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Epochs in Endourology

History of Cryosurgery

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THE THERAPEUTIC USES OF COLD to relieve pain, prevent swelling, and reduce fever have been known for long time.[1] The ancient Egyptians used cold to treat skull fractures and wound infections more than 4500 years ago. The harmful effects of cold on tissue have likewise been described since the ancient times, both in civilian life and in warfare. Hippocrates stated in the *Aphorisms* that cold causes ulcers, hardens the skin, causes pain, and produces febrile rigors, convulsions, and tetanus.[2] In the year 400 BC, the famous Greek general and historian Xenophon narrated in detail the effect of cold on the Greek soldiers. He described two types of injury: the first was total-body freeze, which was readily recognizable. The second was "bulimia," where soldiers collapsed from combined hunger and chilling.[2]

THE NINETEENTH CENTURY

The 19th Century witnessed the first successful application of cold to treat cancer, by Dr. James Arnott (Fig. 1) (1797–1883) from England.[3] He believed that freezing reduced and controlled the inflammation accompanying the cancer and perhaps compromised the viability of cancer cells. Most of Arnott's work focused on the analgesic effect of cold, however. In 1848, he described a method of benumbing the skin by gradually reducing the temperature using a pig's bladder containing water, ice, and salt.[4] In 1850, he described two of his patients who applied congelation to their own faces to treat pustules and nevus.[3] He also illustrated in detail how he relieved the pain of a young woman suffering from advanced cervical cancer using a mixture of ice and salt inserted virginally via a speculum. Although there were several alternative treatment options to relieve cancer-induced pain, including opium and mercury, Arnott believed that the patient's life was actually shortened by the side effects of the drug. He stated:

> I shall show, in the first place, by a report of a case of cancer treated by an anaesthetic temperature or congelation, that it furnishes us with a perfect means of relieving the pain of that dreadful disease, without producing the stupefaction and disturbance of the system that attends the use of narcotics; and that, instead of precipitating the unfortunate patient's fate, like these, congelation, by arresting the accompanying inflammation, and perhaps destroying the vitality of the "cancer cell," is not only calculated to prolong life for a great period, but may, not improbably, in the early stage of the disease, exert a curative action.[3]

From 1854 to 1863, Arnott published several articles and letters giving detailed instructions on the use of his method and comparing it favorably with other forms of inhalation anesthesia.[4]

In 1866, Benjamin Richardson described ether spray.[5] The simplicity and cleanliness of ether spray ensured its gradual adoption and replacement of Arnott's method. However, ether was later replaced by ethyl chloride for cold analgesia after being described by Redard in 1891.[5]

Several scientific developments took place at the end of the 19th Century. In 1877, Cailletet of France and Pictet of Switzerland began developing adiabatic expansion systems for cooling gases, enabling the liquefaction of oxygen and nitrogen in small quantities.[6] Dewar of the U.K. designed the first vacuum flask in 1892, facilitating the storage and handling of liquefied gases; and in 1895, von Linde of Germany began the commercial production of liquefied air.[6] The first physician to use liquid air was Dr. Campbell White from New York, who in 1899 used it to treat various skin conditions.[7] The liquid air was applied to the skin via spray, swabs, or a brass roller.

THE TWENTIETH CENTURY

Liquid air, mostly oxygen, was difficult to obtain, as well as toxic and highly explosive. Therefore, it was little used and was replaced by solidified carbon dioxide by Dr. William Pusey of Chicago in 1907.[8] Pressurized liquid carbon dioxide was stored in cylinders; when released, the decrease in the pressure caused freezing and the formation of white "snow". The snow was collected and compressed into suitable shapes, commonly as a stick

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FIG. 1. Dr James Arnott.

for skin applications. In the 1930s and 1940s, several instruments cooled by carbon dioxide snow were described to treat skin and gynecologic disorders, none of which offered significant advantage over the simple stick.[6]

Until this stage, the physicians who used the cooling devices usually had invented them as well. However, greater engineering was required to develop cryosurgical instruments. Hence, the two professions separated. Temple Fay, a neurosurgeon from Philadelphia, and George Henny developed the first closed cryosurgical system in 1938.[9] They used hollow instruments to deliver a mixture of ice and saline to various tissues (Fig. 2). Fay was fascinated by the observation that metastatic tumors are seen almost entirely within areas of higher segmental body temperature, while the distal extremities rarely harbor metastatic lesions. This finding led him to investigate the effect of cold on advanced malignancies. He concluded that application of subnormal temperature resulted in gross retardation of tumor growth and size and relief of local pain. He also observed that tumors treated with cold underwent marked degenerative and necrotic changes.[9]

