General and local hypothermia of the brain in the treatment of intractable epilepsy

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Twenty-five cases of intractable epilepsy were treated by combined deep general and local extravascular brain hypothermia plus single doses of pentothal (Thiopental) or diazepam. The final local temperature of the brain in 21 patients was below 24°C, the rectal temperatures being 27° to 30°C. There was one death 6 weeks after surgery, and in two patients slight neurological deficits were found at 3 and 6 months postoperatively.

In 15 patients in whom at least 1 year had elapsed since surgery, the frequency and intensity of the seizures were reduced by 50% in two, reduced to a single seizure in five, eliminated in four, and unaltered in four. The fair and excellent results included 60% of the group. In three patients improvement in behavior and emotional stability were observed postoperatively; this change was independent of the reduction of the frequency of seizures. Postoperative changes in the electroencephalogram were less frequent than changes in the frequency of seizures and also were completely independent of the clinical results.

In spite of continuous progress in the pharmacology of epilepsy a significant number of patients (10% to 15%) are not controlled by drugs. In many cases where no surgically accessible focus can be found by electroencephalographic investigations, a desperate situation develops; the physical and mental condition of the patient deteriorates and he has no chance to be helped by any means.

We were impressed by the papers of Tokuoka, et al., and Ommaya and Baldwin reporting improvement of severe epilepsy after local extravascular cooling of the brain. We undertook to treat our intractable cases with high doses of anticonvulsant drugs given during severe general hypothermia plus local extravascular cooling of brain. This paper reports our first 25 consecutive patients thus treated.

Method

A combination of extravascular total body cooling with extravascular cooling of brain was chosen in order to reach an effective level of brain tissue hypothermia rapidly and under standard conditions.

The induction of anesthesia was performed with 0.5 gm of 2.5% Thiopental or 0.5 gm Propanidid with 0.000025 gm Fentanyl, followed by 0.060 to 0.100 gm of succinylcholine administered intravenously. The trachea was intubated and diethyl ether-nitrous oxide-oxygen inhalation anesthesia was administered. This simple and safe combination was chosen because the vasodilatation caused by diethyl ether often completed by the ganglionic blocking agent, Thiameton Spofa, also helped to decrease the body temperature. All patients were paralyzed with d-tubocurarine, and the lung ventilation con-
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FIG. 1. Apparatus for total body hypothermia with Autohypotherm (Heliestrand).

trolled by a respirator during the periods of cooling and rewarming.

Total body cooling was performed in an Autohypotherm (Heliestrand), which works on the principle of forced circulation of cool air (Fig. 1). The cooling was continued until the rectal temperature had dropped to 32° to 29°C. This required varying periods of time depending on the age, body weight, and sex of the patient. The average time required was 120 minutes, the shortest being 40 minutes in a 15-year-old girl weighing 40 kg, and the longest 480 minutes in an 18-year-old boy weighing 85 kg. When the decrease was rapid and steep, active cooling was interrupted when the rectal temperature reached 32°C; in most of these cases the temperature continued to drop 2° to 3°C. When the decrease in temperature was slow, active cooling was continued down to 29°C. When a rectal temperature of 30°C was achieved, diethyl-ether was discontinued and a mixture of N₂O–O₂ was given for the period of local cooling.

The extravascular local cooling of brain was achieved by irrigation of the subarachnoid space or ventricles with cool saline. Two frontal burr holes were made in the usual manner on each side, 3 cm lateral to the midline. The dura and arachnoid were opened, and two fine rubber catheters were inserted in the subarachnoid space directed to the base of the middle cerebral fossa. The proper position of the catheters was checked by free flow of the cerebrospinal fluid. In two patients, two additional catheters were placed in both lateral ventricles.

The cooling fluid was saline cooled to approximately 0°C and stored in a reservoir covered with an ice bag; it was then circulated by means of a 20 cc syringe and three-way stopcock from the reservoir through the catheter into the subarachnoid space. Excessive fluid was drained off through the other catheter. The perfusion rate used was 40 cc per minute; both hemispheres were irrigated alternately. The total amount of the cooling fluid used was 500 to 20000 cc. The local cooling took 20 to 60 minutes. The surface temperature of the brain was measured every
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3 minutes with a thermistor probe (Elektrolaboriet, Copenhagen). The temperature of the deeper brain structures was recorded at the end of the local cooling period when the surface temperature had become constant.

