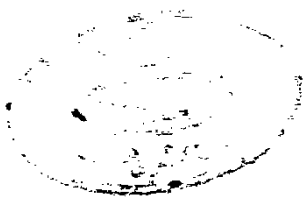
USES OF CRYOTHERAPY IN SURGERY

An Essay

Submitted for the Partial Fulfilment of the

M.Sc. Degree in General Surgery



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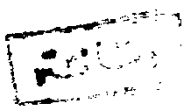

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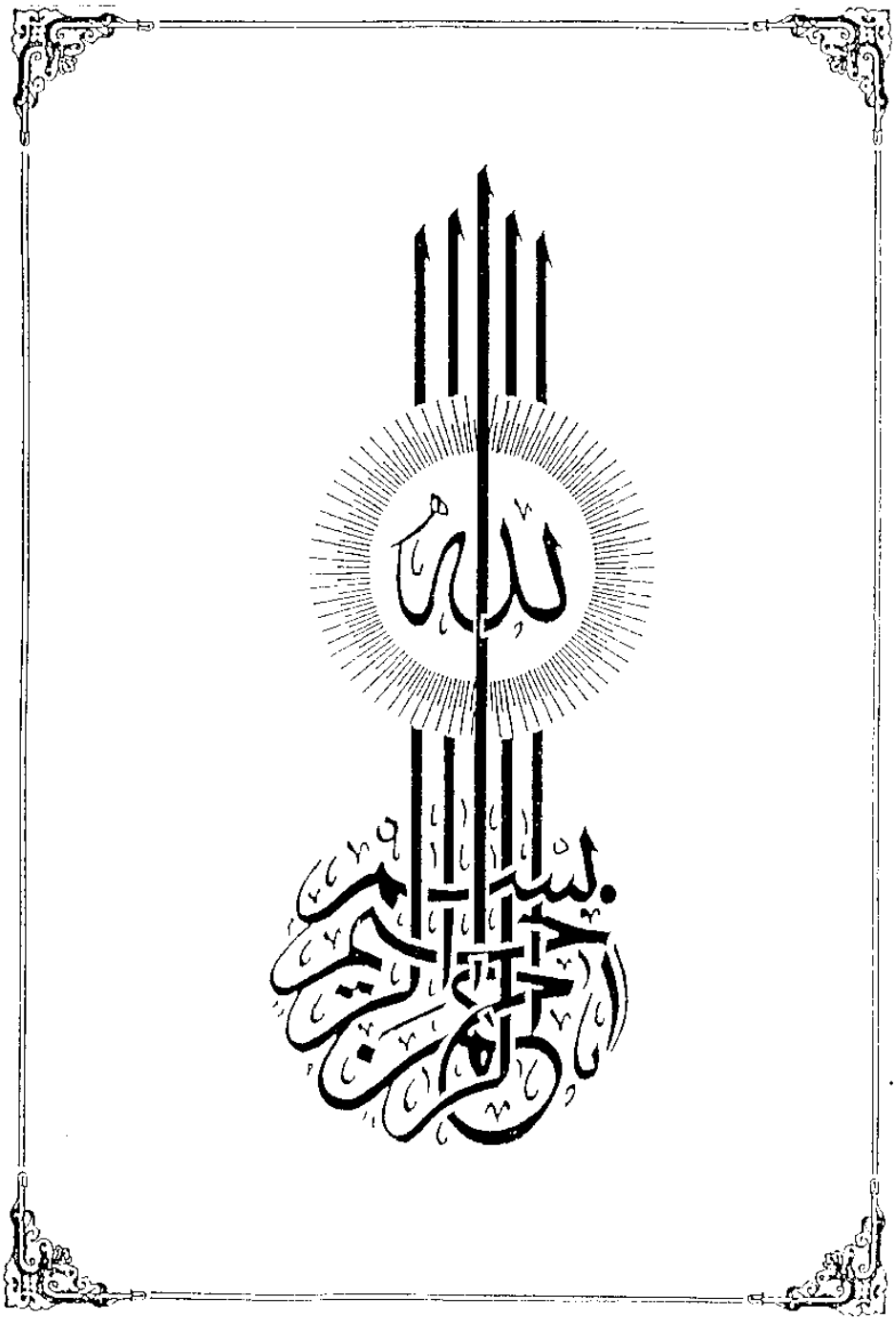
1985

ACKNOWLEDGEMENT

In the course of fulfilling this work, I received a large amount of assistance and encouragement without which this work could not be completed.

In this context, I wish to express my deepest gratitude and appreciation to Prof. Dr. **Hamdy Mahmoud Abdalla,** Professor of Surgery, Faculty of Medicine, Ain Shams University for his fruitful advice and supervision throughout the preparation and fulfillment of this work. His continuous encouragement and professional guidance were highly valuable and I am truly indebted for him.