After the Second World War, liquid nitrogen became available commercially and was introduced into clinical practice by Allington in 1950.[10] The liquid nitrogen was applied to the skin using cotton swabs, which resulted in superficial (2-mm) freezing. Therefore, the technique was used mostly to treat noncancerous skin disorders. In 1959, Rowbotham, a neurosurgeon from England, and his colleagues, who were impressed by the poor results of treatment of brain tumors, developed a complex apparatus (Fig. 3) to apply intense cold to small areas of the brain using a cannula.[11] The cooling agent (95% alcohol) was circulated through the chamber in the vacuum flask (containing solid CO_2 and acetone) to the tip of the cannula, reaching a temperature of $-20°C$.

Tytus and Ries[12] experimented on dog's brain, liver, and pituitary gland using a Freon system. They also conducted preliminary experiments using liquid nitrogen and a probe developed by the Boeing Airplane Company's Research Development Center. They managed to achieve a temperature of $-190°C$.

The first description of a closed liquid-nitrogen system is credited to Cooper and Lee from New York in 1961.[13] The cooling cannula, which is insulated except at the tip, is similar to the liquid nitrogen probes used nowadays. The system was designed to produce cryogenic lesion in the brain for treatment of Parkinsonism and other neuromuscular disorders. Since then, interest in the value of cryosurgery in other branches of medicine flourished. It was used to treat cervical cancers, cancer of the oral cavity and rectum, ear problems, nasopharyngeal an-

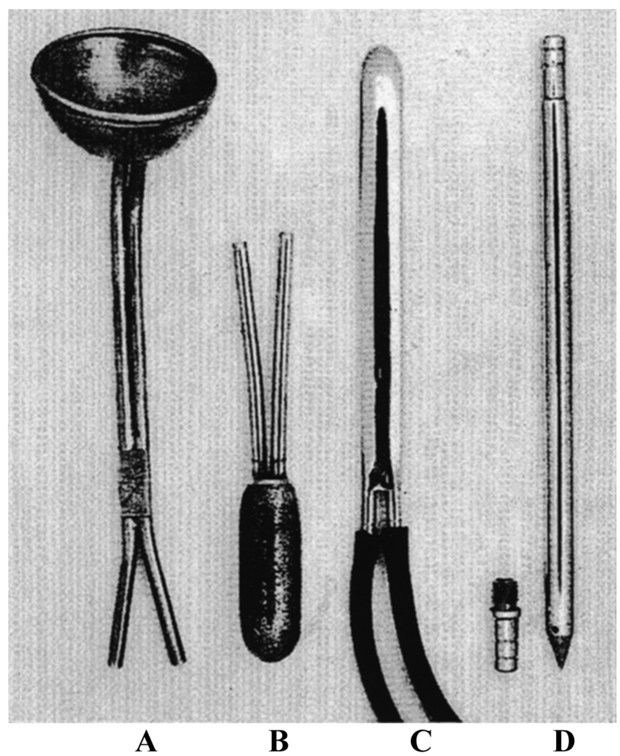

FIG. 2. Hollow instruments developed by Fay and Henny. (**A**) Vaginal cup for cold application to the cervix. (**B**) Vaginal bomb for eroded tumor cavity. (**C**) Hollow knife blade for soft tissues such as breast and brain. (**D**) Hollow pin for deep tumor masses, including long bones. Reprinted with permission from Surgery, Gynecology & Obstetrics (now Journal of the American College of Surgeons).

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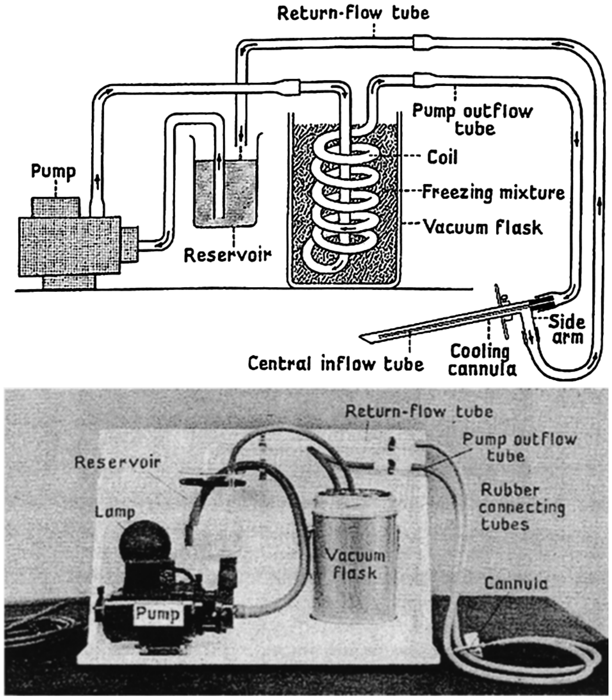

