Effects of Sustained Perfusion Cooling of the Subarachnoid Space

Maurice S. Albin, M.D., Robert J. White, M.D., Ph.D., Collin S. MacCarty, M.D.

ALTHOUGH the clinical application of induced hypothermia has grown steadily during the past decade, knowledge of its basic effects is still far from complete. This is especially true of the effects of cold on nervous tissue. Even though various species of animals have been cooled to near and below 0° C. with a high proportion of survivors [1-4] and although induced hypothermia by whole-body perfusion in the range of 15° to 10° C. has been used clinically on human beings,[5-8] evidence has been accumulating that low temperatures may cause specific damage to nervous tissues.[9-12]

Superficial body cooling of the dog to less than 32° C. is hazardous because of the problems of cardiac alterations and rewarming.[13-15] The morbidity and mortality from sustained cooling utilizing whole-body perfusion, however, are not related to the survival of nervous tissue.[16-20]

The technique of subarachnoid perfusion that we have evolved [21, 22] restricts the cooling to the spinal cord, does not involve extracorporeal circulation of blood and does not expose the cord to ischemia or anoxia from deterioration of the cardiorespiratory system. This method permits a degree of confidence in attributing any structural change or alteration to the effect of cold *per se* on the cord tissues.

Previous communications [21, 22] have shown that the temperature of the spinal cord of dogs can be reduced by subarachnoid perfusion and that two dogs whose cords reached temperatures of less than 10° C. on such cooling for one hour survived the procedure without any neurologic sequelae. Our present report is concerned primarily with the functional and histopathologic effects of sustained, selective low-temperature cooling of the spinal cord of the dog.

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Experimental Method

Using a previously described method,[21, 22] we carried out subarachnoid perfusion from the fourth thoracic to the fifth lumbar segment through silastic catheters previously inserted beneath and tied to the dura after laminectomy. Perfusion was carried out by gravity drip with sterile 0.85 per cent solution of sodium chloride at a flow rate of 10.0 ml. per minute with the perfusate entering at 5.0° C. In the control animal the perfusate entered at 37.5° C. All animals were anesthetized intravenously with sodium pentobarbital, 25.0 mg. per kilogram of body weight, and were operated on under sterile conditions. The animals were grouped as follows: in group A three animals were subjected to cold perfusion for 195 minutes and killed immediately; in group B, five animals underwent cold perfusion for 220 to 250 minutes and were allowed to survive; and in group C, one animal (control) had a normothermic perfusion for 240 minutes and also was allowed to survive. To observe the effects of subarachnoid implantation of the silastic catheters, catheters were implanted 2 inches beneath and sealed to the dura in two animals in group D. These animals were observed for six months and then killed for histologic study (control). To observe the effect of laminectomy alone, laminectomies were performed at the fourth thoracic and fifth lumbar segments in two animals, group E, and the animals were studied neurologically (control). One animal was killed after two weeks and the other in six months for histologic study.

Observations

Observations in all animals perfused were made of the temperatures (1) in the rectum, (2) of the perfusate at the inflow and outflow sites, and (3) of the spinal cord. The rate of flow of perfusate was measured in milliliters per minute. All measurements of temperature were made in degrees centigrade with thermistor probes attached to a tele-thermometer unit.*

In groups B and C, the mean arterial blood pressure and the heart rate were recorded also.

Neurologic Examination

All the animals in groups B, C, D, and E were examined neurologically twice daily for motor and sensory defects and also for signs of unusual behavior.

Motor Function. The classification (grade 0 to 4) used was based on the scale developed by Tarlov [23] for grading the recovery of motor function of the hind limb in his work on compression of the spinal cord: (0) no voluntary movements; (1) perceptible movements of joints; (2) good movements at joints but inability to stand; (3) ability to stand and walk, and (4) complete recovery.

Sensory Testing. (1) Pain was indicated by growling, barking, head turning toward the pinprick applied to the plantar surface of the paw, or attempts to withdraw from it. (2) Position sense was tested by observing the animal's ability to correct an upside-down position of the foot. (3) Touch sensation was determined by thrusting the animal's foot over the edge of the table and noting whether the foot could be returned to its original position, a placing reaction. Both touch and position sense are dependent on good motor power of the limb.

