Cryogenic Freezing of Brain Tumors for Excision or Destruction in Situ*

IRVING S. COOPER, M.D., AND STANLEY STELLAR, M.D.
Department of Neurosurgery, St. Barnabas Hospital, New York, New York

The first report of the local application of cold in the treatment of neoplasms was published in England by James Arnott in 1851. Since that time, there have been many investigations that indicated the potential usefulness of cooling or freezing of biologic tissues in order to destroy malignancies. Smith and Fay reported intensive investigations of generalized lowering of body temperature in an attempt to inhibit neoplastic growth. Most students of this problem, however, concluded that the method of generalized hypothermia was too hazardous and too uncertain in its effects to be employed consistently for the purpose of inhibition of tumor cells.

The local application of cold has been employed more successfully. However, the lack of adequate instrumentation has prevented the realization of the potential value of extreme cold as a surgical tool. Nevertheless, the studies of Rowbotham et al., Hass and Taylor, Bory, Ries and Tytus, and others, have indicated that local application of extreme cold might facilitate the destruction or removal of certain types of brain tumor.

It is the purpose of this report to describe our use of a cryogenic surgical system to freeze various types of brain tumors for the purpose of producing local necrosis of the tumor in situ, or to facilitate the removal of the tumor as a solid frozen mass.

Instrumentation

During this investigation we have employed the cryogenic surgical system developed at St. Barnabas Hospital for physiologic studies in animals and humans, as well as for creation of lesions for physiologic surgery within the nervous system. The same system may be employed for congelation and necrosis of tumors in the nervous system and other parts of the body. A series of graduated, vacuum-insulated freezing cannulae has been developed. These are capable of producing variously sized and variously shaped areas of freezing in biologic tissue (Figs. 1 and 2).

Employment of this system provides for the rapid selection of any temperature between +37°C and -196°C, the temperature of the liquid nitrogen which refrigerates the system. Only the tip of the cooling cannula is not insulated. Thus, the freezing temperatures are applied only to the precise area selected. A more complete description of the entire system has been published in an earlier report in this Journal.

The Biologic Effects of Freezing

Ordinarily, during the rapid reduction of temperature of biologic tissue, the temperature will fall to as low as -15° or -20°C, before ice crystals begin to form within the tissue. This period of extreme coldness below the freezing point but prior to formation of ice crystals is referred to as supercooling.

Following the period of supercooling, there is a rise in temperature or recalorization, back up to the freezing level of -2.8°C. During this period of time the transfer of energy which occurs during the removal of heat from cells is being used to form crystals rather than to lower the local temperature of the tissue fiber. This use of the energy of heat transfer to form crystals is referred to as the latent heat of crystallization. This prior supercooling results from the fact that there are very few nuclei in biologic tissue on which crystals may start. However, once formation of nuclei and crystallization begin, a heat-jump back up to the freezing level will occur. As crystallization proceeds, further application of cold will be followed by additional lowering of the temperature. The eventual

Received for publication April 25, 1963
This study was assisted by a grant from the John A. Hartford Foundation, Inc.
depth to which the temperature of the tissue may be taken will depend on the original temperature of the freezing agent.

Five mechanisms through which extreme cold produces chemical and morphologic destructive changes in tissue have been described thus far.\textsuperscript{15,18,23} These are: dehydration and toxic concentration of electrolytes caused by removal of water from solution; crystallization with rupture of cellular membranes; denaturation of liquid-protein molecules within the cell membrane; thermal shock; and vascular stasis.

The potential usefulness of a cryogenic system for controlled freezing and necrosis of primary or metastatic tumors is demonstrated readily by an examination of the lesions produced consistently by this method in the laboratory animal. The cryogenic vacuum-insulated cannula placed within the liver, kidney, brain, or any other biologic tissue produces a spherical frozen lesion, the diameter of which is directly proportional to the size of the freezing surface and the temperature of the tip of the cannula. The edge of the frozen lesion is demarcated sharply from adjacent tissue. When the lesion is allowed to thaw, the cannula may be lifted from its center without adherence of any tissue to the tip of the cannula. There is no visible bleeding from the site of the lesion. Within a few minutes after thawing, the lesion becomes a very dark blue, indicating deoxygenization, but retains its sharply demarcated spherical character. Subsequent to thawing the frozen lesion may be incised without production of any significant hemorrhage. A control incision in an adjacent non-frozen tissue invariably will produce continuous hemorrhage.\textsuperscript{22} These characteristics of the cryobiologic lesion, which make it an extremely useful instrument for the surgery of tumors within the brain, are illustrated in Fig. 3.

