INDUCED HYPOTHERMIA AS A THERAPEUTIC MEASURE IN NEUROLOGY

A Clinical Study of a "Hopeless" Case

BY

C. B. SEDZIMIR AND D. JACOBS

Regional Neurosurgical Centre, Liverpool

AND

J. W. DUNDEE

Department of Anaesthesia, University of Liverpool

ALTHOUGH hypothermia has only recently been introduced as a therapeutic agent in surgery and anaesthesia, it is already proving of value because of the reduction in tissue oxygen consumption that occurs when the temperature is lowered (Bigelow, Lindsay, Harrison, Gordon and Greenwood, 1950). Recent reports concern its application to cardiac surgery (Lewis and Tuffic, 1953; Swan, Zeavin, Blount and Virtue, 1953) and to general surgery for poor risk cases (Dundee, Gray, Mesham and Scott, 1953; Dundee and Mesham, 1954). Its application in acute head injuries with mid-brain lesions has been reported by Woringer, Schneider, Baumgarter and Thomalske (1954).

In a previous communication we have drawn attention to the value of combining hypothermia with hypotension during major neurosurgical operations (Dundee, Francis and Sedzimir, 1954). The present report deals with a neurosurgical case in which hypothermia was employed, first to increase the safety of hypotension at operation, and later, on two occasions, as a therapeutic measure. The patient survived for twenty-eight days following a massive intracerebral haemorrhage from a saccular aneurysm which was operated upon during the bleeding phase. The artificial reduction in cerebral metabolism is thought to be the main factor responsible for the prolonged survival and the astonishing preservation of function in areas of brain devoid of their main blood supply.

The method of producing hypothermia will not be discussed in detail, but surface cooling was used throughout. Chlorpromazine and hexamethonium were given to produce peripheral vasodilatation. Shivering was prevented by analgesic drugs (pethidine and levorphan) and chlorpromazine (Dundee, Mesham and Scott, 1954).

CASE REPORT

Mrs. S., aged 40, was admitted to a medical ward on 17.3.54. Two and a half hours before admission, while polishing furniture, she was struck by a severe headache and became unconscious. She vomited on regaining consciousness and complained of severe diffuse headache.

On examination, she was found to be drowsy and restless but was able to co-operate for the simpler
tests. Neck rigidity was present. Apart from the optic fundi which were not examined, all the cranial nerve reflexes were normal. Motor power, sensation and reflexes were also normal. There was no abnormality in the respiratory cardiovascular or alimentary systems. Blood pressure was 130/80, pulse 86 per minute and of normal rhythm. A lumbar puncture revealed heavily blood-stained fluid under a pressure of 350 mm. water. On 19.3.54 a full neurological examination revealed no abnormality except for an equivocal right plantar response. Her mental faculties were fully preserved. On 23.3.54 she had another, but less severe, subarachnoid haemorrhage without any localizing signs.

Angiography (25.3.54, C.B.S.)

Under light anaesthesia, percutaneous angiography was performed on the right carotid artery, taking lateral and axial views. During the injection for axial exposures, the opposite carotid artery was compressed in order to ascertain the collateral circulation. The lateral views showed an aneurysm on the middle cerebral artery measuring 10 × 4 mm. and projecting downwards. The supraclinoid segment of the internal carotid artery was in spasm and there was a generalized spasm of the middle cerebral tree. The posterior cerebral artery was filled, but the anterior cerebral artery did not show. The axial views placed the aneurysm 1.5 cm. from the usual position of bifurcation of the internal carotid artery. The anterior cerebral artery was again absent despite the compression. Under such circumstances it is our routine to perform bilateral angiography at once, but for technical reasons left-sided angiography was postponed.

The patient was examined later the same day. She was none the worse for the investigation and declared that the headache was less severe. Four days later, at 8.45 a.m., she suddenly lost consciousness for fifteen minutes. She was incontinent but there were no convulsions. When she came round she was very restless and complained of severe occipital headache. At 11.0 a.m. she did not respond to verbal commands. Her pupils were small and did not react to light. The fundi were normal. There was a supranuclear paresis of the left side of the face, and a gross weakness of the left side of the body. The left leg was not paralysed but there were of good range against gravity and at the elbow there was an appreciable movement of the left shoulder, but no more distal movements were seen in that arm. At 11 p.m. her rectal temperature was 97°F. She responded instantly to any minor stimuli by groans and purposeful movements of the right limbs and the left lower limb. There was an appreciable movement of the left shoulder, but no movement of the left limbs. Her temperature had risen and cardiac and respiratory rates were very rapid. It was decided to re-explore the wound to exclude compression by a blood clot.

Anaesthetic notes (J.W.D.)