Reflexes. The reflexes tested were the flexor reflex, knee jerk, and extensor reflex as outlined by McGrath.[24]

Histologic Study

All the animals in groups B, C, D, and E were included. They were given heparin, exsanguinated, and 10 per cent formalin (500 ml.) was injected under pressure (150 mm. of mercury) into the aortas. The spinal cords were removed and placed in 10 per cent

* Thermistor and tele-thermistor unit made by the Yellow Springs Instrument Co., Yellow Springs, Ohio.

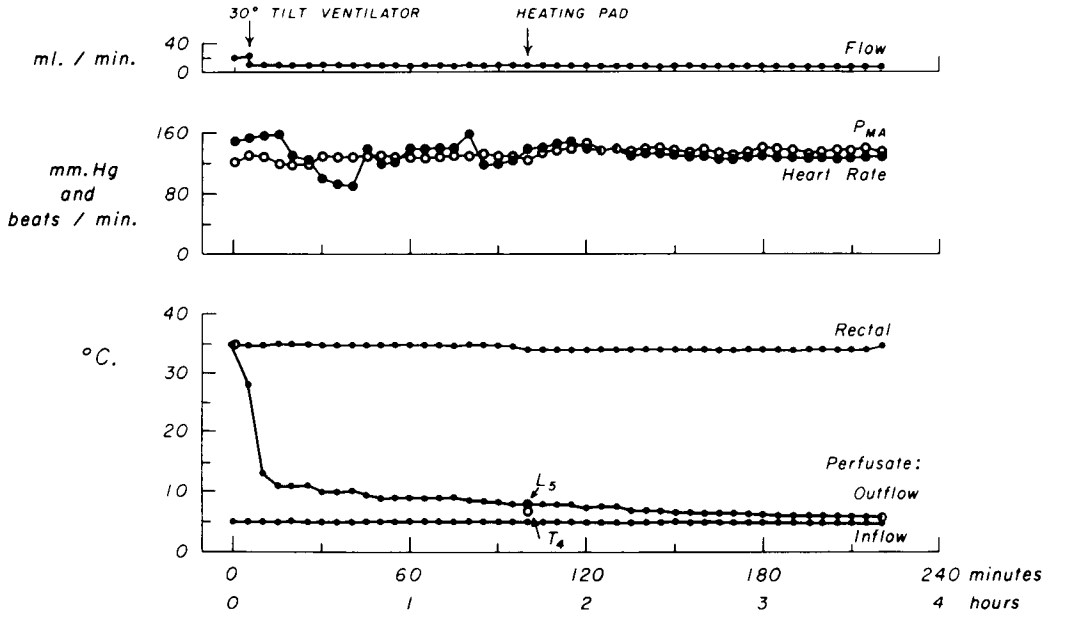

FIG. 1. Temperature curves and cardiovascular responses during prolonged perfusion of the cord with cold fluid.

TABLE 1. Changes in Cord Temperatures of Perfused Animals

Group and Animal	Weight (kg.)	Total Perfusion Time (minutes)	Cord Temperature			
			Preinfusion		End of Perfusion	
			T_4	L_5	T_4	L_5
Group A						
1	9.0	195	35.0	35.0	5.5	6.5
2	8.3	195	35.0	35.0	7.5	9.5
3	6.0	195	34.0	34.0	6.0	7.5
Mean			34.7		6.33	7.83
Group B						
4*	9.8	250	35.0	35.0	6.0	7.2
5*	7.4	230	35.5	35.5	5.8	7.1
6*	9.8	250	35.2	35.2	6.5	7.6
7*	7.8	220	35.0	35.0	5.8	6.4
8†	8.7	220	37.5	37.5	5.2	6.0
Mean		234	35.6		5.86	6.86
Group C						
9 (Control)	10.0	240	37.5	37.5	37.2	37.4

* Heating pad used. Body temperature maintained between 34° and 35° C.
† No heating pad needed.

formalin for at least 36 hours. In groups A, B and C cross sections were made at perfusate inflow and outflow sites and from the intervening area. A longitudinal block was cut from the area between inflow and outflow sites. In groups D and E cross sections were made at fourth thoracic and fifth lumbar segments and from the intervening area. A longitudinal section was cut between fourth thoracic and fifth lumbar segments.

