A History of Cryosurgery: Its Development and Future

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Therapeutic use of cold temperature has existed for a long time in the medical setting, first and foremost for its anesthetizing effects. But the damage that cold can do has also been noted from earliest times and is mentioned in both civilian and military sources, including historical accounts that deal with the effect of cold climates on various body tissues.[1] In comparison, the history of cryosurgery is very short, and in the 19th and 20th centuries, was closely interwoven with developments in low-temperature physics and engineering—developments necessary for refinement of cryosurgical instruments. A review of the history of cryosurgery shows that it has progressed in leaps, and that each leap has usually been triggered by immediately preceding technologic innovations. The fact that the application of temperatures lower than −100°C could induce cell death was supported by Schreuder's investigations.[2] So cold injury has become the basis for a method of lifesaving treatment. Today, the major aim of cryosurgery is destruction of diseased tissue, such as benign and malignant neoplasms, by application of exceedingly low temperature. What follows is an overview of the growth in understanding of cold injury and cold surgery over the centuries.

Ancient Egypt and classic antiquity

As long ago as 3000 BC, the use of cold compresses to treat compound skull fractures and infected wounds was mentioned in an Egyptian papyrus, identified by the historian Breasted as the Edwin Smith Surgical Papyrus.[3] The author cited two places mentioning cryotherapy: the one from the original papyrus, and the other from material translated from hieroglyphic letters by Breasted.[3] The portion of cryotherapy is translated by Breasted as follows: "Thou shalt make for him cool applications for drawing out the inflammation from the mouth of the wound."

The other side of the coin, the prevention and cure of illness caused by cold, was a concern of Greek medicine in the 5th century BC. Hippocrates noted, for example, the effects of cold on the inhabitants of countries with cold climates. But he also recognized its therapeutic properties, advocating the use of cold to control hemorrhages and reduce the swelling of painful joints.[4]

Military campaigns in mountainous regions of the ancient world resulted in a high prevalence of cold injuries. Hannibal's Carthaginian mercenaries, who crossed the Alps with his army in 218 BC, oiled their bodies to prevent frostbite.[1] The forces of Alexander the Great found similar protection using sesame juice.

Some 300 years later, in 25 AD, Celsus described the appearance of the skin after cold injury, and noted that if the injury was severe, dry gangrene supervened.[1] In one of his many treatises, Galen described the loss of sensation that accompanies injury from cold (170 AD): "Pain as a means of diagnosis."[1]

The 12th to 18th centuries

Although he remains unnamed, it is known that a mid-11th-century Anglo-Saxon monk used cold as a local anesthetic.[5] There is evidence that almost exactly 500 years later, refrigeration anesthesia was known to Italian physicians.[6] Another 100 years later, in 1661, Thomas Bartholin[7] of Copenhagen described the use of cold as a therapeutic for a great variety of everyday illnesses. In 1665, Robert Boyle published a monograph on the influence of cold on living animals.[3]

An early 18th century invention had a decisive effect on progress in cold therapy—our familiar mercury thermometer. Invented in 1714 by Fahrenheit and reinvented by Reaumur and Celsius, the thermometer made it possible to measure the actual coldness, or temperature, at which events occurred. So scientists could now attempt to generate ever lower temperatures, could standardize their experiments with cold, and could share results.[2]

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In 1787, Spallanzani published his investigations on the effects a temperature of −24°C had on insects, fish, amphibians, reptiles, birds, and mammals. He also established that water can exist at subzero temperatures without freezing, a physical state later called *supercooling*.