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INTRODUCTION

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Cryosurgery refers to surgery accomplished through application of intense cold to cause tissue necrosis (Crumay, 1975). In order to freeze living tissue, the cell temperature must be lowered to at least -20°C. Ice crystals are formed within the cells leading to cell damage and progressive tissue necrosis (Rains and Ritchie, 1981).

Recently, cryosurgery has proved itself as a very valuable therapeutic modality in many fields of surgery (Gage, 1980).

Cryosurgery is applicable in the treatment of many benign lesions on the body surface (as papillomas, haemangiomas, verrucas, neavi,....), intermediate lesions (as leukoplakia) and malignant lesions (Williams and Holden, 1975) Freezing in situ may be used to destroy cancer, and may achieve cure as well as palliation of distressing symptoms (Gage, 1969). Cancer of the skin is, by far, the most common human malignancy amenable to cryogenic application (Zacarian, 1973).

Preliminary reports of immunological responses to cancer cryosurgery, are not only thought provoking, but offer a challenge and a promise for cancer immunogenesis (Zacarian, 1973).

In short, cryogenic surgery offers an effective method for destruction of unwanted tissues, with anaesthetic properties, haemostasis and remarkable wound healing (Poswillo, 1973).

REVIEW OF LITERATURE

HISTORICAL NOTE

The story of attempts to use cold for therapeutic purposes continues throughout the centuries. It traces its beginning back to the ancient Egyptians 2500 years B.C., who used cold for therapeutic treatment of trauma and inflammation (Bracco, 1980).

In the fifth century B.C., Hippocrates pointed out the clinical utility of cold as a means of relieving pain in trauma and certain diseases affecting the bones and joints. Also, the Arabian physician Avicenna undertook a serious study of cold as anesthesia. In 1661, Thomas Bartholin wrote his first book on the possible use of snow and ice for medical purposes (Bracco, 1980).

The idea of using freezing to kill cells in vivo is more recent. In 1850, James Arnott used the salt/ice mixture for palliative treatment of malignancies involving the skin. However, the first true cryosurgeon was White, who, in 1889, made his first attempt to cure various skin diseases, including epitheliomas and ulcerated carcinoma of the breast, by freezing them with liquid air (Torre, 1976 - Hopkins, 1983).

In 1905, Juliusberg used carbon dioxide spray and Pusey used carbon dioxide snow for the treatment of dermatologic lesions. It was then that the method began to be called cryotherapy (Torre,1976-Bracco, 1980).

In the 1920's, liquid oxygen became available. Irvine and Turnacliff used it for treating several epitheliomas.

In the 1940's, liquid nitrogen became available and replaced liquid oxygen as the cryogen for dermatologic cryosurgery (Torre, 1976).

A real milestone in the story of cryotherapy came in 1961, when Irving Cooper, with his colleague A.S. Lee, managed to achieve an efficient cryosurgical apparatus using liquid nitrogen in a closed probe system. This was used first in stereotactic thalamectomy and then, in the destruction or removal of benign and malignant brain tumours. It immediately became apparent that the possible usefulness of this tool extended far beyond its employment in neurosurgery (Bracco, 1980).

Subsequent improvements in cryogenics have made it possible to apply very low temperatures to almost any part of the body with control and simplicity (Williams and Holden, 1975).

BASIC CONSIDERATIONS
AND
CRYOBIOLOGY

I. EFFECTS OF FREEZING ON LIVING CELLS AND TISSUES

The fundamental aim of cryosurgery is to freeze cells and tissues in order to kill and destroy them. Cell death is induced by a combination of cryobiological effects (Poswillo, 1973).

The response of cells to sub-zero temperatures has been under investigation for many years. As cells are cooled below 0°C, ice crystals form, and liquid water is removed, thus raising the concentration of solutes (Mazur, 1965).

Approximately 90% of cell water is freezable below -20°C (Zacarian, 1973 b). And, most cells are killed by reduction to -20°C, although it is possible that some can survive down to -40°C (Green, 1981).

At least 3 factors contribute to the in vivo cryodestruction of the tissue : physical, vascular, and immunologic (Fig. 1). These factors act simultaneously ; they are triggered by a single phenomenon: crystallization, which is a function of the freezing-thawing rate imposed on the target (Le Pivert, 1980).

A. Physical Factors

Cell integrity, in essence, is dependant not only upon the freezing temperatures achieved, but more significantly to the rate of cooling and subsequent thawing (Zacarian, 1973 b).

a. If cells are cooled sufficiently slowly, they will dehydrate and will not freeze intracellularly.

b. If they are cooled sufficiently rapidly, they will dehydrate less, and they will freeze intracellularly. The cooling velocity required to produce intracellular ice vary for different cells (Mazur, 1965).

