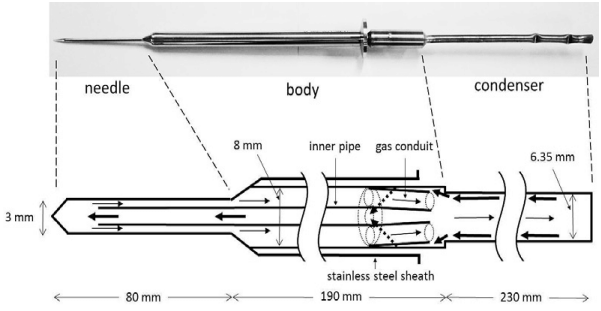
The Evolution of Cryogenics in Medicine

Damian Martinez Pineda '21

A historical perspective on the clinical applications of cryogenics

The field of cryogenics, or the examination of how materials behave at extreme low temperatures, has had a long history filled with constant advancement and ingenuity. Cryogenics has found much success in disciplines such as physics, biology, and chemistry. In medicine, it has added another tool for the removal of tumors and skin abnormalities among other new methods. The first use of cold temperatures in medicine was done by Dr. James Arnott in 1819, where he used a mixture of salt and crushed ice for the palliation of skin tumors. This new method showed the power in using cold substances in dermatology as James Arnott went on to win a prize in 1851 at the Great Exhibition of London (Cooper *et al*., 2001).

From then it seemed that the most logical way forward was the development of substances that could achieve colder temperatures since the salt and ice mixture could only reach -24°C. Although this could reduce pain and hemorrhaging of tumors, this temperature couldn't treat them more effectively. The next improvement didn't come down the road until about 26 years later when the first refrigerants, liquid oxygen and liquid air, were created. They showed promise as they could achieve temperatures that could effectively treat a wide range of skin abnormalities such as lupus erythematosus, herpes zoster, warts, varicose leg ulcers, carbuncles and epitheliomas (Cooper *et al*., 2001). However, the technological capabilities at the time limited its spread and usage since it was quite difficult both obtaining liquid air and transporting it. As a result, a new innovation arrived known as carbonic acid snow in. First introduced by William Pusey it was a novel way to use liquid carbon dioxide gas stored under pressure. When the gas in the can was allowed to rapidly escape it caused a sudden and drastic drop in temperature which resulted in the creation of a fine snow. Pusey's phenomenal before and after images of the treatment of a large black naevus on a woman's face helped propel its use since it showed the power of cold temperatures against melanocytes and its popularity with treating acne. None the less liquid air was still unequivocally the best cryogenic at treating the most conditions. Although, Liquid air's difficulty in acquisition persisted a similar substance was discovered- liquid nitrogen. With these new cryogenic available colder temperatures reaching -196°C were achieved and its similar properties to liquid air led to an explosion in its use which is still prevalent today. With the development of these techniques for cryosurgery physicians needed a way to properly administer these substances to the right places and in right amounts in order to make them more suitable for general use and allow any doctor to have this tool at their disposal. Thankfully Torre and Zacarrian led the way in cryosurgical equipment. In 1965-1967 these two entities created a liquid nitrogen spray. Furthermore, Zacarrian developed a more hand-held version of the spray and even developed the first few copper probes to allow the freezing capabilities of liquid nitrogen to go deeper- initially about 7mm.



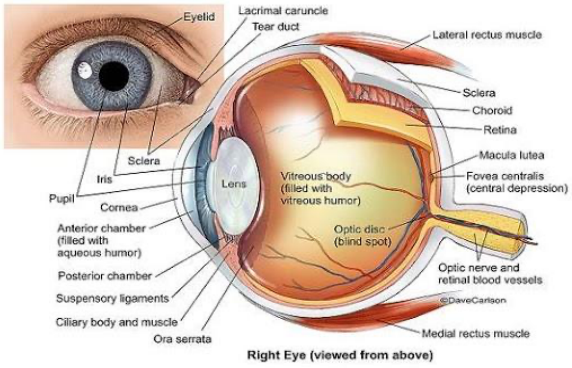
Typical cryoprobe structure (adapted from Google image search)

Alongside ablation cryosurgery the use of cold temperatures in amputations also came in 1938 when Allen showed that limbs packed in ice for 3 hours could then be amputated without the use of anesthetics (Cooper *et al.,* 2001). This technique with the creation of better anesthetics did not persist but it expanded our knowledge and showed the use of colder temperatures in tissue preservation.

