A CRYOGENIC METHOD FOR PHYSIOLOGIC INHIBITION 
AND PRODUCTION OF LESIONS IN THE BRAIN* 

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

(Received for publication May 14, 1962) 

It is the purpose of this report to bring to attention an extension of our cryogenic system for neurosurgery.2,5,6 The physical modality of extreme cold is capable of fulfilling all of the desirable criteria for an ideal method of production of lesions in the central nervous system. These criteria are: reversibility, consistent reproducibility; sharp delimitation; avascularity; variability, when desired; safety; simplicity; and rapidity of application. 

The earliest systematic investigation of freezing temperatures applied to the brain for purposes of physiologic investigation was that reported by Openchowski11 in 1883. Subsequent to this report, there have been intermittent investigations which suggested that the physical modality of cold has the potential of serving as an ideal method of both physiologic inhibition and production of lesions in the brain. 

Hass and Taylor8 investigated freezing lesions in the brain of various animals and reported that this method is capable of producing discrete, circumscribed lesions, which carried no danger of suppurating complications, could be absolutely controlled, was reproducible, produced its effect within a matter of seconds, and was essentially hemostatic. 

Balthasar1 produced localized lesions by freezing in the cerebral cortex of cats and concluded that the use of extreme cold was the most physiologic method available with which to produce inhibition or discrete lesions of the central nervous system. 

Rowbotham et al.12 produced localized cooling, to −20°C., in 3 cases of human glioma. The cannula that they employed was not insulated, resulting in cooling along the entire length of the instrument. However, this experience demonstrated the safety of extreme cold within tumors of the human brain, and indicated the value of an attempt to develop instrumentation that could produce temperatures at a much lower depth in a controlled fashion. Efforts in this direction have been reported recently by Ries and Tytus,15 Donstey et al.,9 Tanve and his co-workers,14 and others. 

The physical factors affecting the rate of transfer of heat at the tip of a cannula to be used for cooling within the brain are: the area of the surface of the freezing tip; the temperature and the rate of flow of the agent passing through this freezing tip; and the thickness and capacity for heat of the metal wall of the uninsulated portion of the cannula. The biologic factors of importance are the coefficient of heat and thermal diffusibility of the tissue and the radius of the lesion to be produced. A more searching inquiry into the physical and cryobiologic aspects of this subject is reported elsewhere.3 

We have developed a cryogenic surgical system which fulfills all of the requirements for safe, consistent, controllable, reversible or permanent production of lesions. The source of refrigeration is liquid nitrogen, maintained at −196°C. This refrigerant is delivered to a brain cannula by a double-layered, insulated withdrawal tube. Both the withdrawal line from the supply of nitrogen and the surgical cannula are constructed as an integral unit, and are insulated by vacuum. This unit,* 

This study was assisted by a grant from the John A. Hartford Foundation, Inc. 

* Manufactured by the Linde Cryogenic Division of Union Carbide Corporation.
which encases the line delivering the liquid, also contains a vent for escape of nitrogen gas as it removes heat from contiguous brain, and thermocouple leads from the tip of the cannula (Fig. 1).

Selected temperatures at the tip are obtained instantaneously and are maintained by an automatic flow-control system. The actual temperature realized at the tip of the cannula is monitored by thermocouples and displayed on a recorder. The surgeon may control this unit completely by manual adjustment of a dial for selection of temperatures. Although various types of insulation have been used in the development of our system, including a heating coil along the body of the cannula, silk insulation, and other methods, our final system employs vacuum insulation, since this is the most efficient type of insulation employed in cryogenic engineering. This insulation insures the fact that only the tip of the cannula removes heat from the contiguous brain. The remainder of the cannula is not cooled—an obvious requirement for its use within the brain. The over-all diameter of the brain cannula is 2 mm.

Physiologic inhibition within the brain is obtained in a temperature range from $+10^\circ$C to $0^\circ$C. Between $0^\circ$C and $-196^\circ$C, the lethal effect of freezing is caused by: removal of water from solution into ice, with toxic concentration of electrolytes; crystallization and rupture of cellular membranes; denaturation of lipid-protein molecules; thermal shock; and vascular stasis.$^{10}$

The lesions produced by this cryogenic method within the brain are spherical, sharply delimited from normal brain, avascular, and consistently reproducible depending on the temperature of the tip of the cannula. Within the brain, with a freezing time of 3 min., a temperature of $-40^\circ$C at the tip produces a lesion with a maximum of 6 mm.; $-50^\circ$C produces a lesion with a maximum diameter of 8 mm.; and $-100^\circ$C produces a maximum diameter of 12 mm. In gelatin, consistent spherical lesions are produced, which are sized somewhat differently than those in the brain, for the obvious reason that there is not a constantly circulating blood stream within the gelatin, which transfers heat to the vicinity of the lesion by convection. However, the consistent nature of formation of lesions by this system may be demonstrated in gelatin solution, as shown in Fig. 2.