FIG. 3. Rowbotham's cooling cannula system. Reprinted with permission from reference 11.

giofibromas, skin disorders, bronchial cancers, and bone tumors.[6]

CRYOSURGERY IN UROLOGY

The first interest in cryosurgery in urology was by Maurice Gonder of New York. In 1964, he and his colleagues started experimenting on canine prostate[14] and concluded that freezing causes necrosis and cellular breakdown. Two years later, they published the first report of prostate cryosurgery in 50 patients with benign hyperplasia or prostate cancer.[15,16] The prostate was frozen using a single 26F liquid-nitrogen probe, only the tip of which was cooled (−160°C). The probe was placed urethrally, and the temperature was monitored continuously by a single thermocuple positioned between the rectal wall and the prostate (Fig. 4). When the thermocouple temperature approached 0° or there was any fixation of the rectal mucosa, the procedure was terminated.

Between 1969 and 1971, Flocks and colleagues[17] treated 11 patients with prostate cancer by open perineal cryosurgery using a flat probe applied to the prostate under direct vision. This technique provided good visibility of the prostate and reduced the risk of rectal damage.

Two years later, the technique was further modified by Megalli and associates,[18] who used a single 18F liquid-nitrogen probe placed in the prostate transperineally. The probe had to be relocated more than once during the procedure to ensure complete freezing of the prostate. The indications for cryosurgery were limited to high-risk and older patients. In addition, complications, including fistula and incontinence, remained significant because of the lack of adequate monitoring techniques. Therefore, urologists started to lose interest in cryosurgery in the late 1970s.

In 1988, Onik and coworkers described the ultrasound characteristics of iceballs,[19] and 3 years later, they published the results of their experiment on dog prostate.[20] They performed cryosurgery on six canine prostates under transurethral ultrasonography (TRUS) guidance, and they concluded that the area of the iceball on TRUS corresponded to the cryolesions on pathologic examination. Onik and his colleagues then demonstrated that TRUS-guided prostate cryosurgery in men with prostate cancer is safe and documented good preliminary results.[21] This was one of the most important landmarks in the history of cryosurgery and led to the resurgence of interest of prostate cryosurgery.

The 1990s have witnessed further developments, including the introduction of thermocouples and urethral warming catheters.[22] In 1996, multiple-port high-pressure gas systems that utilize the Joule-Thompson effect (high-pressure gas changes temperature when released to a lower-pressure area) have also been developed, and third- and fourth-generation cryosurgery machines have been introduced in the 21st Century. These advancements have led to greater efficiency and fewer complications of modern cryosurgery in treating men with localized prostate cancer.[22]

Interest in kidney cryosurgery began more than 10 years ago with experiments by Onik and coworkers on five dog kidneys in 1993.[23] Two years later, Uchida et al.[24] from Japan performed percutaneous cryosurgery for kidney cancer successfully in two patients. Recently, several approaches have been described to access the kidney for freezing, including open, laparoscopic, and percutaneous.[25]

The development of cryosurgery has progressed in stages, usually triggered by technological advancements, and has been closely linked with advancements in low-temperature physics and engineering and with refinement of instruments. The journey of cryosurgery is ongoing, and the current and future technologies have the potential for even greater improvement in efficacy and safety.

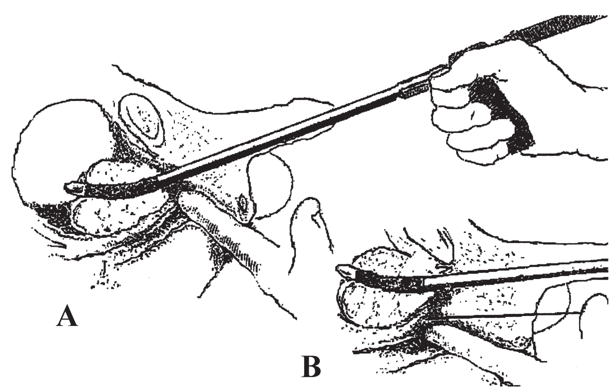

FIG. 4. Positioning of Gonder's liquid nitrogen probe (**A**) and thermosensor (**B**). Reprinted with permission from reference 16.

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