Current uses of cryogenics in medicine

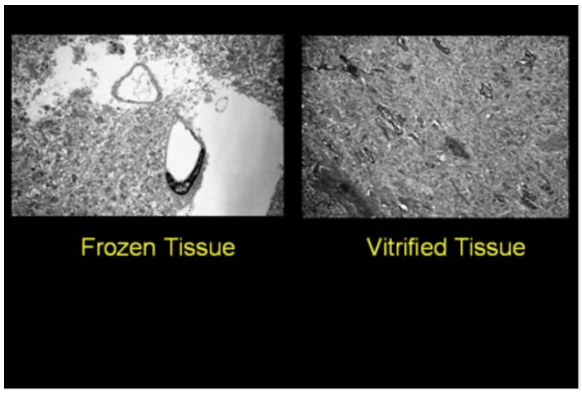
Currently, the use of cryogenics such as liquid nitrogen for ablations of tissues still persist. The impressive thing about its use is that other than later introduction of liquid argon its use and applications haven't changed much since its original discovery in 1950. The procedure for a surface level ablation involves the direct application of the liquid nitrogen with a cotton swab or spray onto the tumor. For deeper tumors the use of image guidance allows a physician to insert cryoprobes through the skin to reach the desired location. A cryoprobe is also quite simplistic as well it comprised of a thin wand like device with a needle like projection at the end and depending on the depth needed a longer tip can be added. From the other end the wand is attached to a tank filled with the cryogen via a hose and for these subcutaneous, below the skin, procedure liquid argon is what is prominently used. Sometime due to the severity or the depth of the condition an incision will be made on the skin to aid the cryoprobe in reaching its destination. Once the probe reaches its destination the trigger on the wand allows the physician to control both when and how much cryogen is used on the tumor. The liquid argon emitted from the probe worked because cells cannot withstand the cold temperatures for a multitude of reasons. The direct application causes ice to form on the exterior of the cell which cause fluids inside the cell to move out of the cell causing it to dehydrate. Alongside the exodus of water from inside of the cell in the water inside the cell can also freeze and forms ice crystals that cause the cell to expand due to the structure of ice being larger than water and the cell will burst. These things happen in conjunction which limits the vascularity of the tumor and in the end causes the tumor to due. Typically, a cycle takes 10-15 minutes with some exceptions that could take longer and in a procedure two or three cycles are used. This procedure with certain modifications of probes can be used from skin to even in gynecological situations with the ablation of warts and tumors of the vulva, vagina, and cervix.

Another prominent procedure used today is cryoextraction which is used in practice of ophthalmology. In ophthalmology it's used for the extraction of a cataract in patients with glaucoma. In this procedure we focus in the lens of the eye which is mostly comprised of water and proteins. The proteins in the lens with age can begin to clump together and cause a clouding of the lens known as a cataract. Currently there are many methods in which this clouded lens can be extracted and replaced with an artificial lens made of plastic or silicone. Procedures include phacoemulsification which is the use of an ultrasonic device to break up the lens into tiny pieces. and then be extracted using a vacuum device. Another procedure includes extracapsular extraction which uses a large incision to take out the capsule in one piece and then the replacement lens is added ("Cataract Surgery", 2009). However, due to other circumstances such as weak zone support of the lens can make extracapsular surgery and phacoemulsification riskier as even experienced and dexterous surgeons could cause damage to the eye. As a result, a third technique known as intracapsular extraction is used. In this procedure the film on the exterior of the eye is cut an incision is made on the edge of the iris. From then support sutures are added to prevent further tearing caused by the incision. Once a properly sized hole is made the cornea is then lifted and the surface of the lens is cleaned with a sponge. Then a cryoextractor is placed onto the lens. The cryoextractor is a specialized cryoprobe that emits cryogenic liquid nitrogen to freeze the lens and due previous efforts to dry the surface of the lens it will allow for the full lens to freeze. Once frozen onto the extractor the lens can then be removed in one piece. From then the artificial lens is inserted using a guide and the incision is closed up. (Hovanesian 2010)



Parts of the eye

With the prevalence of cryosurgery, it can be easy to forget the other uses of cryogenics in medicine but one of the pivotal applications of cold temperatures is its preservative properties of biological cells and tissues. With its use in organ preservation this simplistic application can mean life and death for a patient. Organs during the donation surgery, in cases where the donor is deceased, are flushed with an ice-cold preservative solution comprised of impermeant agents, osmotic molecules that prevent cell swelling, nucleotide precursors to sustain a low metabolic rate, antioxidants, enzyme inhibitors, buffers and electrolytes (Papas *et al.,* 2020). The body cavity containing the organ can then be placed around the organ to further cool it. Once the organ is removed it is placed in a sterilized container and then place in an ice slush solution. The only exception to this process is the kidney which is placed in a specialized machine which constantly pumped with the preservative solution. Although these preservation techniques don't particularly include the freezing of the organs other efforts have made it possible for the freezing of smaller organic substances such as sperm and embryos. This process is known as vitrification. Similarly, to how cryogenics can destroy cells in a tumor in tissues this occurs to any cell. The ice forms in between the cells causing damage to the cell and overall a compromise in the structure of the kidney. In the vitrification process a cryoprotectant is added prior to freezing the cells. This protectant allows the