During the American War of Independence (1775 to 1783), Dr James Thatcher noted in his diary the serious losses of American forces from cold injuries.[8] He recorded, for example, that during 1 sortie, 500 troops were "slightly frozen" after a night in the open. During the Napoleonic Wars, Napoleon's surgeon-general, Dominigue Jean Larrey (1766 to 1842), made detailed observations of the effects of cold on his patients. Dr Larrey described erythema and blistering of the skin after freezing, noting also that gangrene was not inevitable after freezing if exposure was not prolonged. He also described the uneventful healing of wounds caused by cold. Taking advantage of the properties of cold, Napoleon's Grand Army surgeons cooled tissue with surface applications of snow and ice to facilitate amputation.[8]

The 19th century

The first successful treatments of malignant disease with cold in England were reported between 1845 and 1851 by Dr James Arnott (1797 to 1883),[9] who used iced saline solutions at temperatures of −18° to −24°C to treat advanced breast and uterine cancer. Dr Arnott observed, "Congelation arresting the accompanying inflammation and destroying the vitality of the cancer cell, is not only calculated to prolong life for a considerable period, but may, not improbably, in the early stage of the disease, exert a curative action."[10] So Arnott was probably the first physician to use cold to treat malignancies. Although he did not succeed in curing his patients, he considerably reduced the morbidity of cancer, especially the pain, which can still challenge the treating physician today. The greater part of Arnott's work focused on the application of cold in anesthesia.

Although the anesthetizing characteristics of low temperatures were long established facts by the mid 1800s, it was then recognized that low temperatures could be used to destroy parts of a tumor. Although Arnott's contemporaries acknowledged the usefulness of applying cold and began to use freezing techniques locally, further developments in cryosurgery had to await technologic advances, especially the development of improved cryogenic agents.[11]

The German surgeon Johann Friedrich August von Esmarch, a near-contemporary of Arnott's and inventor of the ether mask named for him, was a preeminent authority on military surgery of his time. His conclusions from battlefield experiences initiated fundamental changes in emergency care, hospital management, medical education, and research.[12] Von Esmarch observed that cooling of wounds significantly reduced local inflammation and pus formation. His findings introduced cryotherapy into routine surgical practice, and his great passion for this treatment led to the nickname "Fiete Isebüddel" (Fritz the Ice Pack). He held this remarkable opinion of the benefits of cold:

> The application of cold as a means of fighting hyperemic and inflammatory conditions is not given the recognition it deserves by a not inconsiderable number of contemporary physicians. Although the number of doctors who deny the antiphlogistic properties of cold is not great, many consider it dispensable. I therefore fully expect and am prepared to face forceful contradiction from many sides when I say that of all the means we have at our disposal to fight inflammatory processes, I consider cold to be the most important. Indeed, without this means, I would rather not be a surgeon.[12]

In 1883, Openchowski[13] attempted to localize the physiologic function of different areas within the cerebral cortex of dogs by targeted freezing. This produced peripheral convulsions or paralysis and was the first time that functional mapping of the cortex was performed.

The end of the 19th century witnessed a number of major discoveries in the field of cryogenics. Ether sprays and ethyl chloride were used for cold analgesia, although not for therapeutic destructive freezing.[14] In 1877, Cailletet, in France, began developing adiabatic expansion systems for cooling gases, which led to the liquefaction of oxygen, air, and nitrogen. Liquid air (−190°C) was first used clinically by Campbell-White[15,16] in 1889 for treating diverse skin diseases and was applied locally by swab, spray, or brass roller device.

1900 to 1960

After 1910, liquid air seems to have been infrequently used. Solid CO_2 was the most widely used cryogenic agent in the early 1900s, and there have been attempts to make instruments to facilitate its use, such as copper tips or probes connected to a CO_2 source. Solidified carbon dioxide (−78.5°C), or carbonic acid snow, was first used by Dr William Pusey[17] in 1907 in preference to a salt and ice mixture. This was one of the first demonstrations of successful treatment of skin diseases such as naevi, warts, and lupus erythematosus. He stated, "We have found a destructive application whose action can be accurately gauged and is therefore controllable." In addition, he believed in the low scarring potential of cryosurgery, although he attributed this to regeneration of residual epidermal cells rather than to collagen's resistance to cold.