Further indication of the possible usefulness of extreme cold to congeal and subsequently produce necrosis of malignant tissue, both primary and metastatic, in various parts of the body has been demonstrated by biopsy of various tumors before and after the application of extreme cold. Such a case is illustrated in Fig. 4, which demonstrates the effect of freezing the center of a large ependymoma, located within the third ventricle of the brain. In this case the specimen taken from the center of the tumor which was frozen was found at autopsy to be totally

\textbf{Fig. 1.} Variously sized and shaped vacuum-insulated cannulae which form part of the cryogenic surgical system.

\textbf{Fig. 2.} Lesions frozen in gelatin by 2 vacuum-insulated cannulae $\frac{1}{3}$" and $\frac{1}{4}$" respectively in diameter. The former produced a frozen ice ball $\frac{1}{2}$" in diameter, the latter an ice ball $\frac{3}{4}$" in diameter.
necrotic 8 days following the application of extreme cold. Freezing did not extend beyond the central part of the neoplasm and its periphery was unchanged. Unfortunately, operation was performed when the tumor had already grown quite large and the patient was near a terminal state. There was no clinical change following the operation. The individual susceptibility of different types of tumor to cold, the differential, if any, between malignant and nonmalignant tissue, and the usefulness of repeated freezing and thawing in order to insure total necrosis of the tumor, are factors under investigation at the present time.

**Physiologic Applications of Cryogenic Surgery**

Our development of the cryogenic surgical system was motivated by the need for an instrument capable of producing reversible physiologic inhibition as well as permanent circumscribed lesions within the brain. This system now provides an ideal method for surgery of the basal ganglia for parkinsonism. We have employed cryothalamectomy in a consecutive series of 1000 cases. The mortality rate was 1 per cent while the risk of lasting hemiplegia was .025 per cent. The postoperative course following the freezing thalamic lesion usually is uneventful, and a thalamic lesion of sufficient size to relieve tremor and rigidity is well tolerated, even in the aged. A detailed statistical report of the first 1000 cases of cryothalamectomy will be published separately.

It is our opinion that cryothalamectomy is the treatment of choice for tremor and rigidity of parkinsonism, as well as for relief of intention tremor of multiple sclerosis and certain cerebellar diseases, for dystonia of various etiologies, and for torticollis. In the case of the last syndrome, we have found that simultaneous infliction of bilateral cryothalamic lesions is well tolerated and offers an excellent chance of alleviation of torticollis. The clinical and physiologic implications of this latter study will be published separately.

Cooling inhibition followed by infliction of cryogenic lesions is now being investigated in selected cases of convulsive disorder, as well as in the therapy of intractable pain.

**Cryogenic Surgery for Brain Tumors**

We have investigated the use of freezing necrosis of deep, otherwise inoperable, brain tumors in a small series of 12 cases, which included gliomata, meningiomata, metastatic malignancies and tumors within the sella turcica. This aspect of our investigation represents an extension of our earlier study of chemosurgery for deep intracerebral gliomata.9 This latter investigation demonstrated the possibility of selectively destroying a major portion of deep intracerebral gliomata from within, by placement of a cannula into the tumor and injecting a neurolytic agent into it under roentgen-ray control. The possibilities inherent in such an approach are indicated, to some extent, by the case illustrated in Fig. 5. This patient

---

Fig. 3. (Above) Sharpily delimited spherical lesion formed in kidney of cat by cryosurgical cannula. (Below) Incision in the thawed lesion does not produce significant hemorrhage.
Fig. 4. (Left) Photomicrograph of ependymoma of third ventricle. Section taken from perforated tumor. (Right) Completely necrotic center of same ependymoma following freezing at $-100^\circ$C.