The initial temperature of the brain differed from that in the rectum by 0.4° to 4.0° C. During the period of irrigation, the surface temperature of the irrigated hemisphere dropped to 5° to 6°C in 3 minutes, and rose again during irrigation of the other hemisphere. Nevertheless, during 20 to 40 minutes, the temperature of both hemispheres dropped 0.3° to 10.0°C, so that the final values reached were 18° to 27°C (Fig. 2). There were individual differences in reaction to the local cooling, but in most patients, this final local temperature could be reached easily (Fig. 3).

The temperature of deeper structures, as measured by the thermistor probe at the end of the irrigation, was always higher than that of the surface and rose about 2°C for each additional 10 mm of depth (Fig. 4). As the minimum local temperature was reached a few patients showed a 1° to 2°C decrease of rectal temperature, which continued for 1 to 2 hours.

When the surface temperature of the brain had been stable for 10 minutes, 500 mg of Thiopental (pentothal) were given intravenously in 19 patients and 20 mg of Valium Roche (diazepam) in six patients. The catheters were then removed, the wounds closed in the usual manner, and the patient transferred to the intensive care unit. Controlled respiration was continued, and the patient was rewarmed until the rectal temperature had reached 33° to 34°C. Spontaneous respiration usually returned at a rectal temperature of 29° to 30°C, but it was not yet efficient, and assisted respiration was still necessary.

At the rectal temperature of 34°C the patients were conscious again and artificial respiration was discontinued. When shivering
occurred in conscious patients before a normal body temperature had been reached, it was controlled by Thalamonal to block the metabolic reaction to cold.

**Selection of Cases**

We used this procedure on 25 patients in 1968 and 1969. The youngest patient was an 8-year-old boy, the oldest one a 46-year-old woman. All patients had been given the anticonvulsant drugs in various combinations for years and still were having many seizures per month, or even daily. No selection according to the type of seizure was made in this group, which included typical grand mal, petit mal, and focal seizures. In eight patients, severe behavioral disorders were present, including debility, imbecility, and emotional difficulties.

The electroencephalographic investigation revealed no focus that could be approached surgically, even when finer methods such as nasopharyngeal or sphenoidal electrodes and pharmacological provocation of the seizure were used. The records revealed diffuse abnormality without any localizing signs, typical 3-per-sec spike and wave activity, or massive unilateral epileptic activity.

In all patients, preoperative serioangiographic and encephalographic studies were made in order to eliminate cases with space-occupying lesions or vascular malformations. In three cases, a localized or diffuse hydrocephalus was found as a sign of cerebral atrophy.

All patients had been observed by neurologists for years, and only those were selected for surgery in whom other therapy had completely failed. Most of them were hopeless cases, totally socially handicapped, and surgery was thought to be their last chance.

**Results**

**Number Treated**

The reduction of total body temperature to 28°C was achieved in 17 patients; in eight the rectal temperature dropped below 28°C. Subarachnoid irrigation was performed in 23 patients; additional ventricular irrigation was used in two others. Reduction of local brain surface temperature below 20°C was accomplished in 10 patients. In 11 cases the temperature reached was 20°C to 24°C; in four patients the local cooling was stopped at 25°C to 27°C.

**Mortality and Morbidity**

One 18-year-old boy died 6 weeks after surgery; postmortem examination showed bilateral symmetrical intracerebral hematomas localized in both parietooccipital regions. No obvious correlation with the operative procedure could be found, and it was assumed that the bleeding was of spontaneous origin. In six patients slight neurological deficits (dysphasia, hemiparesis, unilateral facial weakness) were observed in the first 10 postoperative days. All but two recovered completely in a few days. In one patient slight facial weakness was present 6 months after surgery; in the other, a hemiparesis disappeared 3 months after surgery.

**Immediate Course**

Eighteen patients made an uneventful recovery and were allowed to walk 2 or 3 days after operation. In 16 patients, one or two seizures occurred during the first few days. The anticonvulsant therapy has been continued for 6 months after surgery in all patients without any changes.

**Follow-up Examination**

Long-term follow-up was possible in 15 consecutive patients in whom at least 1 year had elapsed since operation. They were seen as outpatients every 2 months, and neurological and electroencephalographic examinations were performed. In those in whom no seizure occurred during the first 6-month period, the anticonvulsant therapy was reduced gradually.

In four patients, the procedure did not change the frequency, intensity, or type of seizures.