The liquid carbon dioxide gas was held in steel cylinders under a pressure of about 800 psi. When the gas was released into the air, the rapid decrease in pressure caused freezing, and a fine snow was formed. The snow was then compressed into various shapes, or pencils, used for different treatments, especially skin lesions. Subsequently, this became an established therapeutic technique in dermatology.[18,19]

Until the beginning of the 20th century, those who used devices that generated cold had usually also invented them. After the turn of the century, the two skills went separate ways. A large measure of engineering know-how was now required to develop cryosurgical instruments and produce cryogenic media.[2]

In the 1920s, liquid oxygen (−182°C) began to be used clinically as a cryogenic agent in the treatment of skin diseases. But liquid oxygen is potentially dangerous because it supports combustion and explodes easily. So it has never become a popular cryogen for cryosurgery.[20] In the late 1930s, Temple Fay,[21] an American neurosurgeon, used local and general refrigeration techniques to treat patients with advanced cancer, eg, glioblastoma, Hodgkin's disease, and other neoplasms including large, symptomatic, inoperable cancers of the uterine cervix and the breast.

In 1942, the development of chlorofluorocarbon refrigerants led to the first closed-cycle refrigeration system in cryosurgery, generating temperatures as low as 0°C, for treatment of chronic cervicitis.[22] The device permitted rapid defrosting and release of the applicator when required. These cryogens with closed refrigeration cycles never became popular because the temperatures they could reach were not as low as those achievable with the relatively inexpensive solid carbon dioxide.[12]

In the early 1940s, Kapitsa in the Soviet Union and Collins in the United States began developing commercial techniques for the large-scale liquefaction of hydrogen and helium, with liquid nitrogen as an abundant and low-cost byproduct.[23] Liquid nitrogen, which can reach temperatures as low as −196°C, became commercially available, and in 1950, this cryogen was introduced to clinical practice by Allington.[24] The liquid nitrogen was applied with a cotton swab, and was soon commonly used to treat skin diseases and diverse non-neoplastic lesions. It was not commonly used for skin tumors because the swab technique produced only superficial freezing, perhaps 2 mm in depth.[12] Before the 1960s, the devices used for cryosurgery were able to freeze to a depth of only several millimeters. With a few exceptions, freezing was used primarily to remove superficial layers of undesirable tissue, most often in dermatology and gynecology.[25,26]

The era of modern cryosurgery

Cryotherapy as a therapeutic technique received a major stimulus from the introduction of the first cryosurgical system capable of delivering liquid nitrogen (−196°C) to trocar-type probes with an insulated shaft and a conductive metal tip. The system was the result of the collaborative effort of Irving S Cooper, a neurosurgeon, and Arnold Lee, an engineer.[27] Their probe was essentially the prototype from which all future cryosurgical probes using liquid nitrogen were developed.[12] The ability of the device to produce an avascular cryolesion in the liver was demonstrated in a feline model.[28] The design of the probes allowed surgeons for the first time to treat lesions deep within parenchymal organs, with minimal trauma to the remaining organ. After the new cryosurgical probe was introduced by Cooper and Lee, cryosurgery experienced rapid growth that lasted until the end of the 1960s.

The pioneering work of Dr Irving S Cooper on treating Parkinson's disease through cryosurgery must be emphasized. At his time, surgical treatment of parkinsonian tremor focused on various techniques used to interrupt the pyramidal tract. During a subtemporal approach for a cerebral pedunculotomy, he inadvertently injured, and subsequently was forced to occlude, the anterior choroidal artery. Much to Cooper's surprise, after emergence from anesthesia, the patient's tremor and rigidity were abolished without any residual hemiparesis. This serendipitous observation helped focus surgical efforts on targets within the basal ganglia and, subsequently, within the thalamus to alleviate the movement disorders associated with Parkinson's disease.[29] He used cryothalamectomy as a surgical technique for primary control of tremor in patients with Parkinson's disease.[30]

