactory for most oral surgery procedures.

The Linde CE-4 cryoprobe unit was used by Cherry (1970), who reported on the treatment of four cases of oral cancer in which the results presented were most impressive. This unit is of the liquid nitrogen type and it was stated that the copper tip reached a temperature of -170°C in two to three minutes.

Gage (1969) gave a resume of the cryosurgical treatment of eighty three patients with oral or pharyngeal carcinoma using the Union Carbide CE-4 liquid nitrogen cryoprobe apparatus. The results of this series were reported to be "acceptable" and the survivors were said to have exhibited less disabilities than is the case after conventional surgical excision.

Two different nitrous oxide cryoprobe machines were used by Chapin when treating a variety of oral lesions. One was the Dynatech Cryosurgical System, the second unit being the Dynafreeze, Model DCG-8400, both of which are activated by a foot control. The Model DCG-

8400 described by the author has no electrical connections and the cryoprobe is permanently connected by means of a six foot long white silicone hose for gas feed and exhaust. The stainless steel tip of this probe is contoured in a concave-convex manner very suitable for use on unusually contoured surfaces of the oral cavity (Chapin, 1976). The author summarized that treatment with these units was very efficient and practical in his office practice.

Solid and Slushed Cryogen and Liquid Cryogen Application

Carbon dioxide has been used as a cryogen for many years in the form of a solid stick or as a slush or snow for the treatment of dermatological lesions. Zacarian and Adham (1966) observed that up to that time cryotherapy of cutaneous lesions had been limited to the use of solid carbon dioxide sticks or cotton-tip applicators soaked in liquid nitrogen. These authors reported successful treatments to basal cell carcinomata with the use of the liquid nitrogen applicator technique but went on to say that they considered both the carbon dioxide stick and the cotton-tip liquid nitrogen applicator inadequate for the treatment of cutaneous carcinomata due to their inability to freeze deeper than 2mm into the skin. This limitation apparently existed despite the low temperatures at source, of -196°C in the case of liquid nitrogen and -78.5°C for solid carbon dioxide.

Torre (1977) discussed carbon dioxide as a cryogen, noting that it is obtainable as non-storable slabs, which can be modelled to a suitable shape, and as storable liquid in cylinders to provide carbon dioxide particles which can be moulded as desired just prior to use. Torre added that carbon dioxide was suitable for the treatment of benign

lesions, but not of malignant lesions, since a satisfactory depth of freezing could not be obtained with this cryogen. That author also referred to the use of carbon dioxide as a slush when mixed with alcohol, ether or acetone, the slush to be applied directly to the tissues.

Poured Cryogen

Occasionally liquid cryogen is poured directly onto tissues and reference has already been made to Cahan's (1968, p.398) report of pouring liquid nitrogen into a bony cavity following the removal of a giant cell tumour (see chapter on the cryo-lesion).

Alternate Cryogens

Other cryogens discussed by Torre (1977) included liquid air which has similar properties to liquid nitrogen but is not so readily available, liquid oxygen (which is dangerous from an inflammability stand point) and liquid helium, the coldest cryogen, which is however expensive and difficult to handle. Nitrogen gas and argon gas are possible cryogens but have proved to have a less efficient freezing capacity than liquid nitrogen.

The liquid flurocarbons (freon 12, 13, 22 and 114) are satisfactory for most dermatological use and produce temperatures down to about -90C. Freon 13 is the coldest of this group but is rather expensive. Torre reported that one drawback with the freons was a "potential toxicity (particularly cardiac toxicity)".

Accessory Equipment

Items of accessory equipment for cryosurgery were also described in Torre's article and some of these are worthy of inclusion here.

Thermocouple-tipped hypodermic needles attached to a pyrometer are necessary to measure the temperature below the surface during cryotherapy. These are of special importance when the operator is treating malignant lesions in order to insure that freezing is deep enough to encompass all sections of the lesion.

Some form of device for measuring the depth of insertion of these thermocouples is needed and in this respect the template modified and used by Zacarian is simple and practical. This consists of a small plastic triangle with three tubular channels which allows the operator to place thermocouple needles at 3, 4 and 5mm depths.

Various methods can be used to confine a cryosurgical spray to the required area and Torre described the use of "neoprene cones" (Fig. 5-7) in six sizes as being suitable for this purpose. These cones were evidently designed originally as filter adapters, but seem to be very useful for containing a liquid nitrogen spray.

A second device, to prevent the unwanted spread of a cryogen spray, mentioned by Torre was the Walsh pressure ring. These are 8, 10 and 12 mm diameter rings attached to a handle (Fig. 5-8) and they can be used additionally to exert pressure around a lesion during cryosurgery in order to stop bleeding if the lesion has previously been biopsied, and also to prevent the spread of cryogen below the

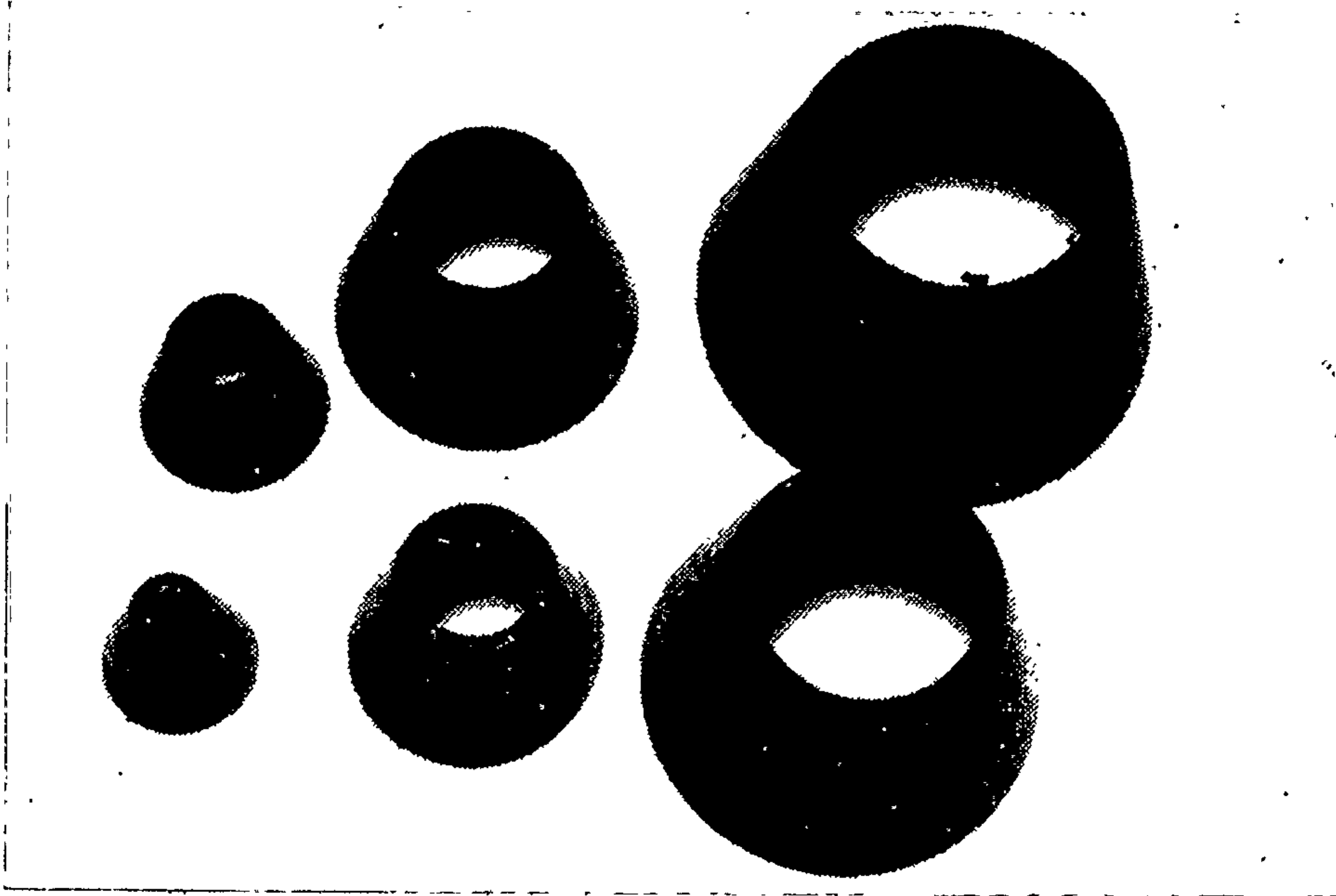


Fig.5-7. Neoprene cones, used to limit cryogen spray. (From Zacarian, Cryosurgical Advances in Dermatology and Tumours of the Head and Neck, 1977. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois.)

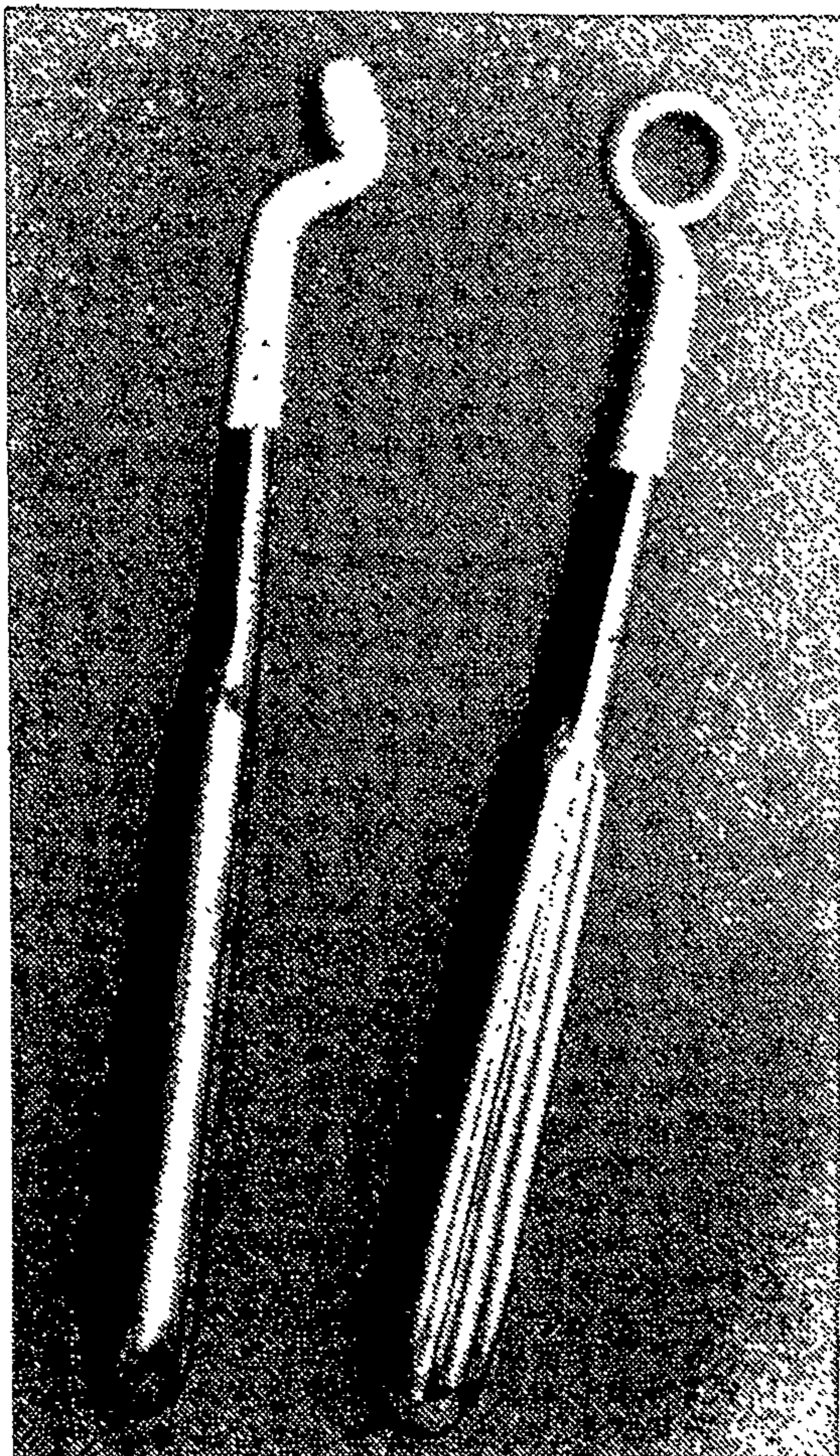


Fig.5-8. Walsh Pressure Rings, used to limit sprayed cryogen. (From Zacarian, Cryosurgical Advances in Dermatology and Tumours of the Head and Neck, 1977. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois.)

surface.

Conclusion

Obviously individual operators will develop preferences for different types of equipment and accessory articles for use in cryosurgery and the aim of this chapter has been merely to acquaint the reader with some of the different options available. It is likewise obvious that some equipment and cryogens are better suited to oral surgery procedures than others and that experience should lead an operator to choose those which will provide satisfactory surgical results.

CHAPTER 6

Advantages, Disadvantages, Complications and Limitations of Cryosurgery

It has already been partially shown in this work and will be further emphasized in later chapters, that there are in reality almost no serious complications attached to cryosurgery and that the advantages of this technique far outweigh any disadvantages which may be encountered.

Probably of more importance in a practical sense is that cryosurgery, like any other form of surgery, has limitations. In order to gain acceptable, successful results from this mode of treatment it is essential to work within the scope of those limitations.

Advantages

A concise list of the advantages of cryosurgery is rather difficult to compile, since several of these factors tend to overlap. However, it is now intended to present the major points for consideration by a surgeon prior to electing to use this form of treatment.

The minimal bodily disturbance to the patient is one of cryosurgery's main attributes and in this regard this type of treatment is very well adapted to elderly patients or patients who are in poor general health (Leopard, 1975). On this particular point Zacarian (1967) made the observation that some older patients suffering from coronary artery disease can often be treated, for example, for actinic or

senile keratoses, by cryosurgery without the need for local analgesia containing adrenaline. That author made the extra point that "with patients on anticoagulant therapy, there is no fear of postcryosurgery bleeding" and this factor will be referred to again later in this text. A fine example of cryosurgery to an elderly and infirm patient was described by Gage et al (1965) in which a seventy-two year old man with hypertensive cardiovascular disease, heart failure and angina was treated for squamous cell carcinoma of the mandible, without surgical resection, under local analgesia. By the following year no apparent recurrence was observed in this case.

The low rate of attendant complications seen in cryosurgery was pointed out by Leopard (1975) and it is really this factor which forms the basis of this chapter. Many authors have given similar opinions, and for example, in describing the results of thirty cases of cryosurgical treatment for neoplasia of the head and neck, Holden and McKelvie (1972) stated that this method of treatment caused the patient no additional discomfort and was "almost invariably a safe and simple procedure" necessitating minimal hospitalization. Those authors in addition advanced the proposal that cryosurgery may in the future become the treatment of choice in surgically inaccessible places where other methods have failed.