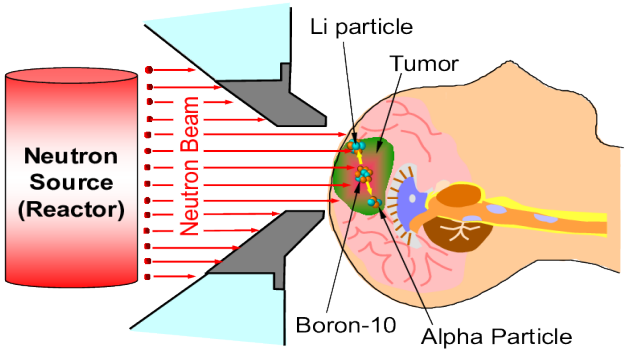


A comparison of frozen vs vitrified tissue

water in the cells to move closer to one another and move very slower and slower but prevents the water molecules from forming into an ice formation. Eventually the water molecules move so close to one another that they stop moving, occurs at below -100°C, and the cell in a sense are solidified. This is used in the preservation of smaller tissues, as mentioned above, primarily for sperm and embryos but efforts in the future will possibly see the rise in its use in larger tissues and possibly organs. (Alcor, na)

The Future

With all its current utilization and rich history the field of cryogenics in medicine seems to be ripe with future endeavors. One such advancement has made headway more recently. This such utilization is in neutron therapy. This form of radiation treatment might seem to not have much to do with cryogenics but in the hardware, it is a key part in its functioning. Much like in the field of chemistry and its use of Nuclear Magnetic Resonance (NMR) which uses a large magnet to flip magnetic fields in the nuclei of the atoms. The magnet is able to emit this energy due to it being a superconductor. Once the energy emitted stops the nuclei flip back and emit a signature amount of energy giving us a fingerprint like spectra. Much like with NMR, the neutron therapy apparatus uses a magnet that is cooled in order to create a superconductor as the cold temperatures reduces the amount of collision between electrons and they move more freely.



Neutron therapy

The value of neutron therapy is that it produces a type of radiation that is more suited for radioresistant tumor types in which conventional radiation doesn't affect it. (Porterfield 2015) The neutron radiation created from these apparatuses is very different from other conventional radiations such as photon, electron, and proton. The former is classified as high linear-energy-transfer (high LET) while the latter is categorized as low linear-energy-transfer (low LET). In low LET the damage is done by activating radicals which are highly

reactive particles that damage the DNA of a cell leading to the reliance of low LETs on oxygen molecules to create these radicals. Another drawback is that low LETs is dependent on the life cycle stage of the cell they are attacking and therefore make it very hard to attack large tumors. With all these difficulties there is a chance for the cell to repair itself due to the fact that this form of radiation generally only effects one strand of the DNA and can't reach others by either lack of radicals created or the cells life stage. On the other hand, high LETs work on a more nuclear interaction and so it doesn't rely on oxygen and its effectiveness isn't determined by the cells life cycle therefore the chance of cellular repair is very small. Neutron therapy's only drawback is how easily it diffuses and so pin point accuracy is necessary in order to not damage other healthy cells. As a result, this technique lies heavily imaging techniques such as computed tomography (CT) scan, magnetic resonance imaging (MRI) and positron emission tomography (PET) scans in order to establish proper orientation of the beams application. The typical procedure can last about 30-60 minutes depending on tumor severity and if metastasis, spreading of tumor to other locations, has already occurred chemotherapy will also need to be done as a supplementary procedure. (Fermilab)

While the work with neutron therapy has seen much application in today's practicing medicine some other developments have gotten close but still have a long way to go before application in the field. One such development is the use of better methods for organ preservation and possibly the use of vitrification for larger organs. Currently organs can only be preserved from of range of 4 to 36 hours depending on which organ it is. For example, the heart and lungs usually last the least ranging from about 4-6 hours for the heart and 6-8 hours for the lungs. While more resilient organs such as the liver and kidneys last 12 hours and 24-36 hours respectively. (Lanese 2019). New research into methods and different solutions have noted that the next step is increasing the max time from 36 to a complete 48 hours, but that is still years if not decades away. This has shifted attention to the use of vitrification. Although the methodology for vitrification is already in use and shown its wonders with its application to sperm and embryos the main problem is that the cryoprotectants used are very toxic to larger human tissues and organs. Along with that there also seems to be a problem with damaging ice formation that occurs in the thawing process. If an organ is thawed out too quickly then fragile organs crack and if thawed out too slowly then the issue with the formation of ice nuclei occur. Studies by scientist such as Fahy have tried using other cryoprotectants at varying and nontoxic levels the thawing process seems to be the limiting factor in further developments. (Scudellari 2017). Alongside technical issues there is a more practical issue of lack of collaboration among fields and partnering grants can help to alleviate this but this only throws a band aid over the wound.

A final complication that needs to be tackled pretty soon is our eminent loss of helium. Helium is a very useful cryogenic in the use of cooling magnets in order to produce super conductors much like the ones used in NMR and Neutron therapy. The problem with helium is that unlike nitrogen which can be extracted from our air helium is created via the nuclear decay of uranium and thus has to be mined. Once it is released it is very uneconomical to recapture and it is so light that it will eventually leave the atmosphere so it is a non-renewable resource that most seem to take for granted. Although there were some efforts to stockpile the gas in the mid 1970's, government policy has forced this stockpile to be sold at below market price, leading to the current increasing prices of the precious element (Forbes 2016). As the future unfolds, it will take many efforts to solve the still-evolving dilemma of helium scarcity.

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