Dr Andrew A Gage's cryosurgical work began in 1964, shortly after Dr Irving Cooper published his early articles on cryosurgery. In that year, Drs Gage[31] and Maurice Gonder were both on the staff of the Veterans Hospital in Buffalo, NY. Together they tested the developed cryosurgical apparatus in animals, freezing the prostate, liver, bone, and other tissues. It was obvious that this could be used to destroy tissue. During the 1970s and 1980s, Dr Gage did a large amount of research on cryosurgery in animals to determine the effects on diverse tissues, including the healing process, examining optimal techniques for different types of therapeutic purposes.[32] During these years and to the present time, Dr Gage[33] has advised many cryosurgical companies on equipment development and provided advice on the research they sponsor.

Around the same time, Dr Gonder modified Cooper's apparatus and was the first to use it for prostate disease.[34] One of the earliest roles of urologic cryosurgery was in the treatment of symptomatic benign prostatic hypertrophy. A single closed-probe system, using liquid nitrogen, was placed transurethrally. This treatment was usually reserved for patients with very large glands and severe symptoms, who were not good surgical candidates for conventional procedures. For unknown reasons, the focus of modern cryosurgery has, since its advent, been on malignant tissue.[35] Perhaps this is, in part, because of the large number of excellent treatment choices available for benign prostatic hypertrophy by the time a multiprobe liquid nitrogen system was developed.[36]

Some scientists used thermocouples to monitor tissue temperature in critical areas. Dr Jeffrey Cohen and colleagues[37,38] developed a urethral warming device, facilitating prostatic cryosurgery. After cystoscopy is performed, a urethral warming catheter is introduced. The rows of cryoneedles are then activated from anterior to posterior, and, generally, two freeze-thaw cycles are used.

The Joule Thomson cryoprobe, a liquid nitrogen probe that achieves cooling by expansion, was developed by Dr Amoils.[39] He performed cataract extraction successfully, but cooling was slow and temperatures were not low enough for tumor work. This system is still widely used in gynecology and ophthalmology.

Dr Charles David Kelman, an ophthalmologist, pioneered cryoextraction of cataracts, the use of freezing to repair retinal detachments, and he designed numerous ophthalmic cryoinstruments in the mid 1960s.[40]

A heater for Cooper's probe was developed by Dr William Cahan,[41,42] who performed cryosurgery of the uterus with a liquid nitrogen probe. Cryosurgery was first reported for the therapy of cervical intraepithelial neoplasia by Crisp.[43] It was quickly adopted as the major form of therapy for cervical intraepithelial neoplasia lesions after appropriate diagnosis. Two decades later, Benedet and associates[44] also reported excellent results with cryosurgery for cervical intraepithelial neoplasia 3 lesions, having treated 555 patients with severe dysplasia, with a failure rate of only 5.5%. These researchers attributed their excellent success rate to careful patient selection and meticulous technique. Similarly, Collins and colleagues[45] and Ostergard and associates[46] used cryosurgical techniques with liquid nitrogen and lesser cryogenic agents in patients with gynecologic inflammatory diseases to treat chronic cervicitis.

In the 1960s, Drs Zacarian and Adham[47,48] attempted to achieve greater tissue depth penetration through the use of solid copper cylinder discs that were cooled by immersion in liquid nitrogen before applying them to the skin. The copper discs had good thermal capacity and better heat exchange characteristics than cotton applicators. They also made it possible to exert pressure on the lesion. Tissue destruction to a depth of 7 mm became possible, but the freezing of large areas of tissue, as needed to treat cutaneous malignancies, was still a difficult undertaking.[49] Dr Zacarian devised a technique for treating superficial lesions measuring several centimeters, in which they are divided into several segments and frozen one segment at a time.[47,50] Known as segmental cryosurgery, it is used to treat benign, premalignant, and malignant lesions of the skin. Later, Dr Jose Carlos d'Almeida Gonçalves[51] created a technique, fractional cryosurgery, to treat tumors with diameters of 10 mm on and around the eyelids. The advantage of Dr Gonçalves's technique is that the final scar is much smaller than the size of the original tumor, most being imperceptible.