Predictability of the extent of cryodestruction by cryosurgery appears to be fairly accurate and Goldstein (1970) stated, perhaps a little over-optimistically, that the cell destruction "can be precisely limited to the diseased tissue". In this regard Leopard (1975) was a little more cautious, saying that cryosurgery was able to produce a "reasonably predictable volume of tissue destruction"

observing that this modality was very well suited to the treatment of "extensive superficial lesions". However, many writers on the subject of cryosurgery have noted the fact that the cryolesion is always sharply demarcated from the surrounding tissue and Neel (1980, p.14) made a definite point of this when referring to earlier neurosurgical work. With the use of modern equipment the predictability of the extent of the cryolesion is becoming more accurate, which obviously adds to the desirability of cryosurgery as a mode of treatment.

One author who did not agree that a cryolesion is predictable was Jolly (1976) and his opinion was that "nothing could be further from the truth". It seems that there is a good measure of disagreement in this matter which must therefore be open to some question.

The repeatability of cryosurgery without the formation of excessive scarring must rank as one of its greatest attributes. A confirmatory statement to this effect came from Gill and Long (1971), who in a critical appraisal of cryosurgery said that in the case of its use to treat small skin tumours "the subsequent healing is of high cosmetic quality". These writers added that in their opinion the results were better than could normally be obtained from irradiation or surgical excision. An important issue in relation to the non-scarring nature of cryosurgical treatment, also emphasized by these authors, was its preferential use in difficult surgical sites, such as the canthus of the eye, where scarring is of course to be avoided if at all possible. In an extremely enthusiastic manner Zacarian (1967) stated that following cryosurgery neither hypertrophic scars nor keloids had ever been reported to that date and in addition reported that he had

personally treated patients who had previously produced keloids following excision or electro-dessication of warts with no keloid formation. Zacarian added that small and early keloids actually responded well to cryosurgery, a point made earlier in this treatise.

The simplicity of repeat applications and the corresponding patient acceptance of the relatively simple procedure of cryosurgery was exemplified in a case treated by Brain (1974). In this instance one patient underwent ten laryngoscopies during 1967 for cryosurgery to multiple laryngeal papillomata, which had previously resisted other forms of treatment, and at the time of writing the author stated that "her larynx now looks normal", indicating an apparent absence of scar tissue formation.

The treatment of "wide areas of premalignant change" and other orofacial lesions which are normally difficult to treat by other methods, is a field in which cryosurgery is most successful (Leopard, 1975). The treatment of oral leukoplakia was mentioned in chapter four of this treatise and of course some of these areas must be regarded as pre-malignant (e.g. sublingual keratosis). Leopard also wrote of the obvious advantage of cryosurgery for the treatment of vascular formations and "certain granulomatous conditions" where management is usually problematical. In regard to oral leukoplakia, Sako et al (1972) presented details of the treatment of sixty cases by cryosurgery and reported that patient acceptance of the treatment was excellent. The results of this series were not particularly good with twelve recurrences in the follow-up period and with four of those twelve developing squamous cell carcinoma, one having died at the time of reporting. In referring to this series however Leopard

stated that the rate of recurrences seen here "has not been substantiated elsewhere to date", i.e. 1975.

The flexibility of cryosurgery has already been amply demonstrated in previous chapters and stands as a major advantage especially when considered in relation to its relative simplicity of application. Over ten years ago some seventeen uses for this type of therapy were listed and this figure has been far surpassed at this date (Holden and Saunders, 1973).

The absence, or relative absence, of pain following treatment could well be regarded as the primary advantage of cryosurgery. Holden and Saunders (1973) attributed this to the fact that "sensory nerve endings are extremely susceptible to cold" and observed, as many others have done, that the actual treatment by cryotherapy in itself is not really painful. Jolly (1976) agreed that cryosurgical treatment was not usually a painful experience but did add that it was during the thaw period that the patient was more likely to complain of pain and especially so in the tongue. A similar report was made by Peck (1974), in an account of cryosurgery for cervical lesions, who stated that of twenty one recently treated cases only one had experienced post-operative pain, and that that was probably due to pre-existing pelvic inflammation.

Palliation is an area where cryosurgery can exhibit its potential for relief of pain to great advantage and De Santo (1972) wrote that in a group of twenty seven patients he had treated in this manner relief of pain, reduction in tumour size and elimination of haemorrhage were successfully obtained. The subject of palliation was likewise

referred to by Gage et al (1965) who stated that they had used cryosurgery to debulk masses in the rectum and pharynx when cure of the disease was deemed impossible. Miller (1974) also wrote very enthusiastically on this topic stating that cryosurgery's "effectiveness in eliminating pain is extremely important for palliative treatment."

The matrix of some important structures can survive cryosurgery and McKelvie (1974) included bone, fascia and large blood vessels in those structures and regarded this situation as "a major asset of this type of therapy". Gage et al (1965) made a special point of bone in this regard stating that following freezing the devitalized bone remained, acting as a scaffold for new bone growth. The matter of the retention of a bony matrix following cryosurgery was investigated in great depth by Bradley and Fisher (1975) who described a necrotic phase, an osteogenic phase and a remodelling phase. These authors described the treatment of three patients with mandibular keratocysts by means of enucleation and subsequent cryotherapy of the surrounding bone with good final results of bone replenishment obtained. A similar study concerning the effects of freezing on large blood vessels was carried out which resulted in the important discovery that although the vessel wall was devitalized by the freeze its "function as a blood conduit was undisturbed", this being due to the fact that collagen and elastic tissue within the wall were hardly damaged at all (Gage et al, 1967).

A further very strong feature of cryosurgery is the lack of post-operative haemorrhage or infection, which is of obvious advantage when one considers the extreme effects which can accrue from these

complications. This asset was briefly referred to by Ablin et al (1969) in a review of the immunological aspects of prostate disease, their observation being that "cryogenic destruction has the advantage of producing little or no post-operative haemorrhage". An interesting additional thought was presented in that, in the case of malignancies, cryosurgical ablation reduced greatly the possibility of disseminating cancerous cells by reason of the infarction produced during freezing. In relation to tonsillectomy, a notorious haemorrhage-producing procedure, Brain (1974) stated that "there is no risk of primary or reactionary haemorrhage" but added that a four per cent increase in the risk of secondary haemorrhage existed with cryosurgery. Brain however reported that in his own cases this secondary haemorrhage had never been severe and had always terminated spontaneously.

Ozenberger (1970) in describing cryogenic surgery for chronic rhinitis reported that it produced "less bleeding and less pain than surgical resection of hypertrophic turbinates". In his series of forty six cases that author tabled, under complications following cryosurgery, two cases of serous otitis (transient), one case of acute sinusitis and five cases of delayed healing which were attributed to either infection and/or exposed bone. As regards the post-cryosurgical situation following cancer removal, Gage et al (1965) similarly reported that although healing was slow, compensation could be found in the lack of serious complications "such as infection or haemorrhage".

Always provided that it is used within its limitations and on suitably selected lesions, such as have already been discussed,

cryosurgery offers a high rate of cure. This was emphasized by Poswillo (1975, A), who after describing several oral conditions to which he considered cryosurgery to be ideally suited wrote that "under certain circumstances and for specially responsive lesions, cryosurgery is incomparable" and that it was of special use in the treatment of disease of the oral mucosa. A very interesting appraisal of an initial test series for treatment of large haemangiomata was presented by Goldwyn and Rosoff (1969), in which five patients with "large, longstanding haemangiomas of the face and trunk" underwent cryosurgery. The results were somewhat mixed, but of special interest was that the more cavernous the type of lesion, the more regression was observed and in two of the cases, both cavernous haemangiomata, "significant regression" was reported. At the time of writing the authors were prompted to say that their initial results were satisfactory enough to warrant further cryosurgical trials. The suitability of cryosurgery for the treatment of leukoplakia has already been mentioned and in this regard Leopard (1975) reported that of over forty cases he had treated during a period of three years only two did not respond.

The very exciting possibility of an invoked immune response following cryosurgery, if proved to be realistic, would be probably the greatest single advantage of this form of treatment. At present no investigators can be specific about this matter but Poswillo's (1975, B) view would seem to be representative. He stated that little evidence could be tabled to establish an immune response being produced by cryosurgery, but that possibly in the future workers will give more evidence of specific immune responses following freezing of malignant tumours.

Disadvantages, Complications and Limitations

It would be quite simple to present a laborious list of drawbacks to the use of cryosurgery, and probably to any other form of surgery, but the aim of this section is to deal with those problems which are of a meaningful nature and then to mention some of the more minor difficulties one may encounter in the use of intense cold on tissues.

One basic disadvantage of cryosurgery is that a complete specimen encompassing all margins cannot be produced post-operatively (Jolly, 1976). While this problem is of no great importance when dealing with small, benign lesions it does assume major proportions in the case of malignant tumours. A partial answer to this serious difficulty was included in an excellent article by Bekke and Baart (1979) who described cryosurgical treatment to twenty one patients suffering from malignant tumours of the mouth. The method adopted in this series was to wait for necrotic tissue to slough off, following freezing, when "another biopsy specimen was taken from suspect areas and, if necessary, freezing was repeated". The majority of patients in this group were quite elderly and while the follow-up biopsy and freeze method has some merit it must be regarded as a second best situation.

Referring to benign lesions Holden (1974) stated that there was a "theoretical disadvantage" that biopsy material could not be made available with cryosurgical treatment but that in reality a section of frozen tissue could easily be removed and sent for immediate examination or kept in formalin for later investigation. Poswillo (1975, B) made an almost identical statement but said that the

specimen was best taken during the thaw period. These specimens do not of course show the full extent of a larger tumour.

The lack of a post-operative specimen for examination following cryosurgery was also referred to by Marciani and Trodahl (1975) who noted that the margins of a lesion "can only be judged clinically" under these circumstances.

Probably the greatest shortfall of cryosurgery is the limitation of the size of the ice ball and this unfortunate reality is closely related to the operator's inability to provide a full post-operative specimen for examination. Bekke and Baart (1979) made several astute observations in respect of this problem, at one point stating simply that "the depth of freezing is limited". In discussing cryosurgical treatment of malignant tumours these authors said that this modality was not yet generally accepted as curative treatment for malignant tumours and that, due to the inherent inaccuracy of cryosurgery and the "limited tissue-destroying capacity of the available equipment", cases for treatment required very careful selection. While it may be possible to argue a case for curative cryosurgical treatment to small malignant lesions, the overall soundness of these writers' judgement would appear to be beyond debate.

The same awareness of the ice ball's limitation was obvious in a discussion of cryosurgery's disadvantages by Poswillo (1975, B) who rightly regarded underextension of the cryolesion as a matter for concern. That author compared excision and electrosurgery to cryosurgery and made the interesting comment that overextension with cryosurgery "is generally less alarming than overextension of

excision or electrosurgery". A practical solution to this problem was suggested by Poswillo who stated that with sufficient experience an operator is able to assess the extent of destruction by the ice ball and so plan a series of overlapping cryolesions to prevent any target tissue from escaping that destruction. While that author is a surgeon of the highest possible esteem it would seem that the overlap method advocated must have limitations which are all too easy to exceed.

Leopard (1975) made an almost identical statement to that of Bekke and Baart when he wrote that "the depth of destruction is limited" in cryosurgery and on that basis gave a similar opinion to that of many other eminent workers in this field, in that cryosurgery had its main usefulness in the treatment of surface lesions. An additional observation by Leopard was that where a lesion was deep the frozen tissue can be excised and the base refrozen but that he saw little advantage in that approach over surgical excision.

The disadvantage of depigmentation of skin following even short periods of freezing is naturally of most importance when facial skin is considered. On this point Leopard (1975) stated that a reduction in pigmentation on the face can occur after freezes of only 20-30 seconds duration and referred to the work of Goldwyn and Rosoff (1969) in this context; however, this was somewhat erroneous as those two writers were discussing the obliteration or reduction of large haemangiomata and were not referring to the inherent pigmentation of facial skin.

Leopard and Poswillo (1974), in referring to depigmentation of facial

skin by cryotherapy, reported that this unwelcome complication would to a large extent be prevented by using a number of short freezes rather than one long freeze.

Post-operative swelling is a troublesome complication encountered with cryotherapy and a prudent operator should warn the patient to be prepared for this problem. Poswillo (1978) made the point that following cryosurgical treatment, near the lips in particular, one often sees a considerable amount of swelling which can last for up to one week. On a more important note, Poswillo stated that although he had not experienced this problem when dealing with lesions on the tongue the possibility of post-operative swelling in this region with consequent compromise of the airway must be kept in mind.

The potential danger of oedema was also emphasized by Holden and Saunders (1973) in regard to cryotonsillectomy in young children with large tonsils and it is patently simple to envisage a situation arising in which the airway could be endangered under these conditions.

Some interesting remarks regarding cryo-oedema were given by Bekke and Baart (1979) who inter alia reported that patients treated for vascular lesions of the floor of mouth or the tongue did not exhibit any marked distress due to post-operative oedema. These authors also observed that cryo-oedema intra-orally was more of a problem with children due to the early childhood anatomy.

Post-operative swelling following cryosurgery for the treatment of lichen ruber planus was reported by Malmström and Leikomaa (1980) who

said that in one group of patients eight out of nine had complained of swelling, but interestingly all were prepared to have further cryosurgical treatment if necessary.

Postcryosurgical pain is not a significant feature, in fact quite the opposite is the general experience; however, some patients do complain of a degree of pain. According to Leopard (1975) one explanation of this is that peripheral nerves adjacent to the freeze zone, which have been subjected to "moderate freezing", may be painful possibly due to the collection of cellular breakdown products. Bekke and Baart (1979) reported that some patients, who had been treated by cryosurgery for oral leukoplakia complained of "pain during mealtime". In one of my personal cases, to be presented in a later chapter of this treatise, postcryosurgical pain appeared as a major feature; however, this was a definite exception to my general experience.

Sako et al (1972) likewise reported postcryosurgical pain stating that "slight to moderate transient pain of about 30 seconds duration" from the reactive hyperaemia immediately following the melting of the ice ball can be noted. As regards later post-operative pain these writers said that, if present at all, it was usually mild and easily controlled by analgesics. It has been my experience that patients sometimes complain of a mild burning or stinging sensation for a few days post-operatively rather than actual pain.

Peripheral sensory nerve damage producing temporary post-operative analgesia, while mostly regarded as an advantage of cryotherapy, is occasionally the basis for complaint by a patient. Leopard (1975)

made very minor reference to this situation merely noting that "there is often reduced sensation following cryosurgery". Bradley and Fisher (1975) made a more significant observation regarding this complication when describing the freezing of mandibular bone following the enucleation of a keratocyst. These authors recognized the fact that the inferior dental bundle would be frozen during the process and reported that regeneration of the inferior dental nerve could be expected after several months of impaired sensation.

Gill et al (1970, B) also made reference to cryosurgical nerve damage when, in discussing cryosurgery for neoplasia, they reported a "remarkable degree of functional recovery which followed the freezing of the sciatic nerve". Of particular interest in this case was the writers' proposal as to how this had occurred, namely that the devitalized nerve sheath may have aided the accurate alignment of regenerating axons and this concept is generally accepted to this day.