Fig. 5. (Left) Ventriculogram demonstrating massive shift of ventricles caused by inoperable deep intracerebral glioma. (Right) Return of ventricles to midline following chemosurgical destruction of center of tumor, followed by necrosis in situ.
had a biopsy of proven astrocytoma in the left parietal lobe. Treatment was given by means of a balloon-cannula placed into the tumor under roentgen-ray control. Absolute alcohol then was injected through the cannula into the tumor in an effort to produce lysis of the neoplastic tissue. The air studies, which were done 11 months apart, show that the shifted ventricular system has now returned to the midline. From this it was concluded that the alcohol had had a destructive effect on the tumor.

A similar approach to deep intracerebral tumors has been employed using the freezing cannula. By means of arteriography, air contrast studies, or brain scanning, the center of an intracerebral tumor may be roentgenographically charted, and the freezing cannula is inserted into this target through a trephine opening. This is performed best under local anesthesia, but may be carried out under general anesthesia if necessary. Various areas of tumor surrounding the tip of the cannula may be frozen selectively and necrosed, the ultimate area of necrosis depending upon the size of the cannula and the depth of temperature at the freezing tip (Fig. 6).

The use of this system to facilitate removal of superficial gliomata offers certain advantages which ease the approach to this type of tumor. By freezing a superficial intrinsic brain tumor into a solid mass, its extraction is facilitated in the following manner. There is immediate shrinkage of the tumor and the adjacent brain, the tumor itself being frozen into solid mass, while the adjacent brain for several millimeters is hypothermic. The frozen mass is totally avascular, while the adjacent hypothermic brain also provides a relatively bloodless field. Gliomata, which ordinarily are gelatinous and difficult to manipulate may be transformed into solid more easily handled tissue. Under visual control the freezing may be stopped at or just beyond the boundary of the tumor and an artificial cleavage plane thus is formed. This cleavage plane is not necessarily the actual border of the tumor. Rapid resection of the frozen tumor is facilitated and further abetted by adherence of the tumor to the brain cannula. The following case report demonstrates the use of the cryogenic surgical system for this purpose.

Case 1. A.L., a 48-year-old male, underwent craniotomy in another hospital because of headaches and left-sided Jacksonian convulsions. Operation revealed a large vascular glioma in the right side of the hemisphere underlying the motor area. It was considered to be inoperable but was confirmed by biopsy to be an astrocytoma. Despite radiotherapy the patient’s symptoms worsened and left hemiparesis and bilateral papilledema developed.

Craniotomy was performed at St. Barnabas Hospital in October 1962. The tumor was exposed, frozen solid by the use of the cryosurgical cannula and removed en bloc. The postoperative course was uneventful and the patient was discharged markedly improved 2 weeks following operation.

Case 1 illustrates the use of freezing of a brain tumor in order to facilitate technically its removal.

The following case report demonstrates the use of the freezing cannula for tumors within the sella turcica.

Case 2. J.B., a 16-year-old girl with signs and symptoms of a craniopharyngioma, was treated
by right frontal craniotomy. A cyst was evacuated and biopsy was taken. The tumor then was frozen with the cryocannula in five separate places (Fig. 7), dropping the temperature to \(-100^\circ\text{C}\) for 3 min. each time. The tumor could be seen shrinking away from the optic chiasm. Recovery was excellent and the patient was discharged on the 8th postoperative day. Visual-field studies showed a slight diminution in the left field including diminution of acuity from 20/60 to 20/80 but studies a few weeks later showed improvement. In the right eye acuity was 20/20 and the field showed expansion.

We also have found this system to offer the possibility of considerable assistance in facilitating the removal of more circumscribed tumors such as meningioma. Certain advantages already referred to, such as conversion of the tumor into a solid, hard, frozen mass; complete avascularity of the tumor; accentuation of the cleavage plane between the tumor and adjacent brain; hypothermia of the adjacent brain; and ease of traction because of adherence of the tumor to the cannula all speed up and facilitate the removal of this type of tumor. The following case report serves as an example.