Between April 1, 1961 and April 1, 1962, I have used this cryogenic surgical system in 150 cases, including surgery of basal ganglia, hypophysectomy, and for necrosis of deep and superficial brain tumors, as well as for cryogenic congelation and necrosis of malignancies elsewhere in the body.$^4$

In the first 100 consecutive cases of cryothalamectomy for parkinsonism, tremor and rigidity were abolished in 90 per cent of the cases.$^7$ There was only one complication, a hemiparesis unrelated to the freezing procedure, and there was no postoperative mortality. Moreover, the postoperative course of each patient was unusually smooth, there being virtually no postoperative mor-
bidity, and the time of postoperative hospitalization was decreased by 50 per cent.

It is my conclusion that this method of cryogenic surgery is the ideal technique for basal-ganglia surgery of involuntary movements, since it provides a reversible physiologic test, the importance of which we have emphasized for many years; a controllable, sharply delimited, completely avascular lesion has a greater margin of safety than one produced by any previously reported method. Furthermore, the method permits flexibility in the size of lesions created in a conscious, cooperative patient which increases the likelihood of a successful outcome of the operative procedure.

During the operative procedure a thermographic record, resulting from monitoring the temperature at the tip of the cannula during the procedure, enables the surgeon to follow the course of events at the site of physiologic inhibition or creation of lesions at the tip of the cannula. An example of such a cryogenic thermograph is shown in Fig. 3.

In addition to the use of this cryogenic surgical system for physiologic inhibition and creation of lesions in basal-ganglia surgery, the cryosurgical probe may be placed into deep, otherwise inaccessible brain tumors, in order to obtain controlled freezing necrosis within the tumor. Similarly, it may be placed into the sella turcica to produce cryogenic congelation and destruction of the pituitary gland.

In cases in which a vascular tumor, such as glioblastoma, is located within the cerebrum superficially, the tumor may be frozen solid, and dissected en bloc, using the plane of cleavage of the frozen mass to effect rapid removal of the tumor. More detailed descriptions of these techniques will be presented in subsequent reports.

SUMMARY

The vacuum-insulated cannula and automatic cryosurgical system described in this report provide an ideal method for physiologic testing and surgical creation of lesions in the central nervous system.

(Discussion follows on next page)

REFERENCES

DISCUSSION

Dr. James B. Campbell: The cryogenic instrument which has become available through recent advances in miniaturized engineering offers extraordinary opportunities for therapy as well as physiological exploration of the brain at depth. Therefore, all of these investigators are to be congratulated, the whole team associated with Dr. Mark, as well as Dr. Cooper and his engineers.

The ability to bring about a temporary change in physiological function gives the patient a greater factor of safety, and the surgeon the assurance of accuracy in placing a lesion. I have had the pleasure of seeing Dr. Cooper turn a Babinski on and off by adjustment of a valve. This is truly impressive. Equally so is the precision of the limits of necrosis created by freezing. His slides I have been able to study at leisure in the laboratory of his colleague, Professor Bergmann of the anatomy department of New York University.

Dr. Mark and his group have shown the value of the cryogenic method in obtaining physiological data. This means of temporary interruption of physiological function, which does not cause a permanent anatomical change, will become increasingly useful. It certainly is going to help greatly in amplifying the means of getting information by bieclectric testing, and it can, as I presume, be used in conjunction with it.

I wonder if Dr. Mark or someone from his group could show us a slide illustrating the electrode that they use in obtaining evidence with regard to physiological changes in deeply seated vital structures at various levels of reduction of temperature.

Dr. Claude Bertrand: Because of the lack of time it has not been possible for the authors to mention the history of the use of deep cold in surgery. I think one should be cognizant of the work done by Clasen and mostly that of Audrey U. Smith in England. For those interested, there is an excellent monograph by Smith on Biological Effects of Freezing and Supercolling, published in 1961.

I believe the use of a cannula for cooling inside the brain has been initiated by Rowbotham, and, in this country, by John Tytus, and in France by Dondey and Le Beau. Particularly, one must remember the work of Dondey in the thalamus. The latter has used it in conjunction with evoked potentials, somewhat in the manner of Vernon Mark and Guiot, Hardy and Fessard for evoked potentials.