Slow healing of tissues following cryosurgery has been remarked upon by some authors. Leopard (1975), for example, stated that healing can be delayed for some weeks in cases where thin mucoperiosteal surfaces have been frozen too harshly leading to the exposure of bone. A similar observation was made by Bekke and Baart (1979), when giving details of actual clinical cases, who reported that when bone had been exposed healing was "significantly delayed" and had taken several months in some cases.

Gill and Long (1971) gave evidence that in the case of prostatectomy by cryosurgery a serious susceptibility to post-operative infection

had been well recognised for a period of time. These authors, in this context, referred to a protracted post-operative period as resulting from inadequate freezing at operation or from necrotic prostate remnants, which required long antibiotic cover to avoid possible septicaemia.

A further commonly reported complication of cryosurgery is that of bullae formation and this matter was coupled together with massive oedema of the lip following cryosurgery by Gill et al (1970, B). Gradual resolution of these conditions was reported to occur during the ensuing 2-3 days.

Leopard (1975) similarly reported that vesicle formation may occur following cryosurgery to mucosa or skin due to excessive accumulation of extracellular fluid. That writer provided a graphic illustration of a typical large vesicle some 24 hours after cryosurgery to an haemangioma of the lower lip.

In Zacarian's fine book on cryosurgery Graham (1977, pp.79-81) described numerous other complications related to the use of this mode of treatment, but it must be said that most of the problems referred to, if in fact occurring at all, would have to be classed as very minor and could not be regarded as grounds for the exclusion of cryosurgical treatment except under very unusual circumstances. The complications referred to included possible infection, which has already been documented in this chapter, idiosyncratic reaction, cold urticaria, cryofibrinogenemia, erythema (which could rightly be listed as a more common problem), and post-operative burning or stinging, which I have also reported from personal observation.

Apart from the difficulties which have been discussed in this chapter there is one small further group which bear special relevance to the use of cryosurgery in the control of oro-facial pain. This subject will be dealt with in detail in a later chapter.

Disadvantages especially related to oro-facial pain control

The following disadvantages are compiled from the work of Nally et al (1984):

- (i) Cryosurgery is not 100 per cent effective.
- (ii) Multiple procedures may be necessary if pain recurs or migrates to previously untreated areas.
- (iii) The hyperaesthetic phase of nerve recovery may bother some patients.

CHAPTER 7

Oro-facial Pain

Oral and facial pain is very common, can be extremely severe and at times encompasses a strong psychological component not so commonly associated with other forms of pain.

In this chapter it is intended to provide a necessarily brief account of the very complex theories of the cause of pain, to outline the anatomy and neurology of oro-facial pain and to discuss the types of pain observed in this region. Trigeminal neuralgia and similar conditions will be examined as a special case, partly as an introduction of the following chapter.

The Definition of Pain

Definitions of pain are as numerous as the pains themselves and depend to a large extent on the standpoint from which one views the problem. Physiologists, psychologists, neurologists and many others all have their own ideas as to what constitutes pain. One dictionary definition of pain is "suffering or distress of body or mind" (The Concise Oxford Dictionary, 1982). Most writers agree that pain is an emotional phenomenon and Wyke described it as "a specific emotional disorder provoked by stimulation of an anatomically discrete system of sensory receptors that is innervated by equally discrete afferent pathways" (Wyke, 1968). This wording was slightly altered in later works by Wyke but contained the same basic principles and is probably as acceptable as any other definition of the state of pain.

Theories of the Cause of Pain

A short, concise account of the theories concerning the cause of pain was given by Hannington-Kiff (1981) when writing on various aspects of pain in general and its control. That author considered three basic theories and entered some constructively critical observations of them. In essence those theories are:

(i) Specificity theory

This theory is that specific nerve endings, pathways and centres in the brain exist which specifically carry pain. From the nerve endings (pain receptors) impulses travel in thin myelinated and unmyelinated peripheral nerve fibres to synapse in the spinal cord with neurons which cross to the opposite side of the cord and ascend to the thalamus, from whence they relay to the post-central gyrus of the cerebral cortex.

(ii) Pattern theory

Here the emphasis is on non-specific receptors. The view is that "sensations are the product of the interpretation by the central nervous system of spatio-temporal patterns of incoming impulses". Pain is thought to be "perception of patterns set up in the central nervous system by the intense stimulation of an array of non-specific receptors".

(iii) Modulation theory

A more complex theory than the first two deals with the control or modulation by the central nervous system of the input of information to that central system. The theory concerns the

relation of thick and thin nerve fibres, the thin fibres being the carriers of pain impulses; here there is partial agreement with the specificity theory. The control of impulse input is thought to be by some neurons which operate as a gate through which all sensory input must pass. Stimulation of the thick nerve fibres, which are sensitive to light pressure, causes a negative feedback from the controlling neurons which closes the gate to further impulses. Conversely, heavier pressure causes a progressive increase in stimulation of the thin fibres, whose threshold is higher, causing a positive feedback from the controlling neurons which opens the gate to a flood of impulses which is recognized as pain. This gate control theory was fully described by Melzack and Wall (1982, p.222), whose original concept it was.

Bonica (1977) provided an interesting overall account of the different theories of pain from prehistoric to modern times, reporting that by the end of the nineteenth century there were three theories. One of those theories corresponded to the specificity theory, one to the pattern theory (i.e. the intensive theory) and a traditional one that "pain is purely an emotional experience or passion of the soul". That author also described the "gate" theory, as originally postulated by Melzack and Wall, in very similar terms to that of Hannington-Kiff.

Neurology and Anatomy of Oro-facial Pain

In this section it is proposed to give an outline of the pain system of the oro-facial region and not to delve into fine anatomical

detail, which is available to the reader in any standard anatomy text.

Probably the most comprehensive account of oro-facial pain mechanisms was presented by Wyke (1976, p.279), the salient points of which will now be examined.

(i) Peripheral facial pain systems

Nociceptive receptors in most tissues are especially sensitive to tissue damage and plexiform, unmyelinated fibres are arranged in skin, sub-cutaneous tissue, fasciae, periosteum, adventitia of blood vessels, fibrous capsules and ligaments of the T.M.J.

Mechanical or chemical damage produces a marked increase in activity of these receptors and nerve fibres and afferent impulses are transmitted to the central nervous system in small diameter nerve fibres. Other small fibres respond to non-traumatic stimuli (e.g. tickling).

Afferent fibres travel in the trigeminal (V1, V2, V3), cervical 2 and 3, glossopharyngeal, vagus and facial nerves. Wyke reported that 15 per cent of fibres in the facial nerve were afferents. All the facial afferent fibres travel to the spinal nucleus of the trigeminal nerve where they synapse and are projected to the cerebral cortex.

(ii) Central facial pain projection systems

From the spinal nucleus of the trigeminal nerve projection

neurons run to the thalamus. It is noted that within the spinal nucleus of the trigeminal nerve the nociceptive impulses are modulated by impulses from other oro-facial receptor systems.

When sufficient activity is generated in the thalamic nuclei it is relayed in four directions, each supplying a specific component in the experience of the individual, namely:

Perception

Relay here is to the inferior paracentral and parietal regions of the cortex, where the individual recognizes the location and physical nature of the pain.

Affective component

This relay is to the frontal lobes. Impulses from the thalamus are propagated simultaneously to different cortical areas. It is in the frontal lobes that the unpleasant emotion of pain occurs. In other words this is where it hurts, so that a patient who has a frontal leucotomy performed still perceives the pain but it does not "hurt" any more.

Memory

Here the relay is to the temporal lobe, where there are recent and long term memory systems. The long term memory system is not so related to the intensity of the pain as to the duration and frequency of it.

Visceral-hormonal reflex component

In this case the relay is to the hypothalamus, the cells of which control the sympathetic and parasympathetic outflow. Stimulation of the hypothalamus produces a complex of visceral effects on, for example, the eye pupils, cardiovascular and gastro-intestinal systems plus hormonal changes connected with pain.

It can be seen from the above account that Wyke did not agree with the pattern theory of the cause of pain, but that he does support the specificity theory and perhaps the modulation or gate theory.

While presenting a somewhat complex account of the anatomy of facial pain, Gregg (1977) seemed to be in general agreement with Wyke and in specific incidences concurred (op.cit., p.28) that nociceptors are the primary receptors for noxious stimuli, that the nociceptive fibres are fine, slow-conducting fibres and that the facial nerve does indeed carry some sensory fibres.

Awareness of facial pain

Wyke contended that in individual patients the intensity of the experience of pain varies from time to time during the day and that different patients vary widely in the degree of suffering from similar lesions. That author also reported that the intensity of pain varies with one's emotional state, attention to daily tasks and with the response to suggestion. He continued with a description of the ways whereby the awareness of pain can be modified as follows:

(i) Peripheral modulation

When peripheral mechanoreceptors are stimulated, for example by rubbing or pressure, the nociceptive impulses are modulated at the central nervous system synapse which leads to less pain awareness. There can be no doubt that Wyke is correct in this matter as one could cite numerous examples in daily life to support this statement.

(ii) Central modulation

(a) Caudal spinal nucleus - neuro-projections from the caudal end of the brain stem reticular system inhibit nociceptive impulses and therefore suppress the awareness of pain. The caudal end neurons can be stimulated by hypnosis, sleep, very high levels of catecholamines (e.g. in high emotional state) and some drugs (e.g. diazepam, morphine), all of which therefore suppress the awareness of pain. Conversely, a reduction in activity in caudal end neurons increases the awareness of pain and Wyke maintained that this occurred in the "triggering" of trigeminal neuralgia, also when the attention of the patient was drawn to the source of pain and, surprisingly, with small doses of barbiturates.

(b) Thalamic nuclei - neuro-projections from the paracentral, frontal, parietal and temporal areas of the cortex to the thalamic nuclei inhibit the bulbothalamic neurons and therefore suppress the response to pain.

(c) Cortex - the excitability of cortical neurons is

continually modulated by activity from the rostral part of the brain stem reticular system and an increase in activity increases the awareness of pain. The rostral part is stimulated by, for example, moderate anxiety, moderate amounts of catecholamines, a moderate amount of alcohol and by caffeine and benzadrine. The rostral area is depressed by, for example, sleep, low carbon dioxide levels in hyperventilation, a large amount of alcohol and by pethidine and general anaesthesia, all of which produce less awareness of pain.

It would seem very difficult for anyone, except another neurological expert, to argue with the work of Wyke who presented his findings in an extremely clear and methodical fashion after many years of research into systems whereby facial pain is recognised by the sufferer.

One writer to agree, at least in part, with Wyke was Bell who devoted a complete book to various aspects of oro-facial pain. In that text the author agreed, for example, that it is the finer nerve fibres which carry pain impulses and gave a classification of nerve axons by diameter (Bell, 1979, p.12). Later in his text, Bell (op.cit., p.330) also agreed that fixing attention on the mouth intensified oral pain and added that bruxism and tooth clenching "compound the problem".

Types of Oro-facial Pain

The occurrence of oro-facial pain carries with it certain overtones

not present when pain is experienced elsewhere and there are abundant references to this fact in the literature. Pilling (1977) for example stated that "when pain of the mouth or face occurs there are added some psychologic factors that do not exist when pain involves other parts of the body". That author related this fact to the sufferer placing special emotional significance on the mouth and face in relation to one's image. Bell (1979, p.7) likewise said that oro-facial pain held "important implications, especially in relation to concepts of body image". These opinions were strongly endorsed by Wyke (1976) who went into some detail on the issue and observed that "pain in the face is charged with particularly intense emotional overtones" and that some of those suffering from chronic facial pain become "social recluses", especially women due to their social need to appear attractive facially. This special problem of facial pain appears to be that the sufferer has the notion that others can see the pain, which is not so with pain elsewhere in the body.

There are numerous classifications of the clinical presentation of oro-facial pain and it is now proposed to record a brief and, hopefully, clear composite summary of the more common locations of oro-facial pain sources.

1. Teeth and supporting structures

Pulpal pain - varies from a transient response to hot and cold, to a lasting response to thermal stimuli, to eventually a severe throbbing increased on the patient lying down (Shafer et al, 1974, p.435).

Periodontal pain – is poorly localized by the patient. "The tooth feels sore or elongated" under chewing pressure, but sustained pressure may relieve the soreness (Bell, 1979, p.169).

Bone pain – is often slow or dull and poorly localized, but severe bone pain becomes easier to localize. There may be unusual radiation of pain (Frost, 1977, p.140). Obviously some lesions, such as fractures, will produce severe throbbing pain which is easily localized.

2. Neighbouring structures

T.M.J. and masticatory muscle pain – is referred to by Cawson under six headings. Dislocation or fracture of the condyle leads to varying degrees of severity of pain and sometimes none. Infection, mainly acute pyogenic arthritis and acute osteomyelitis, is extremely rare. Rheumatoid arthritis seldom affects the temporomandibular joint but can produce severe pain and disability. Vascular pain, mainly temporal arteritis (see later text), leads to pain in the masticatory muscles due to ischaemia. Muscle spasm is one of the principle causes of pain in this area, the pain being usually unilateral, of slow onset, dull and made worse by mastication. There is often an associated locking and clicking of the joint. Lastly, painful conditions of the parotid glands (see later text) may cause severe pain in this area (Cawson, 1978, p.276).

Maxillary sinus pain - usually from acute sinusitis, was described by Howe as being of a dull, throbbing and continuous nature, situated over the infra-orbital area and related to the upper teeth. It was reported also that jolting or bending forward caused an increase in the pain (Howe, 1971, p.8). Chronic maxillary sinusitis seldom produces pain, while antral carcinoma can lead to numbness, hyperaesthesia or pain depending on the site and stage of the neoplasm (Boles, 1977, p.120). Similarly, other sinuses can be the site of pain and Boles recorded that acute ethmoiditis can cause pain at the roof of the nose or behind the eye; acute frontal sinusitis may cause an aching type of pain over the sinus. Acute sphenoiditis, although mostly symptomless, has often been considered to cause a wide variety of pains including pain in a canine tooth.

Pre-auricular pain - as reported by Cawson (1978, p.366) can be caused by otitis media or neoplasms in this region.

Salivary gland pain - was stated by Wyke (1976, p.291) to be due to "irritation of the nociceptive plexiform system in the parotid fascia" by acute parotitis, a neoplasm or distension of the gland following sialolith formation. Wyke also observed that the submandibular gland was more commonly involved in distension than the parotid gland.

Tonsillar pain - is recognised in acute tonsillitis by a typical sore throat made worse on swallowing, with often associated headache and muscle and joint pains. At times there is

referred pain to the ears (Jones, 1978, p.846). In relation to quinsy (peritonsillar abscess) Jones continued that the condition occurs during an attack of acute tonsillitis and is nearly always unilateral with increased pain radiating to the ear on the affected side.

Ocular pain - was reported by Scully and Cawson to occur in and around the orbit in some cases of glaucoma and they observed that refraction disorders in the eye could produce frontal headaches at times (Scully and Cawson, 1982, p.277). Pain in and around the eye was also said to be a characteristic of the rare Raeder's syndrome or paratrigeminal neuralgia (Jurgens and Jurgens, 1977, p.232).