Intracellular ice damage

If the cells are cooled very rapidly, the resulting intracellular ice crystals will be be too small to cause injury. In such a case, the warming velocity could have a profound effect on survival. If the cells are warmed slowly, the unstable crystals may be converted to crystals of damaging size ; but if the cells are warmed rapidly, the unstable crystals can melt before they have a chance to grow. This conversion of smaller crystals to larger ones is termed recrystallization (Mazur, 1965 - Mazur et al, 1972).

Suggestions for the causes of intracellular ice damage include direct disruption of intracellular organelles by ice and osmotic effects produced as intracellular ice melts during thawing (Farrant, 1975).

Extracellular ice damage

When the rate of cooling is slow, the ice crystals occur in the extracellular fluid, and cause cell damage by cellular compression. In addition, the osmotic pressure rises and water is withdrawn from the cells. This exposes the cells to major alterations including dehydration, changes in pH, and concentration and precipitation of solutes (Mazur et al, 1972 - Farrant, 1975).

It has been found that the intracellular formation of ice crystals is the important criterion for the destruction of the cells (Williams and Holden, 1975). Furthermore, Whittaker (1984) has shown that, during cryosurgery, ice crystals form intracellularly and that the resultant cell damage is osmotic rather than mechanical.

Effect of Solute Concentration and Dehydration

At some temperature below 0°C, water begins to freeze, pure ice separates out of solution, and concomitantly the solutes in the residual liquid solution become increasingly concentrated both intra- and extracellularly. When a particular concentration of solutes is reached, the cell is damaged. It is not clear whether this damage is brought about by a direct attack on the membrane by the high ionic strength conditions (i.e. high concentrations of electrolytes can remove lipids from cell membranes (Lovelock, 1954) and can cause large changes in pH (Van Den Berg, 1959)), or is a consequence of the shrinkage of the cell induced by the high external osmotic pressure. However, there is some data suggesting the latter to be the cause (Farrant, 1975).

Denaturation of lipid-protein complexes

Lovelock (1957) points out that lipid-protein complexes such as exist in cell membranes are held together by weak association forces which are inherently unstable. Freezing is sufficient to denature these sensitive lipid-protein complexes of the cells, thus damaging or destroying the cellular membrane. This renders the cell membrane permeable

to ions, so that it slowly swells and bursts. This lysis of the cell may occur during freezing or thawing stage. In addition, lesser membranes of the cell (such as those in the nucleus, mitochondria, ...) may suffer irreversible damage during freezing due to denaturation of lipid-protein complexes.

Thermal Shock

Thermal shock refers to injury of the cell due to rapid change in temperature, which may damage the cell, in some instances, even before freezing levels are reached (Cooper, 1965). The cause of damage is uncertain. It has been suggested that it involves damage to lipoprotein complexes in cell membranes (Mazur, 1965).

In summary, the physical and chemical alterations in cells subjected to cryogenic temperatures are :

- Development of intracellular ice crystals
- Development of extracellular ice crystals
- Cell dehydration with cell shrinkage
- Raised concentration of intracellular electrolytes
- Damage to cellular lipoproteins
- Thermal shock (Green, 1981).

B. Vascular factors

Studies of circulatory changes after thawing revealed a brief period of vasodilatation with maximum blood flow followed by capillary obstruction and vascular stasis (Fraser and Gill, 1967). This cryoinduced

thrombosis is mainly due to the formation of platelet plugs (due to the activation of contact factors and the modification of the endothelial cells) (Le Pivert, 1980). This cryothrombosis completes the cellular destruction produced by the physical phase of the cryoprobe (Green, 1981).

C. Immunologic Factors

As regards the arousal of an immunologic reaction, the development of antibodies have been implicated in contributing to the size of the cryolesion (Evans, 1981). The initiating mechanism may be the liberation, through cryocytolysis, of sequestrated antigens modified by cold. These antigens may be liberated either during the brief interval between thawing and the vascular thrombosis of the tumour or, more likely, out of the cryonecrotic debris.

Another theory, is that cryosurgery could liberate unmodified sequestrated antigens with a sequential method (the destruction of the tumour at a few weeks' interval)permitting an autologous vaccination (Le Pivert, 1980).

Despite the intensity and degree of freezing, a small proportionate number of mammalian cells will survive. Not only normal cells but, even malignant cells will survive freezing temperatures. Genetic differences within cells, perhaps, explains their resistance to the freeze-thaw cycle (Zacazian, 1973 b).