Premedication was with chlorpromazine 50 mg. and hyoscine 1/150 grain (0.42 mg.). Anaesthesia was induced with 100 mg. thiopentone and 20 mg. suxamethonium. An armoured endotracheal tube was passed, the pharynx packed with moist gauze and the anaesthesia was continued with nitrous oxide-oxygen by a T-piece technique.

Details of anaesthetic and operation are shown in figure 1, her immediate pre-operative condition being indicated at A.

First operation (C.B.S. and D.J.)

Right fronto-temporal craniotomy. On opening the dura the whole area of exposed brain showed deep blood-staining. The brain itself was extremely friable. The Sylvian fissure was opened and immediately intracerebral blood clot was encountered. As soon as suction was applied to the clot, fresh arterial bleeding ensued. The aneurysm was then quickly exposed by further suction and the moderate haemorrhage was controlled by gently nipping the aneurysm with dissecting forceps. More of the surrounding blood clot was removed and it was then seen that the main trunk of the middle cerebral artery divided into three branches, a sessile aneurysm sitting astride two of them, while the third emerged from the sac itself. An attempt at clipping off the base of the aneurysm was unsuccessful and a clip was applied to the stem of the artery just proximal to the sac. The bleeding ceased instantly (B, fig. 1). When all the intracerebral clot was removed, it was evident that the anterior two-thirds of the temporal lobe had been destroyed and that the adjoining areas of the frontal and parietal lobes were also involved. Posterolaterally the clot filled the temporal horn as far as the trigone. During further haemostasis a pint of blood was given quickly (C, fig. 1), thus raising the blood pressure to 85 systolic. The dura was then sutured and the wound closed in the usual manner (D, fig. 1).

Post-operative progress.

Within 30 minutes of the conclusion of the operation (E, fig. 1) the patient responded to minor painful stimuli by groans and purposeful movements of the right limbs and the left lower limb. There was an appreciable movement of the left shoulder, but no more distal movements were seen in that arm. At 11 p.m. her rectal temperature was 97°F. She responded instantly to any minor stimuli by groaning, opening her eyes and moving her limbs. The power of the right leg was still as that of the right, but surprisingly there was now movement of the left shoulder, elbow, wrist and fingers. These movements were of good range against gravity and at the elbow there was power against resistance. Noxious stimuli over the left side of the body were localized fairly accurately. The pupils were equal and reacted to light. During the second half of the night her condition deteriorated. At 10 a.m. on 64.54 she showed very little response to painful stimuli, and the right pupil was dilated and fixed. There was no movement of her left limbs. Her temperature had risen and cardiac and respiratory rates were very rapid. It was decided to re-explore the wound to exclude compression by a blood clot.
Second operation (C.B.S.)

The flap was re-elevated. The brain was extremely tense and swollen and was oozing between the dural sutures. The depths of the Sylvian fissure were inspected and there was no evidence to clot. A right frontal lobectomy was performed in order to provide internal decompression for the massive oedema of the hemisphere. The dura was left unsutured, the bone flap was allowed to ride freely.

8 p.m. Despite frequent sponging, tachycardia, tachypnoea and hyperthermia persisted and there was no neurological improvement.

Second hypothermia.

7.4.54 (fig. 2). This was commenced at 12.45 a.m. and continued until 10 a.m. At the onset (a) her right pupil was dilated and fixed and the left hemiplegia complete. Approximately one hour later (b) the pupil became smaller and showed a slight reaction to light. She became more active generally and began to move the left leg freely although the paresis was marked. When her temperature was reduced to normal (c) some movements of the left shoulder and elbow were noticed and her conscious level was slowly but noticeably rising. Although the drugs and ice were discontinued at 10 a.m., she remained uncovered and the improvement reached at this time was maintained for the following thirty-six hours.

10.4.54. Temperature, pulse and respirations started to rise in the evening. A complete right third nerve palsy developed.

11.4.54. Her condition began to deteriorate seriously in the afternoon. Both pupils became dilated and fixed; there was no movement in the left arm and very little movement in the left leg. Her general response to stimulation was very feeble.

Third hypothermia.

5 p.m., 11.4.54. (fig. 3). Three hours after the commencement her pupils became smaller, showing a little reaction to light, and responsiveness was increasing (A).

On 13.4.54, exactly forty-eight hours after the start (B), the following examination was recorded: “She now opens her eyes whenever touched and occasionally follows the examiner with her gaze. There is a partial recovery in the third nerve palsy. Both pupils are of medium size and react to light. She moves her right limbs and left lower limb purposefully and slight movement has returned to her left shoulder and elbow. She shows a delayed response to painful stimuli applied to the left side of her body.”

General management.

Throughout the whole period of hypothermia, in addition to half-hourly temperature, pulse and respiration observations, the patient was attended two-hourly for the purpose of turning, feeding, etc. Water glucose-saline, milk and Casilan were given in rotation by Ryles tube, supplemented with vitamins and potassium. Naso-pharyngeal and tracheal secretions were aspirated whenever necessary. Penicillin and streptomycin were given parenterally.