Elongated styloid process pain - as described by Shafer et al takes the form of "sore throat, otalgia, glossodynia, headache, vague oro-facial pain or pain along the distribution of the internal and external carotid arteries" with associated dysphagia (Shafer et al, 1983, p.864). The cause of pain is the elongated styloid process or an ossified stylo-hyoid ligament. Jurgens and Jurgens (1977, p.229) in considering this syndrome observed that when headache occurs the cause is impingement by the styloid process on the internal or external carotid artery.

3. Referred pain

Here again the clearest account of this class of oro-facial pain

seems to have been given by Wyke (1976, p.296). The main characteristics of referred oro-facial pain, as put forward by Wyke, include the following points. Pain to the face may be referred from three areas, the teeth, the nose and paranasal sinuses and the heart. The nociceptive receptors where the pain is felt are not involved in any pathological process, the afferent fibres from that part of the face are likewise not involved in any pathological process and the non-facial tissue involved has nociceptive afferent innervation embryologically related to the segmental innervation of the area where the pain is felt.

Some typical referrals are from maxillary or mandibular teeth to specific small areas of the face or nose on the same side or to larger areas supplied by the maxillary or mandibular divisions of the trigeminal nerve on that side.

Other common examples of referred pain are:

- (a) From the middle turbinate or antral ostium to the malar and pre-auricular area.
- (b) From the ethmoidal sinus to the same malar and pre-auricular areas plus upper molar teeth.
- (c) From the inferior turbinate and intra-antral mucosa to the cheek and most maxillary teeth of the same side; and
- (d) From the heart (in coronary vascular insufficiency) to the postero-inferior part of the face on the left side.

Gayford and Haskell devoted only a small section to referred pain in their well presented book on oral medicine. They did however provide some other good examples of the referral of pain in the oro-facial region and some of those examples were :

- (a) Severe pain from the eye in acute glaucoma radiating across the side of the face.
- (b) Pain from the teeth (usually lower molars) or from the temporomandibular joint referred to the ear which these authors claim to be "exceedingly common".
- (c) Cervical spondylosis may cause pain to radiate to the face, but almost always with local pain extending up over the occiput. There is neck pain which is made worse by movement; and
- (d) "Pain from oesophageal disease may be referred to the lower jaw and ear" (Gayford and Haskell, 1979, p.194).

It is interesting to note that these writers acknowledged the work of Wyke (1968) in their bibliography.

4. The Neuralgias

(a) Primary (idiopathic)

Paroxysmal trigeminal neuralgia produces violent spasms of pain lasting only a few seconds and mostly in the second and third divisions of the trigeminal nerve (Gayford and Haskell, 1979, p.211). This condition will be examined more fully later in

this text.

Paroxysmal glossopharyngeal neuralgia was described by Gayford and Haskell (p.216) as leading to pain in the ear, angle of the jaw, the throat or upper part of the neck. They also observed that a vagal neuralgia may be associated at times.

(b) Secondary

(i) Extracranial

Mental nerve compression occurs when the mental foramen is high on the alveolar ridge (ridge resorbed) and a denture causes pressure. Pain is produced in the mental region and lower lip (Howe, 1971, p.12).

Nerve entrapment can occur leading to severe pain in the area of distribution and Thoma (1963, p.828) stated that the inferior alveolar nerve was most often affected. Other nerves such as the infra-orbital or mental nerve can likewise be entrapped and produce pain, and Gayford and Haskell (op.cit., p.213) observed that this can occur in Pagets disease or acromegaly. Causalgia is a pain of typical burning quality and is said to arise after injury to a sensory nerve. Shafer et al (1983, p.863) reported that causalgia occasionally occurs after a difficult or traumatic tooth extraction, especially a multi-rooted tooth.

Frey's auriculo-temporal syndrome as described by Mumford consists of paroxysms of burning pain in the temple with

flushing and sweating upon eating. The syndrome is said to be caused by chronic disease of the parotid gland, mostly inflammatory (Mumford, 1976, p.292).

Nasopharyngeal carcinoma, referred to by Cohen as retropharyngeal carcinoma, affects the maxillary branch of the trigeminal nerve first and often later affects all branches causing pain in the areas of distribution of those nerves (Cohen, 1959).

(ii) Intracranial

Post-herpetic neuralgia is estimated to affect up to ten per cent of the patients who have suffered from herpes zoster of the trigeminal area. Cawson (1978) described the pain as variable, some severe and some mild, with at times more chronic type of pain rather than paroxysmal. This condition will be discussed in more detail later in this text.

Posterior cranial fossa tumours can cause pain in the distribution of the trigeminal nerve and the most common lesion to do so is the acoustic neuroma in the cerebello-pontine angle (Gayford and Haskell, 1979, p.212).

Middle cranial fossa lesions, like posterior cranial fossa growths, can produce pain similar to trigeminal neuralgia (Cawson, 1978, p.372). Examples of such lesions would be pituitary tumours or a carotid aneurysm.

Tabes dorsalis can produce pain extending from the nose to a part of the adjacent cheek (Gayford and Haskell, 1979, p.232).

5. Vascular pain

Migraine was originally termed hemicrania but, as pointed out by Blau (1971), this was a misnomer as the pain can frequently be in the mid-line. The pain is paroxysmal lasting hours or days with periods of complete freedom from pain. There are usually associated autonomic disturbances to the gastrointestinal tract or the visual system. The pain can become throbbing and at times made worse by sneezing, coughing or head movement. The cause of migraine is commonly believed to be dilatation of cranial arteries but Blau hypothesized that either dilatation or constriction of those vessels could be the instigator of the condition.

Periodic migrainous neuralgia has numerous synonyms, facial migrainous neuralgia, Horton's syndrome, Sluder's syndrome, cluster headaches, alarm clock headaches and several more. Cawson (1978, p.374) described this phenomenon as being probably due to "oedema and dilatation of the wall of the internal carotid artery and probably also the external carotid".

Cawson also observed that men up to the age of fifty were mostly affected, that the pain occurred in the orbit, temple or maxilla and lasted between one half hour to two hours. The attacks occur one to three times per day and can continue for several

weeks after which time complete remission is common for months or even years.

Giant cell arteritis (temporal arteritis), as clearly described by Gayford and Haskell (1979, p.193), typically causes dull persistent pain in one or both temples, with tenderness of the adjacent scalp. Pain may radiate to the face or occipital region and ischaemia may cause pain in the masticatory muscles. The basis for this condition is chronic giant cell inflammation of the superficial temporal and other large arteries occurring in patients over fifty five and mostly over seventy years of age.

6. Psychogenic pain

There have been myriads of articles and books published on this topic and there can be no doubt of the existence of a strong psychogenic element in some cases of oro-facial pain. Feinmann and Harris (1984) presented their concept of this problem in a clear article and, in short, concluded that these "pain disorders appeared to be linked to stressful life events and long-term life problems". The basic types of clinical pains discussed were:

- (i) Facial arthromyalgia (temporomandibular joint pain dysfunction syndrome) which produces pain in the temporomandibular joint and associated muscles.
- (ii) Atypical facial pain which may be diffuse or localized to the facial bones or alveoli of the jaws.

(iii) Atypical odontalgia (a variant of atypical facial pain) where the pain occurs in the teeth; and

(iv) Oral dysaesthesia, consisting of burning or an alteration of sensation in the tongue, lips, gingiva or denture bearing area.

7. Ictal pain

The final category of facial pain listed by Wyke (1976) was reported to be "the least common of all varieties of facial pain" and is associated with sensory epilepsy. The pain in the face is usually unilateral at onset, but intensifies and spreads, possibly becoming bilateral. The pain is described as throbbing or bursting but later becoming of a burning type.

Trigeminal Neuralgia and Similar Conditions

The clinical features of paroxysmal trigeminal neuralgia, as described by Gayford and Haskell (1979, p.211), are very distinctive. The condition is diagnosed twice as often in females as in males, is rare before forty years of age and mostly occurs between fifty and seventy, is nearly always unilateral and is more common on the right side. Shafer et al (1983, p.854) stated that the ratio of right to left being affected is 1.7:1.

Pain is most common in the second and third divisions of the trigeminal nerve, rarely in the first division. There can be diffusion of pain between the branches of the nerve or the pain can

be confined to one branch (e.g. mental or infra-orbital).

Of diagnostic importance is the character of pain experienced which is often said to be "sharp and shooting like an electric shock or a red hot needle". The pain is of extreme severity and an unexplained feature is that it occurs more commonly first thing in the morning and rarely at night. Paroxysms of pain last a few seconds normally, but between these violent episodes a dull background ache may persist.

One very characteristic feature of this condition is the stimulation of pain from a "trigger zone". Certain facial areas require only the lightest touch to precipitate an attack and such activities as face washing, shaving, eating or teeth cleaning are often enough to initiate a spasm of pain. One commonly expressed "trigger" mechanism is a draught on the face. Between painful periods the "trigger zone", in some patients, is totally refractory, in other patients it is not. Commonly, a number of paroxysms occur at frequent intervals for a period and then a pain-free episode is experienced lasting weeks or months.

The diagnostic essentials of trigeminal neuralgia which are definitive in very nearly all cases consist of:

1. History - the classical history of severe sudden sharp pain of "electric shock" type, plus very often a "trigger zone". This feature is almost completely diagnostic in its own right.
2. Clinical examination - should prove negative in respect to any

pathosis.

3. Special tests (such as radiography) - must be negative. If positive any abnormality must be excluded as a source of pain.
4. Diagnostic local analgesia block - should relieve the pain.
5. Therapeutic trial of Tegretol - should relieve or obliterate the pain.

The prognosis of trigeminal neuralgia is uncertain as the whole condition is open to great variation, but in some cases where treatment has not been afforded suicides have unfortunately been the end result.

Glossopharyngeal neuralgia was also considered by Gayford and Haskell (1979, p.216) and by Shafer et al (1983, p.860). The condition appears to be very similar to trigeminal neuralgia but has no sex predilection and is almost exclusively unilateral. The pain is centred either in the ear or the pharyngeal area and may be "triggered" by swallowing, eating, talking or tongue movement.

Chawla and Falconer (1967) described the location of pain from glossopharyngeal neuralgia as being "in the base of the tongue and faucial region on one side" and in complete contradiction of Shafer et al stated that "males are more often affected than females" and reported that in their own series of cases the ratio had been nine to one. They quoted another researcher who had made "similar

observations" and others who had observed "an equal occurrence in the sexes". These authors also reported the fact that the upper filaments of the vagus nerve are at times affected as well as the glossopharyngeal nerve.

In a lengthy article Bohm and Strang (1962) discussed eighteen of their clinical cases of glossopharyngeal neuralgia and said that it was generally considered that the sex distribution was about equal. These writers, like others, reported that in some cases the pharyngeal branches of the vagus were also involved and contributed the finding that in their clinic "the incidence of glossopharyngeal to trigeminal neuralgia" was approximately one to one hundred.

It is when one considers the aetiology of these conditions that a major difficulty arises, as most texts merely state that the aetiology is unknown. In particular, the cause of trigeminal neuralgia has been considered for many years and historically Shafer et al reported that in the past the teeth, periodontal disease and traumatic occlusion have all been suggested as possible causes, but these hypotheses have proved to be insupportable.

One modern theory which does seem more plausible is that of a circulatory deficiency to the gasserian ganglion causing neural damage, which would seem compatible with the fact of trigeminal neuralgia occurring predominately in older people whose circulation is likely to be more impaired.

Wyke (1976, p.295), following an in-depth discussion of the possible causes of trigeminal neuralgia, stated that there was little doubt

that the condition was due to "loss of the normal degree of presynaptic inhibitory activity that restricts the flow of nociceptive afferent discharges through the spinal nucleus of the fifth nerve" and continued that this may in turn be caused by a "disturbance of function in either the peripheral or the central neurological systems that are responsible for such inhibition". Wyke also suggested that glossopharyngeal neuralgia and post-herpetic neuralgia may be similarly initiated. Interestingly some nine years prior to Wyke's article Graham (1967) suggested that "it seems reasonable to assume that disordered function in the ganglion is responsible for some cases of idiopathic trigeminal neuralgia". It can be seen that this opinion was not very different to Wyke's educated hypothesis.

On this subject Sweet (1977, p.72) went into detail on actual degenerative changes to the myelin sheaths of trigeminal rootlets and published some fine photomicrographs of these nerves (Figs. 7-1 and 7-2) which one must regard as very impressive. As to the reason for this degeneration, Sweet referred to the work of Janetta (1976)(in press at the time of Sweet's writing) in which an artery, or sometimes a vein, was found to be impinging on and causing pressure on trigeminal rootlets. Janetta at that time was reported to have performed one hundred operations to reposition the offending vessel, with extremely good results.

Janetta himself (op cit, p.187) confirmed that he firmly believed trigeminal neuralgia to be caused by compression on the trigeminal root entry zone by the superior cerebellar artery, or the anterior inferior cerebellar artery in the case of first division neuralgia.



Fig.7-1. Cross section of normal myelinated nerve fibre. The dense myelin sheath surrounds the axon. (From H. de F. Webster, Progress in Brain Research, Elsevier Publish. Co., Amsterdam. Courtesy of the Publisher.) No magnification provided.



Fig.7-2. Proliferative degenerative changes in a myelinated nerve fibre in a patient with trigeminal neuralgia. (From F.W.L. Kerr, J. Neurosurg., 1967. Courtesy of the Editor.) Magnification x8,025.

Later, Janetta and Bennett (1981, p.313), again in relation to the aetiology of trigeminal neuralgia, stated that "sclerotic plaques, tumour and vascular compression at the root entry zone" may "produce the forces leading to, or contributing to, ongoing degenerative changes seen in the fifth nerve and ganglion". Janetta alone (1981, p.333), in the same text, described his technique for repositioning the superior cerebellar artery to a horizontal position and concluded (op cit, p.339) by saying that "neurovascular compression of the root entry zone of the trigeminal nerve can now be clearly stated as causal of the vast majority of cases of trigeminal neuralgia".

It can be seen then that there is a certain degree of correlation between the modern theories of the aetiology of trigeminal neuralgia and associated conditions and it would seem possible that a combination of vascular irregularities, ischaemia, pressure and myelin sheath degeneration are so interwoven that they could well eventually be proven to be the cause of these terrible conditions.

Post-herpetic Neuralgia

The condition of post-herpetic neuralgia bears some similarity to trigeminal neuralgia, but is dissimilar in that it follows an attack of herpes zoster and, as previously noted, Cawson (1978, p.372) stated that ten per cent of herpes zoster cases progressed to this painful state. That author described post-herpetic neuralgia as being variable in character, from a pain as severe as trigeminal neuralgia to one relatively mild and more chronic in nature.

One big problem with this condition is that it is very resistant to

treatment and many modes of therapy have been attempted without any great degree of success.

Shafer et al (1983, p.855) reported that post-herpetic neuralgia affects the first division of the trigeminal nerve in most cases, which is precisely different to trigeminal neuralgia. The pain often regresses within two to three weeks but may persist, especially in older patients. On this point Gayford and Haskell (1979) observed that remission was usual in six to twelve months after the initial attack.