TABLE 2. Mean Arterial Pressure and Heart Rate in Perfused Survival and Control Animals

Group and Animal	Mean Arterial Pressure (mm. Hg)		Heart Rate (beats per minute)		Length of Perfusion (minutes)
	Preinfusion	End of Perfusion	Preinfusion	End of Perfusion	
Group B					
4	140	140	140	150	250.0
5	130	150	140	134	230.0
6	120	140	148	126	250.0
7	120	136	150	130	220.0
8	170	140	200	160	220.0
Group C					
9	140	140	150	140	240.0

These blocks were embedded in paraffin, sectioned with a microtome, and stained with (1) hematoxylin and eosin, (2) Bodian's method (silver stain for axons, anterior horn cells), (3) Luxol-fast blue for myelin, and (4) Mallory's phosphotungstic acid-hematoxylin for myelin and glial fibers.

All sections were examined for the presence of edema, condition of axons, myelin, anterior horn cells, nerve roots, blood vessels, presence of glial proliferation and other forms of damage.

Results

CHANGES IN BODY TEMPERATURE

In the animals of group A, body temperature began declining from preinfusion levels after cold perfusion for an average of 50 minutes. Cold perfusion was continued in all three animals for 195 minutes. During that time the body temperature in two animals dropped to 29.5° and 26.0° C. from a preinfusion mean temperature of 35.0° C. To prevent such a drop in body temperature during cold perfusion of long duration, the five animals in group B were placed on a heating pad whenever the body temperature fell to less than

34.0 C. (fig. 1). The animals were ventilated with 100 per cent oxygen to ensure adequate oxygenation and were placed in a 30° head-up position in order to prevent the cold perfusate from extending cephalad, reaching the brain stem and causing cardiorespiratory alterations.

Temperature Changes Within the Spinal Cord (Table 1)

Initial Decline. All the perfused animals showed the greatest initial decline in cord temperature within the first 20 minutes of cold perfusion. The control animal (group C) showed no change in spinal cord temperature during the entire 240 minutes of normothermic perfusion.

Temperatures at End of Perfusion. After 195 minutes of perfusion, with a mean pre-infusion spinal cord temperature of 34.7° C., the spinal cord temperature at fourth thoracic level of the three animals in group A reached a mean of 6.33° C. In the five animals in group B the mean cord temperature at fourth thoracic level reached 5.86° C. after an average of 234 minutes of perfusion.

In groups A and B three animals had to be perfused for 210 minutes, four for 115 minutes, and the last animal for 145 minutes in order for the temperature gradient between fourth thoracic and fifth lumbar levels to reach 2.0° C. or less.

Cardiovascular Changes (Table 2)

In general the five animals in group B showed good stability during cold perfusion; in four of the five animals the heart rate declined slightly. The control animal (dog 9) showed little change.

Neurologic Study (Table 3)

All the animals survived the perfusion, and those in groups B and C showed only transient hind leg weakness for 48 hours, after which no neurologic defects were observed.

In animals with implanted silastic catheters and in animals with laminectomy without perfusion, the findings were essentially the same as those in groups B and C.

Histologic Study (Tables 4 and 5)

Cold Perfusion (Group B). The histologic changes in the specimens from these five ani-

Table 3. Neurologic Findings

Group and Animal	Time, Hr. after Perfusion	Motor Function*	Sensory Function†		
			Pain	Touch	Position
Group B					
4	Same night	2	+	−	−
	24	3	+	+	+
	48	3	+	+	+
	72	4	+	+	+
5	Same night	2	+	−	−
	24	3	+	+	+
	48	4	+	+	+
	72	4	+	+	+
6	Same night	2	+	−	−
	24	3	+	+	+
	48	3	+	+	+
	72	4	+	+	+
7	Same night	2	+	−	−
	24	3	+	+	+
	48	3	+	+	+
	72	4	+	+	+
8	Same night	2	+	−	−
	24	3	+	+	+
	48	4	+	+	+
	72	4	+	+	+
Group C					
9	Same night	2	+	−	−
	24	3	+	+	+
	48	4	+	+	+
	72	4	+	+	
Group D					
10	Same night	3	+	+	+
	24	4	+	+	+
	48	4	+	+	+
	72	4	+	+	+
11	Same night	2	+	−	−
	24	3	+	+	+
	48	4	+	+	+
	72	4	+	+	+
Group E					
12	Same night	3	+	+	+
	24	4	+	+	+
	48	4	+	+	+
	72	4	+	+	+
13	Same night	2	+	−	−
	24	3	+	+	+
	48	4	+	+	+
	72	4	+	+	+

* Motor function: 1 = perceptible movements of joints; 2 = good movements at joints but inability to stand; 3 = ability to stand and walk; 4 = complete recovery.

† Sensory function: + = presence; − = absence.