Having no experience with intense cooling, I imagine my function here is mostly that of stressing the importance of the basal structures of the brain. It is important to have all the tools at our disposal to make these lesions as small as possible. A short while ago, we were doing the second side on a patient 72 years old, on whom the first side was done about 9 months ago. I am sure this would not have been possible had the first lesion been done indiscriminately and had it been too large. Anteriorly, in the thalamus, there is the dorsomedian nucleus. Any encroachment in that direction will cause changes in personality as is well known from other types of surgery, as for pseudo-lobotomy. Also, posteriorly there is the nucleus ventralis posterolateralis. Dr. Mark stated that, in the cases of choreathetosis described, he was aiming at the nucleus ventralis posterolateralis to try to have a maximum effect. We also have found that in choreathetosis one had to section more posteriorly but whether the effect obtained is because of the nucleus ventralis posterolateralis or adjoining fibres is another matter.

Again a word of caution. Because of such excellent results we gradually had been working more posteriorly, and finally we did get persistent localized sensory changes in 4 cases. We are now sectioning a few mm. more anteriorly within the thalamus.

We all are aware that temporary suppression of function does not mean necessarily a permanent and persistent suppression of the symptoms, but it is helpful and it is obtained in 70 per cent of the cases when introducing the electrode.

As far as the lesions resulting from supercooling are concerned, I wonder, and possibly Dr. Miyazaki would care to comment on this, what factors, such as local circulation, may influence the size of the lesion.

In closing, I would like to thank Drs. Mark and Cooper for bringing to our attention the use of this promising method. I think that we should use every means at our disposal including stimulation, recording evoked potentials and temporary suppression of function, within tolerable limits of time, namely 1 to 2 hours on a conscious patient, to limit our lesions as well as we can. This would be another useful tool. In my opinion, I believe these results would compare with ours.

Dr. John F. Mullan: I wonder could it be used in the handling of aneurysms. It would be very nice to expose an aneurysm and, if we could freeze it stiff, keep it from bursting. Would the necessary temperature injure the parent blood vessel before the aneurysm would freeze? Plastics applied to the frozen aneurysm would then seal it permanently. I wonder could either author comment on this aspect.

Dr. John R. Green: I had the pleasure of visiting Dr. Mark last week and was exceedingly impressed by the careful technical skills that have gone into the development of the lesions made by his group.

Not having had the pleasure of visiting Dr. Cooper for the past several years, I have not seen his developments in cryogenic surgery until today.

My particular interest in this field is in its possible adaptation in focal epilepsy. I would like to ask either essayist if he has had patients in whom he has applied this tool to electrocorticography or depth-electrode studies in an attempt to confirm the epileptogenic focus. A reversible lesion of this type would theoretically seem to be a very useful neurophysiological and neurosurgical tool for the localization of the epileptogenic focus.

Dr. Eric W. Petersen: I just want to mention that we have a portable freezing probe similar to Dr. Cooper's which we had made specifically for use in aneurysms. Although I know it will stop bleeding quite readily, I have never had to use it on one yet, because I have not encountered a situation that required its use. It can be charged with liquid nitrogen and it will remain cold for about 15 min. while in use at the operating table.

Dr. Leonard T. Furlow: Any other questions? If not, I shall ask Dr. Mark to close first. I have told him
if there were some questions he would like to refer to one of the co-authors, he should feel free to do so.

**Dr. Vernon H. Mark:** I would first like to thank all the discussers, and particularly compliment Dr. Cooper on his fine presentation.

The question of Dr. Bertrand, I think, will be answered by Dr. Miyazaki of the University of Sapporo, Japan.

As to Dr. Green's question about epilepsy: We have indeed been interested in doing just this, i.e. reversibly altering an abnormal focus with our cooling probe. We have not found a suitable patient as yet.

I should like to introduce Dr. Yuji Miyazaki, who is Associate Professor of Neurosurgery at Sapporo Medical College (an associate of Professor Hashiba who is retiring President of the Japanese Neurosurgical Society) to answer the question of Dr. Bertrand, and Dr. Jean Siegfried of Zurich, Switzerland, a cohort of Professor Hugo Krayenbühl, to answer the question of Dr. Campbell. Dr. Miyazaki!

**Dr. Yuji Miyazaki:** As an official observer of the Japanese Neurosurgical Society, I wish to extend greetings of my colleagues to the members of the Harvey Cushing Society.

The reason that we use radio-frequency current instead of freezing for permanent lesions of the brain is that the lesions produced by radio-frequency current are more uniform and are free from hemorrhage.

We have done chronic sterile operations with production of lesions by cooling and multiple thermocouple recordings within the brains of 20 cats, 4 dogs, and 11 cows. This work will be the basis of a future publication.

[Slide] This shows the relationship between the lowest temperature of cooling and the size of the subcortical lesion. The standard deviation is seen in the small number. There is considerable variation.