As to the neurological cause of pain in post-herpetic neuralgia Mumford (1976, p.291) stated that in this condition there is a loss of large diameter nerve fibres which are believed to have an inhibitory effect on the conduction of pain impulses by small fibres. It can be seen that this reasoning is very similar to that of Wyke (1976), previously referred to in this chapter. Prior to the articles by these writers Taverner (1960) pointed out that in most cases of post-herpetic neuralgia it could be shown that there was defective innervation of the affected skin area and this observation would seem to coincide with the opinion of Mumford that large diameter nerve fibres are lost in this condition.

CHAPTER 8

Cryosurgery for Oro-facial Pain

In the field of oro-facial pain control cryosurgery has found by far its greatest application in the alleviation of the appalling condition of trigeminal neuralgia. It is for this reason that this chapter will mainly consider the role of cryosurgery in the treatment of trigeminal neuralgia and allied conditions, but with some reference to other oro-facial pains.

Here, and in the following chapter it is intended to convey a more clinical approach than has been the case in the earlier sections of this work. Emphasis will be placed on the technique of cryosurgery for trigeminal neuralgia control and results, both good and bad, of that treatment will be considered.

Cryosurgery for General Conditions producing Oro-facial Pain

Some of these conditions have already been mentioned briefly in relation to cryosurgery and now a slightly more specific survey will be presented.

In regard to palliation of pain from oral cancer, and in bone pain Gage (1980) observed that cryosurgery had one of its best indications for use and cited osteoradionecrosis as an example of where immediate and complete pain relief can occasionally be obtained. An in-depth case report of mandibular ameloblastoma curettage followed by freezing of the curetted area was given by Emmings et al (1971), the

patient having originally presented with a painful lump in the left lower jaw. Palliation by cryotherapy in cases of oral cancer was a strong point brought out by Smith and Weaver (1976) when reporting on six years' work in this field. These authors observed that this mode of treatment was especially valuable for patients who refused more traditional treatment.

Painful erosive lesions of the oral mucosa are at times treated by freezing and Leopard (1975) reported having treated "a few cases of longstanding erosive lichen planus" to control pain. On the same note, Poswillo (1978) stated that both lichen planus and aphthous ulceration were not conditions basically curable by cryotherapy, but he agreed that pain from these lesions could be overcome in this manner. Pain from the "oral lesions of Behçet's disease" is "helped considerably" by cryotherapy (Holden, 1972) and herpes simplex ulcers may be similarly treated.

The pain from acute tonsillitis can be alleviated by cryosurgical ablation of the tonsils and von Leden and Rand (1967) gave a good clinical description of cryotonsillectomy, under local analgesia, by means of a liquid nitrogen cryoprobe. There was an important point raised in this report, in that cryotonsillectomy does not produce haemorrhage which is a notorious problem with conventional tonsillectomy. In this particular field Hill (1968) evaluated his operations on forty six patients over a two year period, likewise observing the great benefit of cryotonsillectomy in patients with bleeding problems, and also of minimal scar production. Pearson (1968) referred to having carried out "upwards of 125 tonsillectomies" by cryosurgery and reported a 95 per cent success

rate.

In regard to ocular pain, reference has been made earlier in the history section to the treatment of glaucoma by cryotherapy (Lincoff and McLean, 1965). An interesting series of cases was reported by Aviel (1972) in which cryotherapy was used, in conjunction with incision of the conjunctival and subconjunctival tissues, as a successful treatment of Mooren's ulcer. This condition was described as one in which "pain is an outstanding feature". Of special interest was the fact that the conjunctival and subconjunctival incisions referred to had been previously used alone and had afforded only temporary relief of pain.

The work of Ozenberger and Cook, in the treatment of vascular head and facial pain, was described in chapter four of this treatise. Since that time there has been a paucity of reports concerning cryotherapy for the treatment of vascular pains; however, an interesting case of a somewhat related nature was reported by Hanckel (1967) in which an intracranial extension of a juvenile ossifying fibroma of the maxillary sinus produced headache due to pressure on the internal carotid artery. This lesion was treated by cryosurgery from both palatal and buccal approaches and reportedly a substantial decrease in head pain was achieved.

Inquiries at a number of oral medicine clinics have failed to produce any evidence of investigations into the use of cryosurgery for the treatment of vascular pains, including temporal arteritis. Similarly, no work appears to have been undertaken for the possible control of pain from von Frey's auriculo-temporal pain syndrome by

this mode of therapy.

Paroxysmal Trigeminal Neuralgia

The fact that "valuable applications of cryotherapy" have been found for "localized destruction in the central nervous system" was reported by McKelvie (1974) and it must be said that the same remarks apply to the peripheral nervous system.

Non-cryosurgical treatment

The cryosurgical treatment of trigeminal neuralgia cannot be considered in isolation, since it is often necessary to combine cryosurgery with other forms of therapy in order to satisfactorily control the condition. This fact will become quite clear when case reports are perused in the following chapter.

Before commencing treatment for trigeminal neuralgia it is essential to ensure that one's diagnosis is correct. Haskell (1977) presented the facts that dental pain (e.g. from exposed dentine) can cause a "very sharp pain" and likewise that the mental nerve, when compressed by a denture, can provide a shooting pain "not unlike paroxysmal trigeminal neuralgia".

Gayford and Haskell (1979, p.214) stated that "carbamazepine (Tegretol) provides the only effective medical treatment to date" and that in over 50 per cent of cases complete relief is afforded the patient, while up to 90 per cent gain "appreciable relief". The dosage recommended is 100mg twice a day to start, increasing each two

days until the pain is controlled, usually at about 200mg three or four times per day, but occasionally 1,000mg to 1,200mg per day may be required. The dose should then be gradually decreased until a minimal effective dosage is reached. There are side effects from Tegretol which may prevent its use at times such as ataxia, vertigo, drowsiness or hypersensitivity, and some problem arises in 60 per cent of patients taking this drug. However, the most serious side effect is one of a possible cascading leucopenia and in this connection Gayford and Haskell (1979) cited "three fatal cases of aplastic anaemia" having been induced. Regular white cell counts should therefore be carried out on patients taking this drug.

A partial substitute for Tegretol is to be found in phenytoin sodium (Epanutin), and here Gayford and Haskell recommended a dosage of up to 100mg three times per day.

Whilst awaiting pain relief from Tegretol or Epanutin a local injection of 2 per cent Lignocaine, or better the longer acting 0.5 per cent bupivacaine (Marcaine), will control trigeminal neuralgia, but this procedure can of course only be looked upon as a temporary measure.

For a number of years injections of alcohol or phenol have been used to treat trigeminal neuralgia and in this regard Gayford and Haskell (1979) quite correctly observed that injection into the trigeminal ganglion "is a great art" and only able to be carried out by a highly skilled person. These agents can be injected peripherally but, as Barnard (1980) said, "the results are often disappointing" due to neuritis development in the partially destroyed nerve and fibrosis,

which can produce a secondary neuralgia and render further treatment more difficult. The agents used are alcohol (absolute) or phenol (5 per cent) and these are often painful to inject.

In cases where the above treatments have proved ineffective either thermal coagulation, or neurectomy of the peripheral nerve have often been performed. Here Barnard (1980) pointed out that "irrevocable changes in the nerve" are produced with the added problems of a possible neuroma formation and fibrosis, both of which can intensify the symptoms.

Avulsion of a peripheral nerve has been a further method of treatment to relieve trigeminal neuralgia and was stated by Thoma (1969, p.758) to be "more lasting and more effective than injection with alcohol". It is noteworthy that modern texts are virtually devoid of reference to this form of treatment.

The operation of microvascular decompression of the trigeminal rootlets has been previously referred to in the chapter on oro-facial pain. Two other intracranial procedures for relief of trigeminal neuralgia are radio frequency heat coagulation of the trigeminal rootlets and retrogasserian rhizotomy, both of which appear to be fairly effective (Sweet, 1977, pp.80-83).

Cryosurgical treatment

Only passing mention to cryotherapy was made by Gayford and Haskell (1979), who merely listed this mode of treatment as one method of obtaining neurolysis when dealing with trigeminal neuralgia. Much of

the other literature makes no reference at all to this relatively new modality; however, those authors who do address the subject are generally favourably impressed with the results.

A survey of cryosurgical treatment of sixty four patients suffering from a variety of periperal pains was given by Lloyd et al (1976) of which six cases were of facial neuralgias. In this series a Spembly-Lloyd nitrous oxide cryoprobe system was employed to freeze nerves twice for 2 mins, the tissues being allowed to reach "above 0°C" in the interval. The probe tip temperature was reported as minus 60°C. In respect of the six facial pain patients relief from pain lasted "up to 112 days", with a "median of 21 days". Since the maximum pain relief period of any patient in the series was 224 days the authors' statement that "no patients have developed neuralgia subsequent to treatment" seems rather difficult to understand.

The same group of researchers reported again, some two years later, on the management of 21 patients over a period of twelve months. On this occasion all cases were of intractable facial pain, nine of which were post-herpetic neuralgia cases and will be discussed later in this treatise. The remaining twelve cases included one cancer, eight neuralgias "of unknown aetiology" (including tic douloureux), and three cases of "post-traumatic neuralgia" (Barnard et al, 1978-79). These cases were again treated by two freezes of two minutes, timed "from the establishment of equilibrium in the iceball", by means of a closed nitrous oxide cryoprobe, no figure being given for the length of thaw. A low temperature of approximately minus 60°C was recorded by means of a thermocouple. Three of the neuralgia patients received repeat cryotherapy treatment within the twelve

months. The median period of pain relief was recorded as 116 days and the median sensory loss period as 49 days.

In summary, these authors reported that none of the neuralgia patients had their pain worsened by the cryotherapy, as can occur with neurolytic injection or nerve sectioning. They also stated that cryotherapy appeared to be "a useful therapeutic tool in the management of intractable facial pain".

Barnard (1980) discussed three year's clinical use of cryosurgery for chronic facial pain including 27 cases of non-herpetic origin and stated that much better response was recorded in the non-herpetic group than in 13 post-herpetic neuralgia patients. These non-herpetic patients had all previously failed to respond to other methods of treatment, and had suffered facial pain from between 1.5 and 12 years. It is noticeable that Barnard, using again a nitrous oxide probe, allowed only a one minute freeze, after ice ball stabilization, but carried out two freezes. No thaw period was mentioned. The results showed a median pain relief period of 175 days (maximum 815 days), and a sensory loss median of 60 days (maximum 117 days), but these included both tic douloureux and post-surgical neuralgia patients. Considering the trigeminal neuralgia patients alone, the median pain relief period was 235 days (maximum 815 days), sensory loss was approximately 60 days.

Barnard concluded that cryosurgical blockade of peripheral nerves "offers features which are not shared by any other method".

A further summary by Barnard et al (1981) was presented in which 24

cryosurgical patient treatments were carried out in respect of patients with trigeminal neuralgia. The regimen of freezing was a two one minute technique, using a nitrous oxide probe, with no thaw time recorded. Probe temperatures were stated to be minus 60°C to minus 80°C. Pain relief median was reported as 186 days (maximum 1236 days) and sensory loss median as 67 days (maximum 80 days).

Probably the most thorough and up to date assessment of the cryosurgical treatment of trigeminal neuralgia has come from Nally, the salient points of which will now be examined. This work covers the period from 1959 to 1983 and includes in-depth investigation and practical cryosurgery to hundreds of sufferers from trigeminal neuralgia.

Nally (1984, A) initially reported that the mental nerve was normally exposed under local analgesia, by an incision from the first molar to the canine region just above the mucogingival line, whereas the infraorbital nerve was approached through a Caldwell-Luc incision, under a general anaesthetic. Originally a nitrous oxide cryoprobe was used and freezes of 30 seconds to 3 minutes were employed. It was soon decided however to purchase a liquid nitrogen cryoprobe system.

One extremely important finding by Nally was that very often there was migration of pain from the original source to another branch of the trigeminal nerve, following cryotherapy to the original source. Examples of this were migration to the long buccal nerve, following mental nerve freezing, and to the posterior superior dental nerves and greater and lesser palatine nerves, following infraorbital nerve

freezing. Where this occurred the nerves in question were exposed and frozen for 2 minutes at minus 100°C.

Nally (1984, A) reported in his first article that "pain relief has been maintained over a 3 year period so far", and that cryotherapy was "easily repeated" and was "eminently suitable for elderly patients". A further observation was that freezes of less than 2 minutes, at minus 45°C, may not suffice to give long-lasting pain relief and a temperature of minus 100°C, or lower, should be used for three 2 minute freezes with a thaw interval of 5 minutes. Also recommended was that following cryotherapy Tegretol should be withdrawn gradually, to prevent withdrawal symptoms.

At this point Nally compared central neurosurgical techniques to cryosurgery and stated that although some of those techniques were indeed effective in giving pain relief they were at the same time "potentially more hazardous".

In the second of these excellent articles Nally et al (1984) reported exposing nerves for cryotherapy by means of local analgesia, supported by intravenous diazepam. The nerves discussed were the mental, infraorbital, posterior and middle superior dental, greater palatine and lingual by sub-mucoperiosteal dissection; the long buccal by soft tissue dissection in the retro molar region; and the supra-orbital and supra-trochlear nerves, by percutaneous approach through the eyebrow.

The freezing regimen described at this stage was a cycle of three 2 minute freezes, with thaw intervals of 5 minutes, using either a

nitrous oxide probe, producing a temperature of minus 45°C as measured by a thermocouple, or a liquid nitrogen probe thermostatically controlled at minus 120°C.

In this series some 112 patients were treated, on whom 248 open nerve freezes were carried out, and a considerable amount of statistical data was presented. However, the important facts to emerge were that "cryotherapy appears to work equally well for all nerves"; when pain returned (e.g. after a mean period of 17 months in the case of the mental nerve) it was "less severe" than before the cryosurgery; repeat cryosurgery raised the success rate (from 68% to 91% in the case of the mental nerve) and that small doses of Tegretol controlled the pain, when it returned, post-cryosurgically.

One technically important change in attitude emerges from Nally's two papers, relating to the cryogen to be used for trigeminal neuralgia control. In the first article the author stated that, "it is probable that the fibres that are most vulnerable are pain fibres, since they are of a smaller diameter than the majority of fibres", but in the second article he observed that there was evidence that "unmyelinated small fibres show some structural resistance to freezing at moderately low temperatures and in order to produce pan-necrosis extremely low temperatures should be used as are attainable with a liquid nitrogen system".

Nally (1984, A) maintained that some of his initial failures were probably due to "inadequate freezing" and in 1983 expressed the view that for satisfactory cryotherapy to nerves, for control of trigeminal neuralgia, the following criteria should prevail.

- (i) Nitrous oxide is not a satisfactory cryogen. Liquid nitrogen is required, giving a probe tip temperature of at least minus 140°C;
- (ii) Three freezes of 2 minutes duration, with a 5 minute thaw interval should be employed;
- (iii) Auxiliary foramina should be sought and the nerves frozen; and
- (iv) The cryoprobe must be placed directly on the nerve.