TABLE 4. Summary of Histologic Changes in Spinal Cord of Dogs After Perfusion*

Group and Animal	Site of Section	Edema	Condition of	
			Axons	Mye in Sheath
Group B				
4	All 4 sites	—	—	—
5	Inflow site†	Moderate	Sl. beading	—
	Between inflow and outflow†	—	—	Mild swelling
	Same‡	Moderate	Sl. beading	—
	Outflow†	—	—	—
6	Inflow†	Mild	—	—
	Between inflow and outflow†	Mild	—	—
	Same‡	Mild	—	—
	Outflow†	—	Sl. beading	—
7	Inflow†	—	Sl. beading	—
	Between inflow and outflow†	—	—	—
	Same‡	—	Sl. beading	—
	Outflow†	—	Sl. beading	—
8	Inflow†	Mild	—	—
	Other 3 sites	—	—	—
Group C				
9	Inflow†	Mild	—	—
	Between inflow and outflow†‡	—	—	—
	Outflow†	Mild	Sl. beading	—

* No changes found in anterior horn cells, nerve roots, blood vessels or glial fibers.
† Cross section.
‡ Longitudinal section.

mals appeared to be superficial and minimal. In no case were the nerve roots, anterior horn cells, and blood vessels affected; and in only one section did the myelin sheath show evidence of minimal damage. Mild edema was found in sections from two animals and moderate edema in one. Slight beading and fragmentation of axons were found in three animals.

Normothermic Perfusion (Group C, Control). This animal showed mild edema of the cord at both inflow and outflow sites with slight beading of axons at the outflow site. Anterior horn cells, axons, myelin sheath, nerve roots, and blood vessels were not affected. There was no proliferation of glial fibers.

Effects of Implantation of Silastic Catheters at Fourth Thoracic and Fifth Lumbar Segments for Six Months (No Perfusion, Group D). One animal showed mild edema of the cord at fifth lumbar level with slight beading of axons at fourth thoracic level. The other animal showed mild edema at fourth thoracic level with a mild swelling of the myelin sheath at fifth lumbar level. No changes were seen in other structures.

Effects of Laminectomy at Fourth Thoracic and Fifth Lumbar Segments (No Catheters, No Perfusion, Group E). The animal, killed two weeks after laminectomy, showed moderate edema of the cord at fourth thoracic and fifth lumbar levels and slight beading of axons at fourth thoracic segment. The animal, killed six months after laminectomy, showed mild edema of the cord at fourth thoracic segment. No changes were seen in other structures.

Site of Injury. The histologic study, in general, indicated that most of the damage occurred in the areas of inflow and outflow near the fourth thoracic and fifth lumbar segments. This was also true of the animals with inserted silastic catheters and even in those subjected to laminectomies alone.

Comment

Before the clinical use of induced hypothermia, studies on the deleterious effects of cold on the nervous system were primarily related to problems of cold injury. Blackwood and Russell [25] exposed the tails of rats to salt water at temperatures of 4° to 5° C. for as long as 96 hours and demonstrated that necrosis of skeletal muscles and degeneration in bundles of peripheral nerves could be brought about by cooling. Blair [26] was critical of using the rat's tail in the investigation of frostbite because the tight, binding, connective-tissue ring at the base of the tail may act as a tourniquet causing edema, interfering with the blood supply and producing gangrene. Bielschowsky and Valentin [27] found that after freezing a sciatic nerve of a dog for five minutes all the fibers degenerated. These authors suggested that circulatory stasis might be the mechanism of nerve fiber damage but could not obtain critical evidence on this point. Denny-Brown and associates [28] studied the sciatic nerves of rabbits frozen with carbon dioxide and enclosed for periods of two hours in a chamber through which brine was passed at temperatures between −4° and +3° C. They found that the myelin and axis cylinders of mammalian peripheral nerve are selectively

damaged by exposure to cold, the largest nerve fibers being the most sensitive and the smallest the least sensitive. They also observed that the motor fibers were more sensitive to cold than the sensory fibers. It was found necessary to have the nerve in a completely frozen state for longer than two minutes in order to produce degeneration resulting in complete and lasting motor and sensory paralysis. They found that motor weakness or paralysis always occurred at temperatures of less than 7° C. It is interesting to compare the observations of Denny-Brown and associates [28] on the effects of cold in relation to the size of the fiber and to function with the observations of Lundberg [29] that conduction of A fibers of motor nerves (cat) ceased at 7° to 15° C. whereas conduction of the splenic C fiber (cow and cat) continued at 0° C.