At 9.30 p.m., on 14.4.54 her temperature again reached 98°F for the first time since the onset of this cooling. For the next two days her temperature remained between 98°F and 99.5°F, her skin tempera-

ture between 86°F and 97°F, her respiration between 20 and 24 per minute, and her pulse between 110 and 130 per minute. There was a steady improvement in her general condition.

Subsequent course.

17.4.54. Weak movements of her left fingers were again observed.

19.4.54. She began to respond to verbal commands. She would open her eyes on request and squeeze the examiner's hand. On stimulation movements of the left shoulder, elbow and fingers became more marked. Tonus which had so far fluctuated between flaccidity and slight resistance, became definitely increased. Reflexes were all brisk, the right more so than the left, although the right plantar response was flexor compared with a definite left extensor. She did not utter a word and would not take anything by mouth apart from a few sips of water.

22.4.54. Lumbar puncture: pressure 150 mm.; clear colourless fluid containing 6 lymphocytes per c.mm. and a protein of 120 mg. per cent. Blood: white cells 16,000 per c.mm.; serum chlorides 680 mg. per cent; potassium 19.5 mg. per cent; sodium 360 mg. per cent.

28.4.54. X-ray chest: normal.

30.4.54. Both her husband and the House Surgeon, on separate occasions, reported that she had nodded her head when asked if she recognized the husband. She again looked to be on the point of speaking. For most of the day she sat in an easy chair propped up with pillows, staring expressionlessly to the front or dropping off to sleep. Her mask-like face only altered when attention was paid to her and then her expression changed to one of apparent displeasure at being disturbed, accompanied by an occasional groan or a slight grimace. The right ptosis was slight but there were grossly defective inward, upward and downward movements of this eye. The optic fundi were normal. The power of the left leg was poorer than previously and movements of the left fingers were again absent, but apart from these there was no alteration in the findings recorded on 19.4.54.

2.5.54, 2.15 a.m. She had a fit of coughing witnessed by a nurse and died instantly. Her death was thought to be due to pulmonary embolism.

Post-mortem examination.

3.5.54. The thoracic and abdominal organs were normal.

Brain.

The right cerebral hemisphere was soft and " mushy " throughout, including the occipital lobe and the region of the basal ganglia. The left hemisphere and the cerebellum appeared macroscopically normal, as did the brain stem. The right middle cerebral artery was completely occluded by a clip applied proximally to a shrunken sacular aneurysm. Another clip was in situ on a small branch emerging from the aneurysm. Other cerebral vessels and both internal carotid arteries appeared to be normal.

DISCUSSION

Within a period of fifteen days, this patient suffered from five incidents of
haemorrhage from an aneurysm on the right middle cerebral artery. The first two were purely subarachnoid, the third had a minor cerebral component, and the fourth resulted in a profound cerebral lesion. On the day of operation, during transport to the theatre, a massive intracerebral haemorrhage occurred.

The operation was undertaken on a comatose patient with a dilated and non-reacting pupil, a left hemiplegia and concurrent hyperthermia, hyperpnoea and tachycardia (A, fig. 1). Clinically this was the syndrome of gross interference with mid-brain function, the gravity of which is well known. The aneurysm was still bleeding when exposed, although the blood pressure had been lowered artificially (B, fig. 1). The technical performance of the operation was greatly facilitated by the hypotension produced by Arfonad. In the light of subsequent events such a degree of hypotension was probably only made safe by the concurrent use of hypothermia.

During operation the following facts were established and are stressed in relation to the post-operative clinical findings:

(1) Clipping of the middle cerebral artery 1 cm. from its origin, thus
cutting off the main blood supply to the whole territory of its distribution.

(2) About two-thirds of the right temporal lobe was destroyed by the massive intracerebral haemorrhage, and the adjoining areas of the parietal and frontal lobes were damaged.

Despite the gravity of the pre-operative condition and the profound lesion sustained by the right hemisphere the patient rapidly began to regain consciousness. Activity in the left limbs was apparent within thirty minutes (E, fig. 1). During the next few hours, while her temperature was still just below normal, she responded instantly to minor stimuli and had a normal power in the left lower limb. There was a good movement against gravity in the left upper limb, including the wrist and fingers, and elbow flexion was present against resistance. There was fairly accurate localization of stimuli applied to the left side of the body. The right pupil became normal in size and reacted to light. Over the following twelve hours her temperature, respirations and pulse rates rose...
rapidly, and parallel to this rise there was a deterioration in the state of consciousness until coma supervened. The left hemiplegia recurred and the right pupil became dilated and fixed. The second operation disclosed a massive oedema of the right hemisphere. The right frontal lobe was amputated to provide internal decompression and the dura and the bone flap were left unsutured, again for decompression. In addition to the original lesions there was now a widespread vascular embarrassment with which to contend and despite the extensive mechanical measures, there was no appreciable improvement after this operation. Therapeutic hypothermia was induced in the hope that, in reducing local tissue metabolism, the patient might be tided over the acute phase of vascular embarrassment. It can be deduced from figure 2 that this period of hypothermia was not entirely satisfactory. Shivering occurred frequently and prevented the lowering of temperature to hypothermic levels. The respiratory and pulse rates were, however, rapidly controlled and as soon as the temperature was reduced to normal an increase in responsiveness and movement in the left limbs was again observed.