It is noticeable that Barnard et al (1978-79) did not agree totally with Nally and stated that in their cryosurgical treatment for intractable facial pain "the greater cooling power of a liquid nitrogen system was not required". There is, or was at that time, an obvious discrepancy of opinion, but it must be noted that Nally's views were expressed some five years later than Barnard's and after extensive clinical application of cryotherapy.

There has for years been considerable deliberation as to the causes of trigeminal neuralgia and the mechanism whereby cryosurgery can affect that condition. Possible aetiological factors were discussed earlier in this treatise, in the chapter on oro-facial pain, and the reader is referred back particularly to the work of Wyke mentioned in that chapter.

It is very difficult to clarify the modern concepts of these important considerations, but following basically the writings of Wyke and Nally the more recent ideas seem to have much in common.

The exact cause of trigeminal neuralgia remains unproven. In this condition however it is known that there is large fibre demyelination at the trigeminal ganglion, or root entry zone, which may cause an alteration in pre-synaptic contacts between those large fibres and the pain-carrying small diameter fibres. In other words there is a "short circuit" produced by the large fibre demyelination and a subsequent loss of the normal large fibre inhibition of small fibre (pain) activity, plus an abnormal discharge of pain from innocuous large fibre stimulation (i.e. a "trigger" effect). The cause of the demyelination is postulated to be compression by an aberrant branch of the superior cerebellar artery, or possibly a prominent petrous ridge. It is also considered possible that a central "irritable focus" may be established which enhances the experience of pain, but the basis for the establishment of such a focus is as yet unknown. (Nally, 1984, A).

The action of cryotherapy to peripheral nerves, in relation to trigeminal neuralgia, is postulated to occur both peripherally and centrally. Peripherally it has been demonstrated that a cryolesion produces second-degree injury to a nerve "with complete degeneration distal to the lesion" and it is likely that there is "selective nerve-fibre destruction" of small diameter fibres, assuming that they have been adequately frozen, followed by "incomplete recovery of nerve fibres critical to trigger zone activity". Centrally the temporal cessation of afferent impulses brought about by cryotherapy may interrupt the central cascading mechanism and lead to the "stabilization of any central sensory irritable focus". Finally, it is also hypothesized that healing of the demyelinated fibres in the nerve root, or ganglion region may be induced, which would lead to a

remission of pain (Nally et al, 1984). This last factor is beginning to assume paramount importance in the planning of cryosurgical programmes for the management of trigeminal neuralgia, due to its probable fundamental importance.

Several potential variations in cryosurgical technique are presently under investigation, with the aim of greatly improving the treatment of trigeminal neuralgia. Attempts are to be made to have patients present for treatment at as young an age as possible, and also as early as possible after pain first begins, as treatment under these circumstances has already proved to be more efficient. It is hoped to perfect some new technique for more accurate dissection to locate the long buccal nerve. Courses of freezing, rather than one initial operation, are to be recommended to the patient, in order to block afferent sensory impulses for long periods and hopefully allow better re-myelination of nerves. Freezes of whole trigeminal divisions, rather than individual branches, are to be carried out to block all sensory input into the division in question. In some cases this principle is to be extended to the whole of two, or even three divisions. Hypertension is to be strictly controlled, as this has been shown to be a big factor in trigeminal neuralgia control, and finally some patients are to be recommended psychiatric counselling to overcome anxiety, as this problem is also often a co-existent factor (Nally, 1984, B).

Paroxysmal Glossopharyngeal Neuralgia

This condition was discussed earlier, in the chapter devoted to orofacial pain, and as regards treatment Gayford and Haskell (1979,

p.216) stated that Tegretol should be given in the same dosage as for trigeminal neuralgia and that if this proves ineffective then nerve section, or nerve tract section is indicated.

Lloyd et al (1976) gave a short reference to the description by Brain of the treatment of glossopharyngeal neuralgia by cryotherapy, but went no further into the matter. Brain himself observed that cryo-destruction of the glossopharyngeal nerve was much simpler than conventional neurectomy, following a previous tonsillectomy, when fibrosis can make the nerve identification rather difficult. This author went on to say that actual exposure of the nerve was unnecessary, and that the cryoprobe could be applied to the surface in the lower half of the tonsillar fossa. The recommended freeze period was 5 mins for two freeze-thaw cycles, using a nitrous oxide or freon probe (Brain, 1975). The results of five cases to combat glossopharyngeal neuralgia were given, of which four were initially excellent and one "a complete failure".

Glossopharyngeal neuralgia was briefly discussed by Nally and Eggleston (1983, p.22), in combination with trigeminal neuralgia where they stated that "open nerve freezing by cryotherapy has been shown to be effective in both mild and severe cases". These authors did not go into detail in their short handbook of general oral medicine.

Post-herpetic Neuralgia

This type of neuralgia was also described in the chapter on orofacial pain, when it was noted that the condition was very resistant

to treatment.

One mode of treatment briefly mentioned by Parkes (1975) was the spraying of the affected area with ethyl chloride, which was probably one of the earliest references to any application of freezing in an attempt to combat this difficult condition.

Barnard et al (1978-79) achieved poor results in treating post-herpetic neuralgia despite using both cryotherapy and peripheral nerve section at the one operation. The pain relief, as reported, on a group of nine patients, ranged from zero to only 84 days maximum. It must be noted in this series of cases that a nitrous oxide probe system was employed and the cryotherapy was only carried out in order to allow painless sectioning of the nerves. However, this report does illuminate the difficulty in treating post-herpetic neuralgia by any peripheral interference.

Fourteen patients with post-herpetic neuralgia were treated by cryotherapy alone by Barnard (1980), but again with poor results. In this series freezing was carried out with a nitrous oxide probe, each nerve receiving two one minute freezes interrupted by an unspecified thaw. Pain relief varied from zero to 119 days and Barnard himself agreed that the results in this group of patients was disappointing.

Slightly better results were obtained in a series of 26 patient treatments reported by Barnard et al (1981), where postcryosurgery pain relief varied from zero to 189 days. This group were again treated with a nitrous oxide probe for two one minute freezes, and an unreported thaw period.

One interesting point emerged from an analysis of these last two cryosurgical series reported, and that is that in the first series (i.e. Barnard, 1980) the freeze probe temperature was approximately minus 60°C, whereas in the second series (Barnard et al, 1981), where the results were somewhat better, probe tip temperatures of between minus 60°C and minus 80°C were utilized.

It seems obvious that treatment of post-herpetic neuralgia by means of cryotherapy has not as yet proved to be very effective, as indeed has any other form of treatment, but on the other hand such treatment appears to be in a beginning stage with a considerable amount of investigative work yet to be undertaken.

Causalgia

Causalgia was regarded by Nally and Eggleston (1983, p.22) as "a rather ill defined condition in which pain persists after trauma". In direct opposition to that view, Elfenbaum devoted a complete article to the condition, stating that in dentistry the condition has often been confused with other neuralgias. That author was firmly of the opinion that the condition was an entity unto itself and discussed various methods of treatment (Elfenbaum, 1954).

As to the treatment of causalgia by cryotherapy very little has been reported, but, as briefly mentioned earlier in this treatise, Poswillo (1978) believed that the condition did lend itself to cryotherapy. That author did not, however, elaborate on the matter.

Barnard included a group of eleven patients with "post-surgical

neuralgia" in his survey of cryosurgery to sensory nerves. These cases must fall into the category which would be called causalgia by those who classify the condition as a separate entity. Barnard (1980) was very encouraged by the success in these cases, and stated there was a "good response in post-surgical neuralgia when a clinically identified neuroma was frozen". The results in these eleven cases, using a nitrous oxide probe, showed pain relief of between 35 and 808 days.

It seems obvious that nowhere near enough attention has been paid to the treatment of causalgia by means of cryotherapy, and considering the enormous amount of trauma and surgery which occurs daily, it would seem to me that here a very interesting field is open for exploration in the future.

Whilst not falling strictly under the heading of causalgia one item of interest is the use of cryotherapy to produce post-operative analgesia. This was well demonstrated by Katz et al (1980) who described the use of cryoanalgesia following thoracotomy and observed that those patients who were treated by intercostal cryo-block "had significantly less post-operative pain", in comparison to other patients who were given conventional local analgesic blocks. It would seem that this field could prove of enormous interest to surgeons in the future, and in the case of oral surgery, post-operative oro-facial pain may well be avoided by the use of this technique in more major procedures.

CHAPTER 9

Case Reports

This chapter is to be devoted to an account of some of my personal cryosurgical cases, the majority of which concern the treatment of trigeminal neuralgia. Some additional cases of interest, which do not concern trigeminal neuralgia, will be included in order to provide practical examples of other uses of cryosurgery.

It is hoped that the recorded progress of these cases will provide the reader with a reasonable appreciation of some of the problems encountered in the cryosurgical treatment of oro-facial pain and some ways in which those problems can be controlled.

There is wide variation in the degree of difficulty encountered in controlling trigeminal neuralgia by cryosurgery, or indeed by any other method and, as will be appreciated from the case histories which follow, some of the cases included here represent by far the more challenging end of the spectrum. On the other hand many cases are relatively easily controlled and following cryosurgical intervention the patients remain pain free, or controllable with minimum medication, and again some of these types of cases are included in this report. Without a comprehensive presentation it is impossible to give the reader a satisfactory concept of the advantages and limitations of cryosurgery in the treatment of trigeminal neuralgia and it is for this reason that full clinical details are provided later in this chapter.

Due to the lengthy nature of some of the case reports, a summary will

now be presented, with the full reports following.

The assessments of results have been allocated according to the following criteria;

1. Excellent, where following cryosurgery a completely satisfactory resolution of the presenting condition has occurred and no necessity for further treatment is envisaged.
2. Good, where a substantial improvement in the presenting condition has eventually resulted despite a considerable amount of other therapy being required after cryosurgery.
3. Fair, where some improvement in the presenting condition has resulted after cryosurgery but a good deal of supportive therapy has been required to maintain that improvement.
4. Poor, where supportive treatment following cryosurgery has really failed to achieve any worthwhile improvement in the presenting condition.
5. Unable to assess fully, where due to inability to follow up the patient satisfactorily a reasonable assessment cannot be provided.

Trigeminal Neuralgia

Case	Age	Sex	Site	Cryogen	Result
1.	59	F.	R. Infra-orbital N.	Nitrous oxide	Fair
2.	41	M.	L. Infra-orbital N.	Nitrous oxide	Good
3.	65	M.	L. Infra-orbital N.	Liquid nitrogen	Excellent
4.	64	M.	R. Infra-orbital N.	Nitrous oxide	Fair
5.	79	F.	R. Mental N.	Liquid nitrogen	Good
6.	68	F.	R. Infra-orbital N.	Nitrous oxide	Poor
7.	76	M.	L. Infra-orbital N.	Liquid nitrogen	Excellent
8.	53	M.	R. Infra-orbital N.	Liquid nitrogen	Fair
9.	52	F.	L. Infra-orbital N.	Liquid nitrogen	Good
10.	58	F.	L. Infra-orbital N. (atypical T.N.)	Nitrous oxide	Fair
11.	44	F.	R. Long buccal N.	Liquid nitrogen	Unable to assess fully.
12.	40	F.	R. Infra-orbital and post. sup. dent. Ns.	Liquid nitrogen	Unable to assess fully.
13.	60	F.	R. Infra-orbital and post. sup. dent. Ns.	Liquid nitrogen	Unable to assess fully.
14.	39	F.	R. Mental and long buccal Ns.	Liquid nitrogen	Fair
15.	61	M.	L. Mental and long buccal Ns.	Liquid nitrogen	Initially excellent. Unable to assess fully.

16.	62	F.	L. Infra-orbital and ? post. sup. dent. Ns.	Liquid nitrogen	Initially good. Unable to assess fully.
17.	87	F.	L. Mental and long buccal Ns.	Liquid nitrogen	Unable to assess fully.
18.	59	F.	L. Lingual, long buccal and mental Ns.	Liquid nitrogen	Initially good. Unable to assess fully.
<u>Haemangiomata</u>					
19.	63	F.	R. Max. labial sulcus	Nitrous oxide	Excellent
20.	10	F.	L. Max. gingiva	Nitrous oxide	Excellent
<u>Fibro-epithelial Polyp</u>					
21.	64	F.	R. Mand. alveolar ridge	Nitrous oxide	Excellent
<u>Sublingual Keratosis</u>					
22.	62	F.	R. and L. floor of mouth	Nitrous oxide	Excellent
<u>Chronic Ulcer</u>					
23.	33	M.	L. Lower lip	Nitrous oxide	Good

In regard to the trigeminal neuralgia cases it can be seen that;

1. Age of the patients ranged from 39 years to 87 years, with an average of 59 years.

2. Distribution by sex was female to male of 2:1, and
3. Duration of symptoms at presentation to myself ranged from six months to approximately twenty-seven years, with an average of approximately seven years and three months.

Trigeminal Neuralgia (T.N.)

Case 1

Location:

Right infra-orbital nerve in 59 year old female.

History of over two years pain and medication with Tegretol increased from 100 mg t.d.s. to 200 mg q.d.s. plus Epanutin 100 mg b.d. Pain could not be controlled.

Treatment:

Cryosurgery on 7th July 1980 to right infra orbital nerve, under G.A. using nitrous oxide probe (Spembly-Amoils BMS-40 machine). Two freezes of two minutes with a five minute thaw period.

Result:

Immediate pain relief, but mild twinges on washing face which decreased. Two weeks post-surgical, a shock pain returned, controlled by 200 mg Tegretol b.d. Three months post-surgical, sensation returned and nine months post-surgical, pain returned.

On 3rd June 1981 right infra-orbital nerve was refrozen with liquid nitrogen probe (Spembly D.F.S. - 30 machine) for two freezes of two minutes with five minute thaw. Patient was pain free for two months then controlled with Tegretol 200 mg t.d.s. reduced to 200 mg b.d.

Nine months later a bite guard was fitted, due to nocturnal

grinding. Seventeen months post-surgical, a trigger zone appeared but not severe and twenty four months post-surgical a second bite guard was issued which helped control the pain. Pain migrated to the right long buccal and right mental nerves and on 15th May 1983 these nerves were frozen with a nitrous oxide probe for three freezes of two minutes with five minute thaw intervals. Patient was pain free for four months when pain returned to the right mental nerve. This was controlled by Tegretol 200 mg t.d.s. or q.d.s. Pain then returned to the right infra-orbital nerve, which was refrozen on 2nd November 1983 with a liquid nitrogen probe at minus 140°C for three two minute freezes and five minute thaw intervals. Patient was then pain free, planning a trip overseas and had not reported back by September 1984.

Result assessment: Fair.

Follow up period: 4 years.

Case 2

Location:

Left infra-orbital nerve in 41 year old male.

History of six years pain and Tegretol increased from 100 mg b.d. to 700 mg per day to control the pain.

Treatment:

Cryosurgery on 16th September 1980, to left infra-orbital nerve under G.A., with a nitrous oxide probe (Spembly-Amoils BMS-44 machine) for two freezes of two minutes and a five minute thaw period.