Case 3. M.O., a 67-year-old woman with a suprasellar meningioma, was treated by means of a bifrontal exposure and insertion of the cryocannula (Fig. 8). Temperature was dropped to \(-180^\circ\text{C}\). The main frozen mass of tumor as illustrated was then rocked out of place (Fig. 9) and remnants of the tumor were removed completely by conventional means. Bleeding was minimal. The carotid arteries and optic nerves were protected. Recovery was uneventful except for temporary mental confusion and flippant behavior. The patient was ambulatory in a few days and was discharged on the 13th postoperative day.

The characteristics of the cryogenic surgical system which we have described also have been demonstrated in an investigative series of neoplasms in other parts of the body. We have employed the cryosurgical cannula for freezing of tonsils, to facilitate removal of cataracts of the eye and for otherwise inoperable neoplasms within the gastrointestinal tract, uterine cervix and thorax. Its employment in these more accessible loci corroborate the avascular, controllable, circumscribed nature of the frozen lesion, as well as the fact that it is tolerated by the patient without any generalized reaction.

Comments

Our experience with cryogenic surgery for brain tumors is limited. Therefore, the data and conclusions incorporated in this report

Fig. 7. Case 2. Roentgenogram demonstrating placement of cryosurgical cannula into solid intrasellar craniopharyngioma.

Fig. 8. Case 3. Suprasellar meningioma in situ frozen completely solid by cryosurgical cannula. Lower arrow on cottonoid; retracted frontal lobes point to tumor. Upper arrow points to cannula.
Cryogenic Freezing of Brain Tumors

are presented as preliminary findings. Nevertheless, our studies thus far indicate that cryogenic surgical techniques will facilitate surgery of brain tumors.

By freezing superficial intrinsic tumor into a solid mass its extrication is facilitated by producing immediate shrinkage of the tumor and adjacent brain, transformation of the semisolid tumor into a solid frozen block with production of an artificial cleavage plane between this block and the adjacent tissue, total avascularity of the tumor with decreased vascularity of the adjacent hypothermic brain, and ease of traction of the tumor by its adherence to the cryosurgical cannula.

The use of the cryosurgical cannula to freeze deep, otherwise inoperable tumors, such as thalamic glioma or metastatic tumors, offers the possibility of producing necrosis within the mass of tumor, which otherwise might be unapproachable surgically, and which usually is refractive to roentgen-ray therapy. In such cases operation can be performed under local anesthesia by a trephine opening, the cannula can be placed accurately into the mass of tumor by employing arteriography or other known methods of tumor localization, and the procedure usually is tolerated without incident. Such a procedure can be performed in stages to minimize risk and to decrease the likelihood of postoperative morbidity.

The effect of freezing will vary in different tumors, depending on the location of the tumor, type of tissue, and particularly on the vascularity of the tumor and the adjacent brain. In the case of extremely vascular masses of tumor, such as arteriovenous aneurysms, it may be necessary to occlude temporarily the major feeding arterial channel, in order to obtain satisfactory freezing. If this is not possible, it may be necessary to use more than one cannula in order to dissipate all of the heat being brought in to the extremely vascular mass of tumor. In some cases, it may be necessary to freeze and thaw a deep tumor several times, in order to produce total necrosis of the tumor. Furthermore, one must expect that freezing necrosis will take place only in that part of the tumor reduced to a temperature of $-20^\circ$C. or lower. Therefore, it will be necessary to extend the frozen area a few millimeters beyond that area which one wishes to destroy by freezing necrosis. These, and other technical factors, remain to be perfected.

Conclusions

Within biologic tissue extreme cold is anesthetic, hemostatic, physiologically reversible, controllable, and tolerated without insult to the remainder of the organism. It is completely destructive of the tissue that is exposed to the cryogenic lethal range of temperature. This area of destruction is delimited sharply from adjacent tissues. Therefore, the application of extremely low temperatures within deep brain tumors offers a useful method of congelation and necrosis of this type of tumor within the brain.

Deep freezing also facilitates the removal of superficial brain tumors, either glioma, meningioma, or other types of neoplasm. The extrication by freezing of a tumor is facilitated by producing shrinkage of the tumor and adjacent brain, avascularity of the tumor and hypothermia of the immediately adjacent brain, transformation of a soft
tumor into a solid block with accentuation of the cleavage plane between this block and the adjacent brain, and ease of traction of the tumor by its adherence to the cannula.