The difficulty in evaluating the effect of cold on nervous tissue during induced hypothermia is partly due to the complications of whole-body perfusion techniques and superficial body cooling which in themselves can have deleterious effects. Included are factors such as adequacy of perfusion flow, performance of oxygenator, effects of the extracorporeal circuit on the formed elements of the blood, cardiac irritability, the development of temperature gradients between different organs and within the same organ, and acid-base imbalance. Another difficulty is the problem of defining and quantitating behavioral changes in animals cooled to low temperatures. The literature contains little information concerning the correlation between these behavioral changes and histopathologic findings.

The spinal cord was chosen for this study since it is an integral part of the central nervous system, has easy surgical accessibility, and is sensitive to injury which can be studied clinically and confirmed histologically. It thus seems ideally suitable for studying the effects of cold on nervous tissue *in vivo*.

Cooling of the subarachnoid space by perfusion was developed to make possible the selective cooling of the spinal cord. In animals so treated cardiovascular changes were minimal (table 2), respiratory alterations were avoided by artificial ventilation with 100 per cent oxygen, and body temperatures in the chronic cold-perfused animals were maintained artificially above 34.0° C. when necessary.

TABLE 5. Pathologic Changes in Cords of Animals Six Months After Implantation of Silastic Catheters and After Laminectomies Only at Fourth Thoracic and Fifth Lumbar Segments*

Group and Animal	Site of Section	Edema	Condition of Axons	Condition of Myelin Sheath
Group D				
10	T_4†	-	Sl. beading	-
	Between T_4 and L_5†‡	—	-	-
	L_5†	Mild	- -	—
11	T_4†	Mild	-	-
	Between T_4 and L_5†‡	—	-	-
	L_5†	- -	-	Mild swelling
Group E				
12 (killed in 2 wk.)	T_4†	Moderate	Sl. beading	-
	Between T_4 and L_5†‡	- -		—
	L_5†	Moderate	-	-
13 (killed in 6 mo.)	T_4†	Mild	-	-
	Between T_4 and L_5†‡	—	-	-
	L_5†	—	—	-

* No changes found in anterior horn cells, nerve roots, blood vessels or glial fibers.
† Cross section.
‡ Longitudinal section.

Temperature Changes Within the Spinal Cord. In all cold-perfused animals the sharpest initial drop in the temperature of the spinal cord occurred during the first 20 minutes of perfusion. This sharp initial drop in cord temperature is probably due to an extensive vasoconstriction in the small arterioles in the spinal cord. Meyer and Hunter [30] measured the changes of size of cortical arteries and veins during surface cooling of monkeys and cats and found reduction in the caliber of these vessels beginning at 32° C., becoming more marked at lower temperatures. The changes were most evident in arteries having a diameter of approximately 200 millimicrons, and they estimated a 50 per cent reduction in arterial size and a 25 per cent reduction in the veins at 30° C. and less. The capillary bed in their study appeared pale and poorly defined at 30° C. The spinal cord is supplied with a network of small arteries coming off the sulcal, paracentral, posterolateral,

and anterior trunks which are in all probability reactive to the cold perfusate.[31-34]

Since cold perfusion was carried out from fourth thoracic to fifth lumbar segment, it was expected that the greatest drop in temperature would occur at the vicinity of the inflow site, the perfusate being warmed by the cord blood as it passed to the outflow area. This would account in part for the development of the temperature gradients between inflow and outflow sites. Contributing to the explanation of the higher spinal cord temperatures at fifth lumbar level and a lower one at fourth thoracic level is the finding of Bolton[35] that the poorest collateral circulation of the spinal cord is at a zone between first and third thoracic segments. Zülch[36] found that the fourth thoracic segment has the sparsest vascular irrigation of the spinal cord. Conversely, the sacral and lower lumbar segments of the spinal cord have the richest blood supply[31, 32] which might account for the higher temperature there. Thus, not only is the perfusing fluid gradually warmed as it passes from inflow to outflow site, but also the blood flow contributing warmth to the spinal cord becomes greater in the region of the outflow site.

Neurologic Findings. The similarity of neurologic findings among all the animals leads one to believe that cold itself was not responsible for the early transient defect, but that this was due to trauma of surgery or manipulation of the catheters or to both.