Result:

Pain free for five months, then 200 mg Tegretol b.d. controlled

pain. Six months post-surgical, no pain in infra-orbital area and patient stopped taking Tegretol, but pain began in left palate.

On 1st April 1981, under L.A. plus I.V. Diazepam cryotherapy was performed to the left greater palatine, lesser palatine and posterior superior dental nerves, with a liquid nitrogen probe (Spembly DFS-30) for three freezes of two minutes plus five minute thaw intervals. Patient was pain free for four months, then pain was controlled by Tegretol 200 mg t.d.s. reduced to 100 mg q.d.s. and later increased to 200 mg t.d.s.

Ten months after second cryotherapy a new diagnosis was made, namely atypical facial pain and patient was placed on Prothiaden and sent to a psychiatrist. No trigger zone could be found. Three months later patient stated that he only took Tegretol as he was "afraid of pain returning". To September 1984 there was no further complaint of neuralgia from the patient.

Result assessment: Good.

Follow up period: 4 years.

Case 3

Location: .

Left infra-orbital nerve in a 65 year old male.

History of three years pain and medication increased from Tegretol 100 mg b.d. to 1,000 mg per day and later 200 mg q.d.s. plus Epanutin 100 mg nocte.

Treatment:

Cryotherapy to left infra-orbital nerve, on 28th October 1980, using liquid nitrogen probe (Spembly D.F.S.-30) at minus 100°C with two freezes of two minutes plus a five minute thaw

interval.

Result:

No post-surgical pain. Patient placed on 200 mg Tegretol q.d.s. for six weeks. Sensation began to return after one month. No further complaint of pain to September 1984.

Result assessment: Excellent.

Follow up period: 4 years.

Case 4

Location:

Right infra-orbital nerve in 64 year old male.

History of 17 years pain and patient taking 1,200 mg Tegretol per day, but pain not controlled.

Treatment:

Cryotherapy on 30th October 1980 to right infra orbital nerve, under G.A. using nitrous oxide probe (Spembly BMS-40) with two freezes of two minutes plus a five minute thaw period. Patient placed on Tegretol 200 mg q.d.s. for one month then reduced to 200 mg per day.

Result:

Pain free for five weeks then pain occurred in right long buccal nerve (treated with absolute alcohol injection). Three months post-surgical right superior posterior dental nerve frozen, due to pain, with liquid nitrogen probe (Spembly DFS-30) at minus 100°C for two two minute freezes plus a five minute thaw.

Two months later the upper right second molar region was frozen locally due to pain with two two minute freezes and five minute thaw (cryogen not specified). In the next three months the pain migrated to the right supra-orbital and right zygomatic

area.

On 2nd July 1981 the right supra-orbital nerve was cryotherapied with a nitrous oxide probe (Spembly BMS-40) for three two minute freezes and five minute thaw periods. After two months the patient was "best for 15 years" but after a further three months a trigger zone occurred in the right upper lip. This was controlled with Tegretol 200 mg b.d. Six months later occasional pain occurred in right infra-orbital area, but controlled with Tegretol 200 mg b.d.

On 30th March 1983 cryotherapy was needed to right infra orbital nerve. This was carried out with a nitrous oxide probe, with three freezes of two minutes plus five minute thaws and patient was placed on tegretol 200 mg per day.

Three months later pain occurred in the in inner canthus of the right eye and two months after that the right supra-orbital nerve was frozen with a liquid nitrogen probe at minus 140°C for three freezes of two minute and five minute thaw periods. Two months later patient was "delighted" and the "best for 15 years".

Some pain occurred five months after in the right infra-orbital area and the right infra-orbital and posterior superior dental nerves were frozen with a liquid nitrogen probe at minus 140°C on 26th July 1984.

Up to September 1984 patient was very happy and only had occasional twinges but the case will need continued follow-up.

Result assessment: Fair.

Follow up period: 4 years.

Case 5

Location:

Right mental nerve in a 79 year old female.

History of 25 years pain and alcohol injection in the early stages of the condition. Patient taking 600 mg Tegretol per day but the pain was not controlled.

Treatment:

Cryotherapy on 12th May 1981 to the right mental nerve under L.A. with a liquid nitrogen probe, for three freezes of three minutes and five minute thaws.

Result:

Sensation returned in nine months. Pain returned, not severely, after thirteen months and was controlled with Tegretol 200 mg per day. The right mental nerve was re-frozen on 17th June 1982 using a liquid nitrogen probe with two freezes of three minutes and a five minute thaw.

Up to September 1984 patient remained pain free.

Result assessment: Good.

Follow up period: 3 years and 4 months.

Case 6

Location:

Right infra-orbital nerve in a 68 year old female.

History of four years pain, worsening. Had right infra orbital nerve avulsed and three phenol blocks and has needed Tegretol 200 mg t.d.s. to 1,200 mg per day plus Diazepam 5 mg nocte to control the pain.

Treatment:

Cryotherapy on 28th January 1982 to the right infra-orbital

nerve under G.A. using a nitrous oxide probe with two freezes of three minutes and a five minute thaw.

Result:

Pain free for only two days but Tegretol 200 mg b.d. controlled pain.

Pain returned after four months and on 22nd April 1982 the right infra-orbital nerve was re-frozen with a liquid nitrogen probe for two freezes of three minutes and a five minute thaw.

One month later pain returned to upper right canine and first bicuspid region. The right posterior superior dental nerves were frozen on 1st July 1982 using a liquid nitrogen probe with one freeze of three minutes. Pain developed again in the same area one month later and six months later a trigger zone occurred in the right infra-orbital area.

The right infra-orbital nerve was re-frozen on 3rd February 1983 and the patient was pain-free for five months. Then pain was controlled by Tegretol 200 mg b.d. Thirteen months later the right infra-orbital nerve again required freezing with a liquid nitrogen probe for two three minute freezes and a five minute thaw. After that 200-400 mg Tegretol controlled pain and later only 200 mg Tegretol every 2-3 days was needed.

The patient has since developed further pain and at September 1984 was still receiving treatment.

Result assessment: Poor.

Follow up period: 2 years and eight months.

Case 7

Location:

Left infra-orbital nerve in a 76 year old male.

History of pain for many years and the patient had an alcohol injection 27 years prior to presentation. Tegretol 400-1,200 mg per day required to control the pain.

Treatment:

Cryotherapy on 11th May 1982 to the left infra-orbital nerve under G.A. using a liquid nitrogen probe for two freezes of three minutes and a five minute thaw.

Result:

Sensation returned after three months. No complaint of pain up to September 1984.

Result assessment: Excellent.

Follow up period: 2 years and 4 months.

Case 8

Location:

Right infra-orbital nerve in 53 year old male.

History of pain for 5-6 years. Tegretol could not control the pain.

Treatment:

Cryotherapy on 27th May 1982 to the right infra-orbital nerve under G.A. using a liquid nitrogen probe with two freezes of three minutes and a five minute thaw.

Result:

Pain free for ten months then pain returned, but Tegretol 800 mg per day controlled pain.

Sixteen months after cryotherapy a right gasserian coagulation was performed. Since then 400 mg Tegretol per day has controlled the pain up to September 1984.

Result assessment: Fair.

Follow up period: 2 years and 4 months.

Case 9

Location:

Left infra-orbital nerve in a 52 year old female.

History of eight months pain. Patient had a phenol block (11th November 1981) and a left Dautrey's operation (T.M.J.) on 29th April 1982.

Treatment:

Cryotherapy on 1st July 1982 to the left infra-orbital nerve using a liquid nitrogen probe with two freezes of three minutes and a five minute thaw.

Result:

Slight pain seven months post-surgical. Eight months post-surgical pain returned and 800 mg Tegretol per day needed to control the pain.

One year post-surgical pain became uncontrollable and the left infra-orbital nerve was refrozen on 16th September 1983 using a liquid nitrogen probe (freeze details not recorded).

No further pain, up to September 1984, had occurred.

Result assessment: Good.

Follow up period: 2 years and 2 months.

Case 10

Location:

T.N. of atypical type of left infra-orbital nerve in a 58 year old female.

History of pain for a number of years in various areas, but especially the left infra-orbital and maxillary left central and

lateral alveolus areas.

Treatment:

Cryotherapy (not carried out by myself) on 8th April 1983 under G.A. to the left infra-orbital nerve using a nitrous oxide probe for three one minute freezes (no thaw period recorded).

Result:

Patient much improved two weeks post-surgical and referred for full upper denture occlusal correction.

Six weeks post-surgical patient was relatively pain free and sensation was returning. Tegretol 100-200 mg b.d. was prescribed.

Six months post-surgical patient was vastly improved and further occlusal adjustment to dentures made the patient more comfortable.

Eleven months post-surgical there was a little residual pain in left infra orbital area, but the patient was transferred to a previously attended pain clinic for treatment for atypical facial pain or cluster headaches.

Result assessment: Fair.

Follow up period: 11 months.

Case 11

Location:

Right long buccal nerve in a 44 year old female.

History of 3 years pain which was controlled initially by 200 mg Tegretol t.d.s. or q.d.s. Patient had cryosurgery to the right infra-orbital and posterior superior dental nerves in December 1981 using a liquid nitrogen probe at minus 120°C for three two minute freezes.

A trigger zone appeared in the right long buccal area and in February 1982 the right long buccal and mental nerves were frozen using a liquid nitrogen probe at minus 120°C for three two minute freezes. Pain was then controlled with Tegretol 200 mg q.d.s. It was discovered that the patient had had three nervous breakdowns and had been in a psychiatric hospital. Later Tegretol 200 mg b.d. controlled the pain.

Pain returned to right infra orbital area in December 1982 and Tegretol 300 mg q.d.s. reduced to 200 mg q.d.s. controlled the pain. Cryotherapy was performed to right infra-orbital and posterior superior dental nerves on 15th December 1982 using a liquid nitrogen probe at minus 120°C for three two minute freezes. In January 1983 a trigger zone occurred on swallowing and Tegretol 200 mg q.d.s. plus Epanutin 50 mg b.d. controlled pain.

In February 1984 pain in the right infra orbital area was controlled with an alcohol injection but five months later pain returned to the right long buccal area.

Treatment:

Cryotherapy on 23rd August 1984 to the right long buccal nerve using a liquid nitrogen probe at minus 140°C for four freezes of two minutes and five minute thaws, plus an alcohol inferior dental nerve block.

Result:

One week post-surgical occasional pain mainly in right infra-orbital area. Tegretol 100 mg q.d.s. prescribed.

Three weeks post surgical, patient totally pain-free.

Result assessment: Unable to assess at present.

Follow up period: 3 weeks.

Case 12

Location:

Right infra-orbital and possibly the right superior posterior dental nerves in a 40 year old female.

History of two and a half years of pain.

Tegretol 200 mg t.d.s. reduced pain but the patient developed an allergy to Tegretol. Epanutin 100 mg t.d.s. controlled pain but pain returned in August 1982. The right infra-orbital nerve was frozen on 15th September 1982 using a liquid nitrogen probe at minus 120°C for three two minute freezes and five minute thaws.

This left a dull pain which 200 mg Epanutin per day controlled.

Pain returned in May 1984 and Epanutin 200 mg b.d. controlled it for a time. In August 1984 pain became worse.

Treatment:

Cryotherapy on 23rd August 1984 to the right infra-orbital and posterior superior dental nerves was carried out using a liquid nitrogen probe at minus 140°C with three freezes of two minutes and five minute thaws at each site.

Result:

Only brief transitory pain one week post surgical, 100 mg Epanutin per day prescribed.

One month post-surgical, slight attacks of pain, but in mid posterior hard palate. Epanutin 100 mg b.d. controls the pain.

Result assessment: Unable to assess at present.

Follow up period: one month.

Case 13

Location:

Right infra-orbital and superior posterior dental nerves in a 60

year old female.

History of pain for six years. Tegretol 200 mg t.d.s. then 200 mg q.d.s. controlled pain but the patient developed an allergy to Tegretol. Epanutin 100 mg t.d.s. was prescribed, but by March 1979 pain was out of control. In April 1979 the right infra-orbital nerve was frozen with one two minute freeze (cryogen unspecified). Pain migrated to the right mental nerve which was frozen by two one minute freezes (cryogen unspecified) in March 1980. Severe pain returned to the right infra-orbital nerve which was re-frozen for two one minute periods on 18th April 1980.

Pain was controlled until November 1980 when the right infra-orbital nerve was frozen with a nitrous oxide probe at minus 45°C for two three minute freezes and a five minute thaw. The patient was then pain free until August 1984 when pain returned to the right infra-orbital area.

Treatment:

Cryotherapy on 30th August 1984 was carried out, under L.A. plus I.V. diazepam, to the right infra-orbital and superior posterior dental nerves. A liquid nitrogen probe at minus 140°C was used with three two minute freezes and five minute thaws.

Result:

One week post surgical, patient was pain free and very happy and was to be seen in three months.

Result assessment: Unable to assess at present.

Follow up period: one week.

Case 14

Location:

Right mental and right long buccal nerves, plus a trigger zone in the right zygomatico-facial region in a 39 year old female. History of six years pain in different areas, originally the right infra orbital area. Tegretol 300 mg per day and later 200 mg t.d.s. were used to control the pain. In April 1982 pain began in left long buccal or mental area, which was controlled by Tegretol 200 mg b.d. In September 1983 pain returned to the right infra-orbital and left long buccal nerves which were frozen on 28th September 1983 by unspecified cryogen.

Pain then migrated to the left infra-orbital area but by January 1984 pain was severe in the right infra-orbital area and on 9th February 1984 the right infra-orbital and posterior superior dental nerves were frozen with a liquid nitrogen probe at minus 140°C for three two minute freezes and five minute thaws. Severe pain occurred post-surgically and Tegretol 200 mg q.d.s. plus Epanutin 100 mg b.d. were needed to control pain completely.

By September 1984 pain was localized to the right mental and long buccal areas, with a trigger zone at the right zygomatico-facial area.

Treatment:

Cryotherapy on 6th September 1984 was carried out on the right long buccal and mental nerves using a liquid nitrogen probe at minus 140°C for three two minute freezes and five minute thaws in both sites. Also a 1 ml injection of absolute alcohol was given at the right zygomatico-facial area.

Result:

Four days post surgical, still a severe trigger zone at right zygomatico-facial area, but other areas totally pain free.

One week post-surgical, patient had had one day severe pain in right zygomatico-facial area, but was then very much better. Tegretol reduced from 1,200 mg per day to 800 mg per day.

Two weeks post-surgical, patient was very much improved with only 2-3 very short attacks. Tegretol 200 mg q.d.s. controlled all pain.

Result assessment: Fair.

Follow up period: 2 weeks.

Case 15

Location:

Left long buccal and left mental nerves in a 61 year old male. History of six years pain on left side, originally diagnosed as atypical facial pain and treated with antidepressants. Diagnosed as T.N. in 1983 and the left mental nerve was frozen using a liquid nitrogen probe at minus 140°C. The patient was then pain free for one year, until pain commenced in the left long buccal nerve.