[Slide] This shows the relationship between duration of freezing and the size of the lesion. Here again, the size of the lesion tends to increase as the duration of cooling increases. There is still a great deal of variation even when the temperature and the duration of the cooling are constant. It is important to mention that depression of the temperature below 0°C, at the tip of the probe (e.g. -5°C, for only 1 min. 15 sec.) will produce a significant subcortical lesion.

[Slide] As Dr. Balthasar showed in 1937, some lesions from cooling in the brain have hemorrhage within the lesion itself. We have found the incidence of gross hemorrhage to be greatest when the rate of cooling is very rapid. The hemorrhage always is confined to the subcortical lesion and may be present even 6 weeks after the lesion is made.

**Dr. Jean Siegfried:** We do have some physiological evidence in the form of evoked potential studies. That gave us the idea of the volume of central nervous tissue in which electrical activity is modified by local cooling.

[Slide] This shows the classical response evoked in the lateral geniculate body by stimulation. It is a photographic summation of 10 responses. The cooling probe is in the lateral geniculate body, and there are attached two pairs of electrodes, A and B. A records the response right at the tip of the cooling probe, and B records 2 mm. away. The first frame is a control at the temperature of the body. Then we start to cool. You see at the top of each frame the tip of the cooling probe and the bottom is the recording 2 mm. away. When we start to cool, the response increases. At between 20°C and 18°C, the shift is modified largely at the tip of the cooling probe, but not too much 2 mm. away. By rewarming, the response comes back to normal.

Now, if we stay for a short period of time, or as long as 20 min. just above 0°C, the response is modified largely but comes back to normal by rewarming. If we cool below 0°C, the response is modified rapidly at the tip of the cooling probe in less than 1 min. If we stay for less than 2 min., the response never will come back to its normal shape. Then 2 mm. away the response starts to increase and then is modified. The classical array of the lateral geniculate response is still obvious. Even if we stay for a period of 12 min., or 1 hour, the response 2 mm. away is almost coming back to its normal shape, when we warm.

**Dr. Irving S. Cooper:** The reason that literature was not reviewed in my presentation was because of the time limit, the 10-min. total that is allowed for the presentation.

However, in the paper, which was sent to the discussers, there were a couple of hundred references reviewed, a few of which I should like to mention.

[Slide] This is the first machine that I found reported, made exclusively for application of cold to the brain, developed by Oopenchowski who reported in 1888 that he used evaporation of ether by a warm jet of air to apply freezing temperature to the cerebral cortex of dogs in order to study physiological localization within the cortex. I might add, in this regard, this raised an interesting point, which remains to be clarified. That is, some of his dogs had convulsions after the application of cold.

The first report I could find in the American literature was that of Hass and Taylor of Chicago, in the department of pathology at Presbyterian Hospital.

Balthasar reported a series of cold lesions in the cerebral cortex of cats from Riehert's laboratory where, of course, they use radio-frequency current. Balthasar stated, in his opinion, based on his work with lesions in the cat, cold was the safest, least hemorrhagic, and the most physiologic way to produce a lesion in animals. Rowbotham and his associates also employed a cooling cannula in several cases of gliomatous tumors in humans. Rey and Le Beau and others are working currently on this problem. In our experience, the size of the lesion has been constant and is not modified a great deal by time. In a 3-min. lesion, 70 per cent of the lesion appears during the first 30 sec. and is enlarged only 30 per cent thereafter in volume during the next 2 min. and 30 sec.

We have made several hundred lesions in animals and have not observed hemorrhage in lesions of this relatively small size. We have explored the use of this probe applied to blood vessels in dogs. If extreme cold is applied to the wall of the vessel itself, it will produce necrosis. It is conceivable that extreme cold could be used for temporary arrest of arterial bleeding. We have not yet been able to do this. We have used it in many other instances with our general surgical colleagues. It is my opinion that this constitutes a new and very unique surgical tool. We are using it in localized metastases, for example, and with very encouraging results, and thus far without any instance of hemorrhage.
I might add that, in regard to a paper presented earlier in the day, we are also concerned with the possibility of vaccination of malignancies. Bory, who is a cryobiologist, has written that cold, if it could be properly engineered, has much better potential as an anticancer agent than either coagulation or radiotherapy or excision, because of its ability to necrose in a predictable fashion, depending upon known physical laws, because of its anesthetic qualities and its lack of hemorrhage as a serious complication. He also proposed the interesting possibility that, if one could rupture the walls of the cells of the tumor in situ, one might produce an antivaccine.

We have been operating on some rats with tumors and with some interesting results, which we shall present at a later date. But it does provide an exciting possibility of using this surgical tool for treatment of selected neoplasms.