Dermatologist Rodney Dawber[52,53] investigated the mechanism of damage from cold injury, ie, factors causing cellular injury including intra- and extracellular ice, hypertonic damage, sensitization, circulatory changes, and immunologic events. He came to the conclusion, "The local tissue response to freezing includes local tissue necrosis, vascular stasis and excellent healing."[54]

In 1968, Ralph C Marcove and coworkers[55] introduced cryosurgery into orthopaedic oncology for the treatment of primary and metastatic bone tumors by repetitive freezing. Since then, more orthopaedic surgeons dealing with skeletal tumors have adopted the technique, and clinical results and experimental data on cryosurgery, with specific reference to the skeletal system, have been published regularly.[56-62]

In Kiev in the 1980s, Dr Nikolai N Korpan began fundamental theoretic, experimental, and clinical studies on modern cryosurgery in cooperation with engineers and designers. Korpan's[63] theoretic aspects have provided further details on the unexpected roles of modern cryogenic technology and cryosurgery in different areas of medicine, especially in oncology. Innovative studies with an experimental model investigated the dynamic temperature field of the frozen zone, defined the four-phase effect of low temperatures on living tissue, and explored the effect of freeze-thawing processes using temperatures of varying intensity, from −40°C to −180°C, with disc-shaped cryoprobes with diameters of 5 to 50 mm, and a laparoscopic needle with a diameter of 10 mm in vitro.

Professor Korpan's[64] experimental foundations are based on pioneering studies of biologic living substances (tissue and cells) in animals (dog liver and dog pancreas) provide a platform to understand the mechanisms of damage and the pathogenesis of frostbite during low-temperature exposure. This gives rise to a new concept concerning the technical requirements of cryosurgical equipment to perform modern cryosurgical operations, especially in oncology.

A unique phenomenon observed and discovered by Dr Korpan[64] in living substance, namely, the "lunar eclipse," provides important insights into the mechanisms of damage. The "lunar eclipse" occurs immediately after freezing, during the thawing process, the snow-white pancreas parenchyma, frozen hard to an ice block and resembling a full moon with a sharp demarcation line, gradually assumed a ruby-red shade and a hemispherical shape as it grew in size from the vascular side to the periphery. This snow-white cryogenic lesion dissolved in the same manner in all animal tissues. A similar phenomenon has been observed by the author in nature, namely the moon during a lunar eclipse. Both phenomena appear to be part of living nature. Vascular changes and circulatory stagnation are commonly considered to be the main mechanisms of biologic tissue injury during low-temperature exposure, especially in cryosurgical oncology. So discovery of the "lunar eclipse" phenomenon suggests that cold surgery is the first surgical technique to use angiogenesis, cryoaponecrosis, and cryoapoptosis in the treatment of cancer. Korpan formulated what are believed to be the pioneering clinical and technical requirements for modern cryosurgery, most importantly, the need to freeze tissue at extremely low-temperatures and follow with deliberate thawing. In addition, Korpan's[63-65] pioneering work was done in pancreatic cancer and large liver metastases, lymph-node cryosurgery, locally advanced breast cancer, local-regional disease recurrence, and the subcutaneous cryosurgical treatment of breast cancer and in curative and palliative anorectal cryosurgery. For the first time, a prospective randomized trial comparing the efficacy of liver cryosurgery with the gold standard of resection has been conducted by Korpan.