Treatment:

Cryotherapy was carried out on 20th September 1984 to the left long buccal and left mental nerves under L.A. plus I.V. Diazepam using a liquid nitrogen probe at minus 140°C with three two minute freezes and five minute thaws at both sites.

Result:

One week post-surgical, the patient was totally pain free, very happy and "had never felt better".

Result assessment: Immediately excellent. Unable to assess fully at

present.

Follow up period: one week.

Case 16

Location:

Left infra-orbital and possibly the left posterior superior dental nerves in a 62 year old female.

History of six months pain on left side, originally thought to be due to retained roots of teeth, but the pain persisted following their removal. Then diagnosed as T.N. and up to 1,200 mg Tegretol per day needed to control the pain.

Treatment:

Cryotherapy was carried out on 20th September 1984 under L.A. plus I.V. Diazepam to the left infra-orbital and posterior superior dental nerves using a liquid nitrogen probe at minus 140°C with three two minute freezes and five minute thaws.

Result:

One week post-surgical, the patient had experienced mild pain only at the corner of the mouth and upper left lip and had not needed to take Tegretol. Tegretol 400-600 mg per day was prescribed, but the patient to reduce this if possible and was to be seen in three months.

Result assessment: Initially good. Unable to assess fully at present.

Follow up period: one week.

Case 17

Location:

Left long buccal and mental nerves in an 87 year old female.

History of nine months pain in left mental region. Tegretol 600

mg per day, even when Epanutin 100 mg b.d. added, could not control the pain.

Treatment:

Cryotherapy was carried out on 27th September 1984 to the left long buccal and mental nerve, under L.A. plus I.V. Diazepam using a liquid nitrogen probe at minus 140°C with three two minute freezes and five minute thaws at each site.

Result:

Immediately no pain and patient to be seen after one week and for later follow up.

Result assessment: Unable to assess fully at present.

Follow up period: Only immediately post-operative.

Case 18

Location:

Left lingual, long buccal and mental nerves in a 59 year old female.

History of right side pain nine years previously and had right infra-orbital nerve sectioned six years previously and the right mental nerve sectioned five years previously. The patient presented on 22nd June 1983 with pain on the left side and taking Tegretol 200 mg per day. The left lingual, long buccal and mental nerves were frozen on 8th July 1983 at minus 70°C (regimen unspecified). Tegretol 200 mg t.d.s. then controlled the pain. Pain later returned very severely.

Treatment:

Cryotherapy was carried out on 27th September 1984 to the left lingual, long buccal and mental nerves under L.A. plus I.V. Diazepam using a liquid nitrogen probe at minus 140°C with three

two minute freezes and five minute thaws at each site.

Result:

Immediately pain free. One week post-surgical the patient had had only one attack of pain and was to be followed up.

Result assessment: Initially good. Unable to assess fully at present.

Follow up period: one week.

Haemangiomata

Case 19

Location:

Mixed cavernous and capillary haemangioma of right maxillary labial sulcus (Figs. 9-1 and 9-2) in a 63 year old female. A rather thick lesion. The lesion was tender and irritated by a full upper denture.

Treatment:

Cryosurgery under L.A. was carried out on 7th November 1983 using a nitrous oxide probe, with three sections being frozen for one minute each and a five minute thaw allowed and then an overall freeze of the lesion for one minute.

Result:

One week post-surgical the patient had a fair degree of pain and the full upper denture was irritating the area. The denture was eased.

Two weeks post-surgical the lesion was about 2/3 healed and the pain was far less.

Three months post-surgical the lesion had totally disappeared.

Result assessment: Excellent.



Fig.9-1. Case 19. Haemangioma of the right maxillary labial sulcus with cryoprobe ready for application.

Fig.9-2. The same case as in Fig. 9-1 three months following cryosurgery.



Follow up period: 3 months.

Case 20

Location:

Capillary haemangioma on gingiva in upper left central to first premolar region (Figs. 9-3 and 9-4) in a 10 year old female.

History of lesion for at least two and a half years.

Treatment:

Cryosurgery was carried out under L.A. in two sections on 28th February 1985 and 12th March 1985, using a nitrous oxide probe with a thirty second freeze at two sites at each appointment.

Result:

Two weeks after the first freeze the first section of the lesion had resolved and two weeks after the second freeze the lesion had almost disappeared, the result being judged as excellent.

Result assessment: Excellent.

Follow up period: 4 weeks.

Fibro-epithelial Polyp

Case 21

Location:

Small fibro-epithelial polyp on lower right alveolar ridge of long duration in a 64 year old female. Probably due to denture irritation.

Treatment:

Cryo-surgery was carried out under L.A. on 5th November 1984 using a nitrous oxide probe with two thirty second freezes and a five minute thaw.



Fig.9-3. Case 20. Haemangioma of left maxillary gingiva.

Fig.9-4. The same case as in Fig. 9-3 four weeks after the first sectional freeze and two weeks after the second sectional freeze.



Result:

One week post-surgical a typical slough was observed. Three weeks post-surgical the lesion had totally disappeared.

Result assessment: Excellent.

Follow up period: 3 weeks.

Sublingual Keratosis

Case 22

Location:

Severe sublingual keratosis of total floor of mouth in a 62 year old female.

History of longstanding sublingual keratosis of floor of mouth. The patient smoked 12-15 cigarettes per day and had had Fungilin treatment to the lesion with no improvement noticeable. A biopsy on 6th December 1984 disclosed only hyperplastic mucosa.

Treatment:

Cryosurgery was carried out under L.A. over a period, the lesion being treated in sections. A nitrous oxide probe was used for all sections.

On 20th December 1984 the right side was almost totally treated in three sections with one forty five second freeze at each site plus a five minute thaw. The left side was treated in five sections, at different appointments between 31st January 1985 and 1st April 1985 with one freeze of thirty five seconds at the first four sites and one freeze of forty five seconds at the fifth site.

Result:

After the first treatment the patient suffered a good deal of

pain. This was probably due to too large an area being treated initially and some bone being exposed. However the right side of the floor of mouth was devoid of lesion four weeks post-surgical.

The remaining treatments produced progressive elimination of the lesion and on 29th April 1985 the lesion had been totally eliminated.

Result assessment: Excellent.

Follow up period: 4 months.

Chronic Ulcer

Case 23

Location:

Severe chronic ulcer of left lower lip in a 33 year old mentally retarded male.

History of at least three months ulceration of lower left lip, almost certainly due to trauma from chewing the area. A biopsy on 24th November 1983 showed no evidence of malignancy.

Treatment:

Cryosurgery was carried out under L.A. on 14th December 1983 and 16th February 1984 using a nitrous oxide probe with one freeze of sixty seconds on the first occasion and of thirty seconds on the second occasion.

Result:

One month following the second freeze the lesion was very much improved. Two months following the second freeze only residual scar tissue was present. There has been no further complaint from the patient.

Result assessment: Good.

Follow up period: 2 months.

Comments

The results of this series show that very satisfactory treatment can be provided by means of cryotherapy for haemangiomata, fibro-epithelial polyps, sublingual keratosis and some forms of ulceration.

In regard to the trigeminal neuralgia cases, it can be seen that the results are mixed and only short follow up has been possible in some instances, due to the fact that the work was carried out overseas. However the early results are promising and two factors must be kept in mind in relation to cryotherapy for the treatment of trigeminal neuralgia. Firstly, the treatment is easily repeated and well accepted by most patients and secondly, with cryotherapy to sensory nerves, the quality of life is well maintained for the patient whereas some other forms of treatment leave the patient with permanent loss of sensation, which is at times quite intolerable.

CHAPTER 10

Discussion and Conclusion

The contents of this treatise were designed to review the more important aspects of cryosurgery and in particular assess its value in the management of some forms of oro-facial pain and oral lesions.

A variety of changes in the way in which extreme cold has been used therapeutically over the years have been discussed and some of the interesting historical details of cryosurgery have been included. In this context it is especially important to emphasize that cryogenic surgery, as we know it to-day, really has a history of little more than twenty years and in the specialized field of oro-facial pain control one can only look back ten or twelve years to the beginning of this form of therapy. During these few years big steps have been taken in the advancement of knowledge regarding cryotherapy, but those most involved in research into and the use of this mode of treatment would be among the first to agree that there is still a clear need for a much more detailed understanding of several facets of this technology. Until that understanding is forthcoming cryosurgery must be regarded as a developing science.

Like most other forms of therapy the application of intense cold must not be looked upon as some magical panacea for all ailments that beset mankind. It is fundamentally important to understand that cryotherapy must be used within its limitations and equally within the limits of the operators knowledge and experience.

As to the very complex consideration of the means by which cold

destroys tissue, an attempt has been made to analyse the more generally accepted theories. Although a considerable amount of research has been done in respect of this particular matter it must be admitted that no concrete proof has been presented to specifically identify the means by which tissue necrosis is induced by the action of extreme cold. The vast weight of evidence strongly suggests that the most important factors involved in cryosurgical tissue destruction are intracellular ice crystal formation (and possibly extracellular ice formation), mechanical injury to the cell membrane by that ice, denaturation of cell membrane protein complexes, vascular stasis leading to ischaemia and infarction, a rapid freeze and slow thaw which maximizes the intracellular ice formation, the absolute temperature produced in the tissue and finally repetition of freeze/thaw cycles and the duration of those cycles.

Those lesions which are specially suited to treatment by cryosurgery have been discussed and from an oral surgery standpoint some of the most suitable appear to be haemangiomata, mucosal hyperplasia, leukoplakia, mucous retention cysts and epithelial dysplasia. Other uses for cryosurgery in the oral cavity include the freezing of bony cavities following tumour resection and the primary treatment of specified bony tumours, the treatment of selected small malignant lesions and palliation in the case of larger lesions. Relief of orofacial pain represents a further important use for cryosurgery and will be referred to later in this chapter.

A description has been provided of the main types of cryosurgical equipment and cryogens together with brief mention of some accessory items. In current practice the vast majority of cryosurgery is

carried out by means of a cryoprobe or a liquid nitrogen spray unit. The cryoprobes in common use utilize either liquid nitrogen circulating inside the probe or the Joule-Thomson principle of a compressed gas expanding through a small orifice inside the probe. In the second case the gas employed is almost universally nitrous oxide.

The various advantages, disadvantages and limitations of cryosurgery have been detailed and from the evidence presented it seems reasonable to conclude that the advantages greatly outweigh the disadvantages. The major advantages of this technique are minimal body disturbance (of prime importance with frail patients), excellent patient acceptance, repeatability without serious scar formation, simplicity, flexibility and relative absence of pain or haemorrhage post-operatively. Additionally cryosurgery can be used to treat otherwise difficult to manage lesions such as widespread pre-malignant lesions and it uniquely preserves structure in such vital tissues as bone, large blood vessels and nerve sheaths.

The main disadvantages and complications of cryosurgery are the absence of a complete post-operative biopsy specimen (of great importance in malignant cases), the limitation of the volume of the ice ball attainable (and consequently the volume of tissue destruction), cutaneous depigmentation and post-operative swelling, which is especially important in the pharyngeal region. A list of other minor problems associated with cryosurgery has also been presented.

The more specialized section of this treatise has examined the role

of cryosurgery in the treatment of some forms of oro-facial pain, particularly trigeminal neuralgia. A general outline of the theories of the cause of pain has been given and the features of oro-facial pain, as opposed to other forms of pain, have been examined. The main point brought out in this connection is that the face has great emotional significance, especially in women, and the patient with facial pain has a feeling that other people can "see" their pain. Another factor of great importance is that facial pain (e.g. trigeminal neuralgia) can be extremely severe and the combination of these two important features has led to a number of suicides in past years. A consideration also referred to has been the fact that oro-facial pain can be especially difficult to diagnose by reason of psychogenic overtones and in addition that trigeminal neuralgia can at times be mimicked by other conditions such as dental pain or mental nerve entrapment. However specific criteria for the diagnosis of trigeminal neuralgia have been provided namely a classical history, negative pathosis upon clinical examination, negative results from special tests, pain relief from a diagnostic local analgesia block and finally relief of pain from a trial of Carbamazepine. These results will provide a definitive diagnosis in very nearly one hundred per cent of cases.

The methods of management of trigeminal neuralgia, both non-cryosurgically and by cryosurgery, have been examined and the reports of a series of cases have been presented. In particular the work of Nally has been discussed in detail and his criteria for satisfactory cryotherapy for trigeminal neuralgia has been detailed.

Some salient points in regard to cryosurgical treatment of trigeminal

neuralgia are important to consider. This method of treatment offers the patient the option of a very easy operation in place of a difficult and at times dangerous neurosurgical intervention, giving the patient a new hope for the future. Some cases of trigeminal neuralgia are extremely difficult to manage and cryosurgery is not totally effective; however the treatment can easily be repeated and can be utilized in combination with other therapy. It must likewise be said that many cases are very effectively treated by cryosurgery and present the patient with a new life. As pointed out cryosurgery is a developing science and this is particularly so in regards to the management of trigeminal neuralgia. The results over the years have improved and there is general optimism among workers in this field that in the future substantially better results will be recorded. Consideration is being given to the use of different freeze/thaw cycles, colder temperatures and variations of techniques for the freezing of different nerves. Other factors warrant investigation, such as blood pressure control and anxiety control while a course of serial freezing of nerves, as opposed to one initial operation only, is to be instigated.

A series of case reports have been presented, the majority of which concern the treatment of trigeminal neuralgia. The histories of some of these cases confirm previous submissions in this text as to the difficulties encountered at times in treating trigeminal neuralgia. It is probably better to approach trigeminal neuralgia with the concept of total management of the condition rather than with the expectation of a first time cure in all cases. The very difficult cases to control require perserverance and belief on behalf of both patient and operator, but given those requirements nearly all cases

can be brought to a satisfactory result. The developing nature of cryosurgery is reflected in the changes in techniques which can be observed in the cases presented, the obvious aim of those changes being to arrive eventually at the optimal method of treatment.

In beginning to use cryosurgery or recommending its use by others there are important points to observe. While the technique is indeed a relatively simple one, like most other tasks it is not quite as simple as it appears. It is essential to know what to treat and then how to treat it. The selection of equipment and cryogens is of prime importance, as is of course the selection of lesions which are suitable for cryosurgical treatment.

Providing the guidelines of cryosurgery are carefully followed this modality can offer both operator and patient most rewarding results, from a technique which is readily accepted by the patient in nearly all cases.

As to the future of cryosurgery it is anticipated that the results will improve as further experience is gained and techniques and equipment are further modified. Research is being undertaken into various aspects of cryosurgical work, for example the exact nature of the effects of cryosurgery upon sensory nerves in trigeminal neuralgia and impulse transmission within those nerves and similarly investigations into the possibility of cryoimmunity for such lesions as cancer and oral ulceration are proceeding. It seems reasonable to expect that the results of this research can only increase the effectiveness of cryosurgery in the years to come and in respect of trigeminal neuralgia, workers in this area are very confident that

nerve freezing techniques will very shortly assume the position of first choice in the treatment plan for this appalling condition.

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