The cryogenic surgical system and its series of freezing cannulae provide a simple, rapid, controllable and safe method for the application of extreme cold to the surgery of neoplasms of the central nervous system. The advantages inherent in this system make it a valuable addition to the present techniques of brain-tumor surgery.

References

9. Cooper, I., and RIKLAN, M. Cryothalamectomy for abnormal movement disorders. St. Bar-


Discussion

Dr. Collin S. MacCARTY: Dr. Cooper has introduced an ingenious device for the production of reversible and permanent lesions in the depths of the brain for the treatment of hyperkinetic disorders. Our experience is quite limited with this instrument.

[Slide] We have, however, recently operated upon some brain tumors, utilizing the instrument described by Dr. Cooper. The probe was in the tumor, a glioblastoma, for 21 min. at -60°C.

[Slide] This is the ball of tumor that was removed.

[Slide] This is a meningioma frozen for 4 min. at -60°C. It is true that the probe is a magnificent handle for the elevation of the tumor.

[Slide] This is the bed of the tumor. This tumor was not entirely frozen, incidentally.

[Slide] This Sturge-Weber malformation was frozen for 8 min. at -50°C. I think the frozen venous vascular anomaly is obvious there and the area of freezing of the brain is obvious, as Dr. Cooper has shown in his cases.

[Slide] This cannula was not pulled out with a frozen ball sticking on it but the area was melted. As Dr. Cooper has indicated, there is no bleeding from the frozen area, but there was some oozing around the zone between the frozen area and the brain.

[Slide] This represents the real problem, as I see it. This was the amount of resection done in the Sturge-Weber malformation. You can realize, from a technical point of view, a time-consuming procedure, and one couldn't freeze the entire parietal-occipital malformation simultaneously.

One other thing that concerned us with the present equipment. Gliomas are rather extensive in our ex-
Cryogenic Freezing of Brain Tumors

experience and they don't grow concentrically. In other words, the extensions of the tumor cannot be frozen selectively, so there are limitations at least in this regard to this treatment. It seems to us that a superficial supratentorial tumor might be frozen successfully and removed; however, the more extensive gliomas cannot be frozen selectively and removed without destruction of surrounding brain tissue.

In our laboratory, Doctors Kerr and Svien have been doing cryogenic hypophysectomies on animals through the transnasal approach. This, it seems, is a method worth further investigation and possibly be utilized for certain intrasellar tumors and hypophysectomies.

The idea of attacking pinealomas and small deep circumscribed tumors appeals to us. We, however, have not as yet had any experiences in this regard.

DR. WILLIAM B. SCOVILLE: I can add little to this most intriguing contribution by Dr. Cooper, except that of praise, a modicum of history and physiologic conjecture.

Historically the local application of cold has fascinated neurophysiologists for nearly a century. Trendelenburg, Cairns and others, all carried out local cooling of cerebral cortex and found a limited spread to deeper structures. Fay and Smith did monumental work finding neoplastic brain tissue was more sensitive to cold than normal and the brain was relatively safe even in extreme cold. Rowbotham, in England, inserted a CO2 and acetone mixture in a tube into the brain with a \(-74^\circ\)C. Even then there was excellent thermal insulation.

Dondey in Paris is carrying out freezing lesions on the basal ganglion, duplicating some of the work of Dr. Cooper; and Negrin, in New York, has chilled the spinal cord and recently the brain surface with cold irrigations.

Five years ago, Dr. George Becker and the speaker carried out experiments at the Hartford Hospital on the possible benefit of local chilling of that part of the brain surface supplied by the middle and anterior cerebral arteries, as a possible substitute for general hypothermia in operations for cerebral aneurysm. Simple continuous irrigations by ice cold saline at 60\(^\circ\)C. over the brain surface were performed bilaterally on 18 cats and 3 human patients. Chilling the surface to 60\(^\circ\)C, was accompanied by no permanent ill effects nor serious changes in vital signs. Needle thermocouples again demonstrated that the brain is an excellent thermal insulator and that the spread of cold was limited largely to 2 cm. Certain temporary physiologic effects occurred in 1 patient, with loss of consciousness only during the application and complete amnesia for the procedure afterwards bringing up the implications of possible use for anesthesia.