In two patients, there was a 50% reduction of seizures and the type of seizures became minor; only a single major seizure was observed postoperatively.

In five patients, only single minor seizures occurred during the follow-up period. The reduction in the number and severity of seizures in this group was striking, and the patients and their family were fully satisfied with the result.

In four patients followed for 17 to 22 months, no seizures were reported after surgery.

In three patients, a striking improvement in behavior and emotional stability was
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found postoperatively, independent of the reduction of the frequency and severity of seizures.

Electroencephalography

The electroencephalographic records after operation were interesting. In one patient (Case 5) completely free of seizures since surgery, the postoperative EEG was normal (observation period, 22 mos). In three others (Cases 1, 3, 10), only slight EEG improvement was found; two of these have been free of seizures, and the other showed no clinical improvement. In one patient (Case 9) who has not had any seizure since operation, the electroencephalogram has been the same as the preoperative one. In 11 patients the electroencephalogram has not changed substantially, even in those in whom the number of seizures has been reduced (Table 1).

Anticonvulsants

There were no significant differences in clinical results related to the drug used. Two patients of the “excellent” group were given Valium, the other two Thiopental. In the “no change” group, one was given Valium and the other three Thiopental.

Discussion

Local cooling of the brain, either as a single procedure or combined with the total body hypothermia, has been used by several authors for protection of the brain against ischemia, in patients with intracranial brain tumors and in cases of intrac-

### TABLE 1

* The clinical and EEG results in 15 consecutive patients followed for more than 1 year postoperatively

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Type of seizure*</th>
<th>Average Number of Seizures Monthly</th>
<th>Minimal Surface Temperature</th>
<th>Drug Used†</th>
<th>Clinical Result‡</th>
<th>EEG Postop</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24 M</td>
<td>GM</td>
<td>20</td>
<td>26° C</td>
<td>T</td>
<td>I</td>
<td>slight improvement</td>
</tr>
<tr>
<td>2</td>
<td>19 M</td>
<td>M</td>
<td>40</td>
<td>24° C</td>
<td>T</td>
<td>II</td>
<td>no change</td>
</tr>
<tr>
<td>3</td>
<td>25 M</td>
<td>GM</td>
<td>25</td>
<td>26° C</td>
<td>V</td>
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<tr>
<td>4</td>
<td>26 M</td>
<td>GM</td>
<td>10</td>
<td>22° C</td>
<td>V</td>
<td>II</td>
<td>no change</td>
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<tr>
<td>5</td>
<td>20 M</td>
<td>GM</td>
<td>15</td>
<td>21° C</td>
<td>V</td>
<td>I</td>
<td>normal</td>
</tr>
<tr>
<td>6</td>
<td>16 F</td>
<td>M</td>
<td>5</td>
<td>22° C</td>
<td>T</td>
<td>II</td>
<td>no change</td>
</tr>
<tr>
<td>7</td>
<td>31 F</td>
<td>GM</td>
<td>20</td>
<td>22° C</td>
<td>T</td>
<td>II</td>
<td>no change</td>
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<tr>
<td>8</td>
<td>15 M</td>
<td>GM</td>
<td>15</td>
<td>21° C</td>
<td>T</td>
<td>II</td>
<td>no change</td>
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<tr>
<td>9</td>
<td>18 F</td>
<td>GM</td>
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<td>19° C</td>
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<td>I</td>
<td>no change</td>
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<tr>
<td>10</td>
<td>28 F</td>
<td>GM</td>
<td>30</td>
<td>22° C</td>
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<td>IV</td>
<td>slight improvement</td>
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<tr>
<td>11</td>
<td>19 M</td>
<td>GM</td>
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<td>III</td>
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<tr>
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<td>60</td>
<td>18° C</td>
<td>V</td>
<td>IV</td>
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<tr>
<td>13</td>
<td>13 F</td>
<td>GM</td>
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<td>14</td>
<td>17 M</td>
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<td>15</td>
<td>31 F</td>
<td>M</td>
<td>80</td>
<td>19° C</td>
<td>T</td>
<td>IV</td>
<td>no change</td>
</tr>
</tbody>
</table>

* GM = major seizures, PM = minor seizures, M = mixed seizures.
† T = Thiopental (pentothal); V = Valium Roche (diazepam).
‡ Clinical results: I = no seizures following surgery, II = single minor seizure, III = 50% reduction in number of seizures and substantial change of the type of seizure, IV = no change from preoperative frequency, intensity and type of seizure.