In the 1990s, the development of intraoperative ultrasound and its use in monitoring the freezing process renewed interest in cryotherapy.[66-68] The ultrasound image helped identify the site of the lesion, guided the placement of the cryoprobe into the lesion, and monitored the freezing process. This provided a great advantage over earlier techniques.[12] In addition, the development of an array of endoscopic and percutaneous access devices in the 1990s stimulated the use of cryosurgery in the treatment of visceral disease, especially tumors.[63,64,69-71]

The renaissance of cryomedicine in the last 2 decades also has stimulated cryosurgical research. The first large-scale study in Europe, involving the treatment of bronchial carcinoma with a specially designed rigid probe, was published by Dr Maiwand[72] in July 1986 and was followed by an article by Dr Jean-Paul Homasson and coworkers[73] in August of the same year. A few years later, Maiwand and Homasson described the appropriate techniques they had developed to treat bronchial carcinoma.[74,75] Cryosurgery for endobronchial disease has become a common technique used worldwide.

Cryomedicine has contributed to transfusion, transplantation, and treatment of tumors, and will satisfy medical requirements in the new millennium from the viewpoints of regeneration, plasticity, minimally invasive, and tailoring surgery, promising quality of life and therapeutic strategies for elderly patients. Dr Sajio Sumida and colleagues[76-80] described the results of cryomedical treatments on the basis of nearly 40 years of experimental and clinical experiences. In vitro and in vivo observations of extra- and intracellular ice formation, and microcirculatory failures depending on disseminated intravascular coagulation after in situ freezing, have been recorded in detail by Prof Sumida and associates since 1970.[81,82] Cryosurgery for cancer is intensified with the combined uses of chemotherapy, especially high-dose chemotherapy. Previous studies have shown that intravenous infusion of cryopreserved autologous or genetically identical (allogeneic) stem cells rescues lethally myelosuppressed patients with leukemia, aplastic anemia, immune deficiency diseases, lymphoma, and solid tumors, whose immunosuppression is a result of lethal high-dose chemotherapy or radiation.[83,84] It is interesting and important that the thawed stem cells differentiate to form colonies in a culture medium and regenerate not only into blood cells but also into epithelial cells and hepatocytes in organ recipients after transplantation.[85]

Basic research on cryopreservation by Dr Sumida paved the way for the understanding of the mechanisms involved in cryosurgical operations.[86] This insight explains the complex phenomenon of the cryolesion, which consists of intra- and extracellular ice formation; mechanical and osmotic lysis (including dehydration); recrystallization resulting in mechanical and osmotic cell lysis; cellular ischemia and swelling (edema); disseminated intravascular coagulation; and, ultimately, necrosis, oncosis, aponecrosis, and apoptosis.

During the past 20 years, cryosurgical treatment of tumors in various organs has been reported in the liver,[63,64,87] pancreas,[63,64,88] rectum,[63,64,89-91] breast,[63,64,66,92,93] skin,[54,63,64,94-96] lung,[97-99] brain,[100] prostate,[101,102] uterus,[103] oral cavitiy,[64,104,105] bone,[2,106,107] and in cardiac surgery.[108,109]

Until recently, the devices used for cryosurgery were not highly effective and were able to freeze only lesions of the superficial skin layers. The best use of modern cryosurgery is dependent on highly developed cryotechnology. Experience in the use of cryosurgery to treat uterine fibroids and malignant tumors of the kidney, breast, pancreas, and other organs is now accumulating.[66,67,110,111]

In 1998, to investigate the role of cryotherapy as treatment for benign prostatic hypertrophy, a 3-patient pilot study was performed.[35] The goals of the procedure were to decrease the volume of the transition zone while avoiding cryoinjury to the urethra, bladder neck, external sphincter, rectal wall, and neurovascular bundles.

In modern cryosurgical urology, cryoablation represents a vital treatment option for prostate cancer. Extensive clinical experience in treating prostate cancer with cryosurgery has clearly demonstrated the efficacy of this method in decreasing prostate volume, as measured by ultrasound in postcryosurgical biopsies.[35] Morbidity is low compared with other treatment modalities, and it continues to decrease with experience and equipment evolution.[112,113] The goal of modern cryoablation is to encompass the target tissue in addition to a "surgical" margin for thorough treatment. The periprostatic fascia is encompassed during the freeze to cover potential extracapsular involvement. So the minimal invasiveness, repeatability, low morbidity, and quick recovery time, coupled with excellent efficacy, all contribute to make cryosurgical operations attractive and viable therapeutic options in the battle against prostate cancer.