On reconsidering the case history, it would seem that on the first and second occasions the hypothermia was not maintained over a sufficient length of time for this type of profound vascular disturbance. In contrast to these, at the third therapeutic hypothermia the temperature was well reduced and maintained at low levels for seventy-two hours. The improvement in the general responsiveness, oculomotor paresis and paralysis of the left limbs steadily progressed as the hypothermia continued. Within forty-eight hours she recovered consciousness sufficiently to open her eyes and occasionally to follow the examiner’s activities (B, fig. 3). Five days later she began to respond to verbal commands and would open her eyes or grip the examiner’s hand by request. Some movement even returned to the left fingers. She remained mute, however, although giving the impression of making an effort to speak, up to the time of her sudden and unexpected death. This took place twenty-eight days after the first operation and hypothermia and eighteen days after the third one had concluded. At post-mortem the extent of destruction of the right hemisphere was such that it is surprising that it had functioned at all. The actual cause of her sudden death was not apparent.

On the morning of the operation the patient was judged, by clinical standards, to be moribund and to be inoperable in ordinary circumstances. If desperate surgery were to be undertaken, it would be impracticable without artificially inducing hypotension. Despite the considerable cerebral destruction by haemorrhage and by the clipping of the middle cerebral artery, the rapidly recovering consciousness and the degree to which the hemisphere retained its physiological function during the immediate post-operative period can only be ascribed to the hypothermia. Without this, one would have expected that, immediately post-operatively, the patient would have been in the state which developed twenty hours after the operation, i.e. eighteen hours after the conclusion of the cooling. The standard surgical decompressive procedure did not produce any beneficial
Details of the third hypothermia and subsequent course.

**Drugs:**
- ■ represents 25 mg. chlorpromazine.
- □ 50 mg. pethidine.
- ▽ 2 mg. L-methorphan (Dromoran).
- ▲ 50 mg. hexamethonium.

All drugs were given by deep intramuscular injection with or without hyaluronidase.

Effect. On two further occasions this patient was subjected to induced hypothermia while *in extremis*. In each of these there was a surprising degree of clinical improvement paralleling the reduction of the pulse and respiratory rates and of the temperature. Our observations certainly indicate that this improvement was directly related to the efficacy and the length of the cooling.

In this case the benefits derived from the induced hypothermia are so strikingly significant that the potentialities of this therapeutic measure are well worthy of further exploration. Two groups of cases would seem to lend themselves to this form of therapy:

(a) Intracranial ischaemic lesions, arterial or venous, in which the hypothermia is used in order to allow the brain to survive with a lowered metabolism, while the blood pressure would be maintained in the hope of opening up whatever channels of collateral circulation exist.
Pyrexias of hypothalmic and brain-stem origin, either post-operative or following head injury.

Much experience is, however, still to be gained before hypothermia could be an established procedure apart from its use as a supplement to anaesthesia.

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We are also grateful to the Sisters and Nurses of Walton Hospital whose kind co-operation made such a study possible.

REFERENCES


ANAESTHETIC APPOINTMENT AT GLASGOW UNIVERSITY

The University of Glasgow in conjunction with the Western Regional Hospital Board has created a Senior Lectureship in Anaesthetics to organize and direct a Department of Anaesthetics at Glasgow University and Glasgow Royal Infirmary. This appointment carries the clinical ranking of Consultant.

The University and Regional Board has selected for this appointment Dr. Alex. C. Forrester.

Dr. Forrester is Chairman of the Anaesthetic Services Sub-Committee of the Central Consultants' and Specialists' Committee (Scotland), and is the Scottish representative of the British Medical Association Anaesthetic Group, London. He is a Consultant Anaesthetist at Glasgow Royal Infirmary, with which he has been associated for the past 18 years.

During that time, Dr. Forrester has participated in the clinical teaching of anaesthetics to medical students and post-graduates at the Infirmary. In the field of research Dr. Forrester has interested himself in the early introduction of curare into anaesthesia, and circulatory changes during anaesthesia.

He has taken time to visit many other Departments of Anaesthesia in this country and abroad, spending some time in the U.S.A. and Canada.

Dr. R. C. O. Saunders has been appointed Assistant to the above post.