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The protective effect of local hypothermia of the brain has been proven in experimental animals, and different techniques of local cooling have been developed. The original concept of treating epilepsy by local hypothermia of the brain and by single doses of anticonvulsant drugs was based on experiments performed on animals by Baldwin, et al. They concluded that, in the Rhesus monkey, local cooling of the brain temporarily suppressed the epileptiform activity of the penicillin focus and that the same effect could be achieved by single intravenous doses of Dilantin in normothermic animals. When, however, the same drug was given under local brain hypothermia, the effect was permanent and the epileptiform activity did not disappear even after rewarming the animal. They suggested that the blood-brain barrier could be affected or temporarily inactivated by hypothermia so that the effective level of the drug could penetrate cerebral tissue.

There are two weak points in this theory. In man, Tokuoka, et al., reported fewer seizures and improved behavior after ventricular irrigation with cooling fluid, even without giving any drugs. Ommaya and Baldwin did not use any drugs in their first reported human cases, and the effects on seizures also were encouraging. On the other hand, no significant uptake of Dilantin during local brain hypothermia was observed by Baldwin, et al., in experimental animals. It is still not clear whether the good clinical results are caused by deep hypothermia of brain alone or by the combination of hypothermia and a single dose of the drug. We believe this uncertainty still has not been solved even by the experience we have reported. This can only be clarified by a study of the deposition of the drug in human cerebral tissue. Such a project has been started at the Neurosurgical Clinic in Prague, and results will be reported later.

The choice of technique for local brain hypothermia appears to be important. In normothermic patients Tokuoka, et al., used ventricular irrigation with cool Ringer's solution. Negrin and Ommaya and Baldwin also irrigated the subdural and eventually the subarachnoid space in normothermic patients. To achieve a constant level of deep local hypothermia of brain, we decided to combine the local extravascular cooling of brain with total body cooling. The mean values of the brain temperature achieved in our patients have been significantly lower than those reported in other studies. Even under these conditions the gradient of temperature appeared to be rather steep, the deeper structures of brain being more resistant to surface cooling. If the actual temperature of brain tissue could be maintained below 25°C for at least 30 minutes, as proposed by Baldwin, et al., in the experimental animal, the combination of local cooling with the total body cooling would be the easiest, safest, and most effective way. This method enabled us to attain deep tissue hypothermia as quickly as possible and to maintain it for a reasonable period even after having finished the irrigation. Moreover, our experience showed there is no incidence of ventricular fibrillation as in cases of total body pervascular hypothermia.

As far as we know, follow-up data regarding the postoperative changes in the electroencephalograms of patients treated in this way have not been published. In our studies, the electrographic and clinical results were apparently unrelated. This important fact suggests that the action of a single dose of anticonvulsant and/or local hypothermia need not necessarily affect the mechanism that triggers an epileptic seizure. In other words, we postulate that the mechanism of a seizure can be blocked selectively. Further detailed investigation should be conducted to support this idea.

An interesting result of the new method was the improvement in behavior and emotional stability we observed in certain patients after surgery. Tokuoka, et al., and Baldwin have reported similar experiences. As the behavioral changes do not necessarily depend on the reduction in the frequency of seizures, direct action of the drug and/or local hypothermia have to be presumed.

Thus, local brain hypothermia and single doses of anticonvulsants can be considered to be a useful method of treatment in certain cases of epilepsy. Even though our patients were intractable and hopeless cases, the results appeared comparable to those with other methods of surgical treatment of epilepsy. The excellent and fair results totalled...
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60% of our group, and the mortality and morbidity were low. The main advantage of the method consists in the fact that no permanent anatomical lesion is made and that the procedure can be repeated if necessary. One must, however, take into account that the follow-up period in our patients has been too short for final evaluation and, therefore, the follow-up of this group has to be continued for at least 3 to 5 years after surgery, before valid conclusions can be reached. Nevertheless, we think that even short-term results are significant because of the approach to combined treatment of epilepsy which they suggest.

Although there were fair to excellent results in 60% of the patients, the mode of action of the deep hypothermia of brain and that of simultaneous single doses of anticonvulsant drugs are not yet completely clear. However, changes in the function of the blood-brain barrier and the increased accessibility of the drug to nerve elements during hypothermia seem to be the most likely causes of the reduction of the frequency of seizures. Further research has to be done to prove this concept.

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Received for publication January 13, 1970.
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