Tracing the evolution of modern prostate cryosurgery, one can perceive the main scientific and technologic tendencies in the development of cryosurgery as a part of medical science and scientific technology. Because of the limitations of this application, more sophisticated closed cryoprobe systems have been developed and represent a major step forward in the evolution of cryosurgical technology. This technology involves multiple cryoprobes that are controlled using a computer microprocessor, allowing fine-tuned control of the freezing process. The long, thin cryoprobes can be inserted deep into the prostate gland for thorough coverage, with percutaneous access. Multiple commercial instruments are currently available for the closed system application. The most commonly used cryogens are pressurized, supercooled liquid nitrogen and argon gas. Both are efficacious for freezing. Liquid nitrogen systems supercool the cryogen and then force it under pressure through the cryoprobes. In practice, this instrumentation can be slow, requiring several minutes to establish a baseline critical temperature. This is because the liquid nitrogen naturally boils as it moves through ambient-temperature cryoprobes, and the probes themselves must be cooled by continuous inflow of liquid nitrogen before nadir temperatures are achieved. In contrast, argon gas–based systems operate by supplying high-pressure gas to the cryoprobes through a Joule Thompson port, resulting in ablative temperatures.[64,114]

For the first time, new cryosurgical operations have been developed and used with clinical success in patients with lymph node metastases after breast cancer surgery, melanoma extirpation, and hypernephroma extirpation performed by conventional methods.[115]

As a professor at New York University School of Medicine and director at The New York Blood Center, Dr Arthur W Rowe[116] is a pioneer in cryobiology of the cellular components of blood. Prof Rowe has published and lectured extensively on cryopreservation of red cells, leukocytes, platelets, bone marrow, peripheral blood progenitor cells, and umbilical cord blood. During his 24 years as editor-in-chief of the journal *Cryobiology*, he recognized the importance of cryosurgery as a science and not just a technique; as such, he was instrumental in publishing seminal articles on cryosurgery by leading medical specialists in the field. His experimental investigations have been among the milestones in the practical use of low temperatures in various medical fields.

The future

The cryosurgical approach is an elegant method that has become an important branch of surgery, with a wide variety of applications across the range of medical specialties, from dermatology to oncology. A great deal of progress has been made recently in understanding its pathophysiologic effects and in improving its practical applications. Although cryosurgery began to be investigated on a scientific basis only in the second half of the 19th century, cold therapy has, in fact, been used empirically for millennia. In the interim, the discipline has attained a high level of precision, finely adjusted to the meticulous procedures required by modern surgery. Over the last 4 decades, it has become an important, widely used, and increasingly indispensable method of treatment, providing excellent results that are equivalent, and often superior, to those with other surgical modalities.[117]

Improvement in imaging technology and further development of cryosurgical apparatus will continue to broaden the usefulness of cryosurgical techniques.[63,64,118] Cryosurgical techniques will be at least complementary to conventional excisional surgery, finding use particularly in situations resistant to conventional surgery, including in patients with multiple morbidities. The new generation of cryosurgical engineering is the result of military and space technology with a high freezing power, which is provided by achieving working surface temperatures of cryoinstruments and cryoprobes in contact with the freezing biologic object at the level of $-180°C$ and lower.

But it is also possible that the advantages of cryosurgery may make the technique directly competitive with excisional surgery in many situations. In fact, in oncology, cryosurgery has several well-known advantages over classic surgery: it is effective in inducing tumor cell necrosis; it spares more normal tissue than does resection, with less risk of hemorrhage and dissemination of cancer cells; it makes the treatment of unresectable tumors possible, particularly those involving large vessels; it allows retreatment; and it apparently elicits an immunologic response to antigens in the frozen tissue.