Presently, after witnessing the extraordinary sensitivity and delicacy of the new cryosurgery machine as developed by Dr. Cooper and the Linde Division of the Union Carbide Company, the Department of Neurosurgery at the Hartford Hospital has procured such a machine. Its cannula freezes only at its tip. It has a diameter of less than 2 mm., smaller than the lead of a pencil; and it can in a matter of seconds freeze its tip to \(-200^\circ\)C. without adhering to brain substance upon reheating and withdrawal. This means that its uses may become myriad and they constitute a challenge to physiologists, to neurosurgeons and perhaps to anesthetists alike.

By its use we can cause temporary and reversible paralysis of function in various areas in the deeper structures of the brain. Formerly one could only stimulate or destroy these areas. From our small, and others' large, experimental work on cold, it appears that the brain, with its protecting thermal insulating property and the development of the Cooper-Linde smallest cannula, permits a trial application of cold to minute areas of the basal ganglia and even close to the reticular substance and hypothalamic areas, thus opening up new vistas of drug, anesthesia, pain and psychic research.

Lastly, the ability to freeze tissue into solid blocks with a return of blood flow after rewarming offers hope for its added use in vascular anomalies and angiomas. It will not freeze blood vessels when blood is in motion. But if one could occlude for 30 or 40 sec. the incoming artery, permitting a freezing of the whole mass and its contained blood, remove the mass, and then rewarm the surrounding tissue, one might find this instrument a valuable tool. And for larger lesions Dr. Cooper and the Linde Division can perhaps construct small grids or disks with finger projections which will freeze surface lesions to any desired diameter and measurable depth. Such an instrument as this could harness and delimit cold to such precise parameters as to convert it into a figurative knife which may cut through all tissue except blood vessels. A pleasurable thought to a surgeon!

DR. HENRY T. WYCH: I would like to show a few slides on cryogenic therapy, in deference to my former chief, Dr. Temple Fay.

About 25 years ago, Dr. Michael Scott, Dr. Augustus McRavey and myself were working with Dr. Fay using localized and generalized refrigeration therapy. However, the temperature ranges were not as low as shown by Dr. Cooper's experiments today. With the technique employed, a metal bomb was placed into a cavity of a partially extirpated glioma. The bomb was frozen in situ, so that ice and frosting accumulated about it. After thawing out and removal of the bomb, the cavity was debrided. The bomb was then re-inserted for further refrigeration.

One patient with glioblastoma multiforme survived for a period of 2 years, following the initial surgery. The first slide illustrates the cellular characteristics of the tumor before freezing, while the second slide illustrates the effect of cellular response to prolonged refrigeration. However, the brain tissue 1 cm. away from the bomb revealed that the brain cells went on growing in the usual manner. As a rule, life expectancy in these patients was not prolonged.

Dr. Fay devised ingenious probes and applicators for various parts of the body. The slide shown illustrates the various probes used.

I would be interested to know if Dr. Cooper had any measurements of the fall of temperature gradient in the brain, as one proceeds from the ice ball to the periphery of the tumor. Whether the life expectancy is increased with this method in these cases remains to be seen. However, I do agree that the method has useful application for other conditions besides brain tumors.

DR. IRVING S. COOPER: One reason I thought I would...
I think the point about the edge of the tumor is obviously the point that must be made in any surgery of tumors. You either have to cut it all out or what is left is going to grow back. I can't answer that problem yet, Henry, as far as freezing is concerned. I do think that in placing a cannula into a tumor, one should go down to the liquid-nitrogen temperature and then, perhaps, use three or four cannulas in order to encompass the whole large tumor.

I appreciate the discussion. I feel that freezing, as has been noted before, has many merits, among which the greatest may be safety and controllability. I think that our instrumentation, this vacuum-insulated machine and its controllability, is excellent. However, obviously it will be modified as time goes on. I can conceive of new coils which we might put into the tumors in order to be more efficacious in our freezing. I think those developments will come as more surgeons apply themselves to possible use of this physical agent.