Histologic Study. From the histologic study as a whole, it appears evident that most of the damage occurred in the area of the inflow and outflow tracts. This was true in the animals in which the silastic catheters only were used and even in those subjected to laminectomy only.

The histopathologic findings of this study appear to be superficial with only one small area of damage to myelin, the rest of the damage mostly localized to the region of the inflow area, fourth thoracic level, and outflow area, fifth thoracic. One might also presume that generalized damage to the spinal cord by such low temperatures would affect the anterior horn cells and also damage the nerve roots and small capillaries within the cord substance; yet these structures showed no evidence of alteration. The discrete, superficial, spotty damage found can be explained by the trauma associated with manipulation of the inflow and outflow catheter within the subarachnoid space, the insertion of the thermistor needle within the cord, and the trauma associated with laminectomy.

Effects of Anesthesia. Oreshchuk[37] was able to induce sleep in dogs and abolish conditioned reflexes and sensation by running cold saline solution at 6° to 8° C. through a plastic tube beneath the spinal cord and dura at the first thoracic segment. No information was given as to the temperature within the spinal cord. The phenomenon was reversible, the animal awakening within five minutes after the perfusion was stopped.

In our study, all the animals were anesthetized with intravenously injected sodium pentobarbital. When perfusion was of long duration, the animals appeared to be in a satisfactory plane of surgical anesthesia during the entire course of cold perfusion. Within five to 15 minutes after termination of cold perfusion, however, these animals were moving about and actively responding to painful stimuli making it necessary to re-anesthetize the animals in group B in order to remove catheters, repair dura and close the incisions. The initial surgical procedure (the laminectomies and insertion of silastic catheters) and the setting up of monitoring equipment took about two hours, and the subarachnoid cooling lasted a minimum of three hours (table 1)—making a total of five hours of anesthesia necessary.

The control animal (dog 9), perfused at a normothermic temperature of 37.0° C. for four hours, showed signs of awakening after one hour of perfusion and had to be re-anesthetized. To test the duration of pentobarbital anesthesia, four dogs were given sodium pentobarbital intravenously, 25 mg. per kilogram of body weight, and all animals showed signs of responding to painful stimuli by the end of three and one-half hours. This may indicate that the surgical plane of anesthesia noted during the last two hours of cold perfusion may not be entirely due to the sodium pentobarbital. It is interesting to speculate whether the cold exerted a central anesthetic effect via spinal cord pathways. This will be the subject of a future communication.

Summary and Conclusions

The temperature of the spinal cord in the dog was reduced selectively by perfusion of cold fluid through the subarachnoid space.

Sustained cooling of the spinal cord to mean temperatures as low as 5.86° and 6.33° C. had no deleterious effect on the spinal cord of dogs which could be attributed to cold *per se*.

Spinal cords of dogs were maintained at low temperatures for four hours, without any neurologic sequelae and with little histopathologic evidence of cord damage. All five animals so treated survived the four-hour subarachnoid cooling.

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FOCAL EPILEPSY Craniotomy for focal epilepsy is usually performed using local anesthesia to ensure an exact electroencephalographic location of epileptogenic foci. In a series of 46 operations with general anesthesia, the clinical and electroencephalographic results compared favorably with a similar control series performed with local anesthesia. With the onset of general anesthesia the normal awake encephalographic pattern disappeared. Epileptogenic focal discharges tended to diminish and frequently disappeared completely. During the operation, whenever electroencephalographic location was required, halothane was discontinued. Two to three minutes later the encephalogram showed the characteristics of the awake state, or of light somnambulance. The focal abnormalities reappeared, frequently more pronounced. The patients were apparently asleep; they reacted to painful stimulation but later claimed amnesia for the period of examination. In two patients epileptogenic foci not present before operation were activated by general anesthesia. (*Gordon, E., and Wilden, L.: Le Fluothane en Neurochirurgie, Anesthesie, Analgesie, Reanimation 19: 225 (April–May–June) 1962.*)

BRONCHOGRAPHY Contrast-medium used for bronchography under local anesthesia remains for as long as 48 hours, and insufficient respiratory function results in many patients with lowered vital capacity or maximum breathing capacity. Sometimes pneumonitis or pleuritis with elevated temperatures occurs. It is best to postpone operation for a few days. Relaxant-nitrous oxide oxygen anesthesia with aspiration of the contrast medium is the preferred technique. (*Kovats, F., Nyredy, G., and Szucs, S.: Tuberkulosearzt 16: 492 (Aug.) 1962.*)