In dermatology, the use of cryosurgery has many advantages; its results are often as good as, and many times are better than, those of other modalities. Generally, it is less time consuming and less expensive than other treatments; most treatments can be performed in an outpatient clinic. But the apparent simplicity of the cryosurgical technique has led some physicians, especially those with less experience, to treat small lesions while slighting the rigor of the surgical protocol. When the results are worse than those reported internationally, some surgeons are likely to attribute their failure to the method, rather than questioning their skill level or technical knowledge. It should be stressed that even for small skin or mucosal lesions, the cryosurgical protocol must be observed as carefully as for any other surgical procedure.[119]

The economics of cryosurgery cannot be overlooked. Cryosurgery has clear cost advantages; the costs associated with cryosurgical procedures are usually considerably lower than those of excisional surgery, and cryosurgery is very well suited to ambulatory care settings.

On the larger scientific stage, more highly promising developments have taken place in the realm of cryosurgery. Studies of the effects of cryosurgery on a number of tissues, including the prostate, indicated that there is an immunologic response to antigens in the frozen tissue.[120] This discovery of immunogenic effects, with cure or regression of metastases of prostate cancer after cryosurgery, led to a hope of similar results in other fields of oncology, which, until now, has only been only partially fulfilled. But experimental work in rodents with tumors induced by viral and chemical agents has shown the existence of cryoimmunology in these animals.[121-123]

Coinciding with the development of cryosurgery, a new field of science has arisen, namely, cryobiology, which studies the effects of subzero temperatures on biologic systems. Cryobiology has undergone spectacular progress and has developed in two directions: first, improving the understanding of the pathophysiology of cryodestruction of cells and tissues and, second, creating techniques of cryopreservation of living cells, tissues, and organs. It may be expected that a good understanding of cryobiology will dramatically increase the effectiveness of cryosurgical treatment.[63,124]

As with other specialties, the organizational establishment of cryosurgery is of some significance to its further development. The first International Congress of Cryosurgery was held in Vienna, Austria, in 1971, and 3 years later, the International Society of Cryosurgery was founded.[125] The last Combined Meeting of the International and European Societies of Cryosurgery was organized in London, and the 13th Meeting of the International Society of Cryosurgery was held in Crete. In the interim, cryosurgery has been successfully introduced to specialties other than oncology and dermatology.

In conclusion, the use of cold as a treatment measure has a long history, culminating in the benefits of cryosurgery, whose full development cannot yet be foreseen. Certainly, cryosurgery may be regarded as one of the tools that a physician may choose to treat a variety of neoplastic and nonneoplastic diseases. As with any tool, it requires a physician skilled in its use, with the judgment to choose the right tool for the task at hand.

A crucial factor that has influenced the development of cryosurgery is the standard and the technical competency of cryogenic devices, ie, the efficiency of modern cryosurgery in curative and palliative practice depends primarily on the technical proficiency of the cryosurgical devices used to perform cryooperations.

Various companies have marketed cryosurgical devices. Although they are reasonably complicated automatic systems, they do not satisfy the main requirement, namely, the very low temperatures required for cryoactivity. This is undoubtedly why the cryosurgical method has not spread more extensively and why its possibilities have been neglected.

The results of experimental and clinical studies showed that during cryoactivity, the temperature of the working surface of the cryoinstrument, which is in contact with the pathologic tissue or human organ, should not be higher than $-170°C$.

It has been shown that successful use of cryosurgery can be reached only through development of effective medical-technical appliances. Successful application of modern cryosurgery, especially for various kinds of cancer, will be possible in the near future because the necessary technical cryosurgical devices have become available.[126-128]

Modern cryosurgery achieves efficiency and effectiveness through good, uncomplicated surgical results, a high cure rate, and a high quality of life for patients. The "power of cold" needs to be understood and accepted by many more surgeons and other therapists.

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