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Hypothermia in the Treatment of Critical Head Injury

C. G. DRAKE, M.D. and T. A. JORY, M.D., *London, Ont.*

ABSTRACT

Because of the beneficial effect on the character and mortality of experimental brain injury, 21 patients with critical brain injury (thought to be incompatible with life using standard methods of treatment) were subjected to artificial hypothermia (28°-36° C.) for two to 10 days. Nine died and 12 survived, but six of the survivors are permanent invalids with dementia. The hazards are staphylococcal pneumonia, which occurred in eight cases and contributed to all the deaths, and gastrointestinal ulceration with bleeding and perforation, which was fatal in another. The results in patients with clots did not differ from those without. Youth was the only common factor in the successful cases. Prognosis was hopeless in the presence of large fixed pupils. About one in four of these critical cases will fare well, but it is evident that a large proportion have such gross or microscopic tearing of deep cerebral structures that in the event of survival there will be severe mental and physical handicaps.

PATIENTS with critical brain injuries are of special concern to the surgeon and his nursing staff, for there is no more difficult group to treat, and after a mortality rate of at least 50%, the survivors are only too often permanently crippled in mind or body.

Hyperthermia is a feature of this state, and has long been treated by aspirin, sponging, fanning, ice water enemas, and special nursing care. The tide might be turned by such procedures, but in a high proportion of cases the brain swelling is relentless and fatal.

There is good evidence to suggest that drastic reduction of body temperature has a profound effect on the character and mortality of experimental brain injury. Rosomoff[1, 2] developed a medial lethal injury ($L.D._{50}$) which could be expected to kill 50% of normothermic dogs. This acute injury to the brain at normal body temperature resulted in wedge-shaped hemorrhagic lesions with edema of the affected hemisphere, shift of the internal structures across the midline, and transtentorial and brain stem herniation. Post-traumatic and inflammatory reaction in the form of cerebral edema and leukocytic response was marked and progressive.

In contrast, when injuries to the brain of the same magnitude were produced with body temperatures of 25° C. or less, the lesions were partially hemorrhagic and the post-traumatic inflammatory reaction was markedly reduced. Cerebral edema developed to a mild degree immediately after injury and thereafter its progression was slight. The leukocytic response was absent or minimal, even 36 hours after injury. Significantly, the mortality dropped to 7%. There was evidence, microscopically, that the inflammatory response was more advanced at the end of seven days with well-developed macrophagic and fibroblastic activity. The protection seemed to be effected by modification of the response to injury, hypothermia producing a more rapid transition from the exudative to the reparative stage of the reaction.

However, in the presence of severe experimental injury the mortality was the same (100%), in spite of the fact that hypothermia delayed the time from injury to death by five times. Rosomoff then showed that hypothermia exerted a worthwhile effect after experimental brain injury had been produced. $L.D._{50}$ lesions were produced in groups of normothermic dogs and at variable times after injury, ranging from one to 12 hours; hypothermia was induced, maintained for one hour, and the animals were then rewarmed. If hypothermia was begun within three hours of injury, there were no deaths. If the delay was longer than seven or eight hours,

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From the Department of Surgery, University of Western Ontario, London, Ont.

there was no protection and the mortality reverted to 50%. Another striking set of experiments showed that hypothermia protected dogs against massive cerebral artery ligation, presumably because of the early development of collateral circulation.

Therefore, it would appear that hypothermia would be of value in the treatment of human brain injury provided that its induction was effected early in the evolution of the inflammatory response. Benefit would derive from the reduction of metabolic activity, lessening of brain swelling and cellular response, and lengthening of the time interval provided for the development of collateral circulation to areas which might otherwise become infarcted.

It is difficult to assess the therapeutic value of hypothermia, since no standard selection of cases is possible in the face of the very diversified nature of brain injury. We chose, therefore, to base this study on the analysis of 21 patients with closed craniocerebral injuries, thought to be incompatible with life, treated by standard methods. Each patient was in extremis with hyperthermia (104°-108° F.), decerebrate rigidity, and failing vital functions. This is the group most often subjected to hypothermia, but even here the injury was not standard, since 10 patients had had clots evacuated and in the others the interval between injury and the development of the critical state varied from one hour to three days. Four patients had fractures, but there were no known serious visceral injuries. Body temperature was reduced to levels varying between 28° and 36° C. by means of refrigerated blankets and/or plastic ice packs, and maintained at that level for two to 10 days. Tracheotomy was performed on all patients except two children, and nutrition was sustained by intravenous and nasogastric tube feeding. Urea was used in only two cases. Those patients not having burr holes were subjected to an angiogram to rule out the presence of a clot.

The technique of hypothermia is straightforward, but requires a special and dedicated nursing team around the clock. This continuous and expert care is a major factor in the recovery of these patients, and unfortunately is not usually available on the general wards. However, no one who has not seen it can imagine the dramatic change that takes place with the reduction of body temperature to levels below 36° C. The patient is quiet with a slow pulse and respirations, as though asleep, whereas a few hours ago he was cyanotic, rigid and sweating with gasping periodic breathing and a temperature near or at the maximum register of the thermometer.

Of the 21 patients in this study, nine died and 12 survived, but six of the 12 survivors are chronic invalids. Four are under permanent institutional care with severe dementia (two with hemiplegia) and two are just able to live in their home environment.

Two of the patients who died point out the hazards of this treatment. The first was admitted

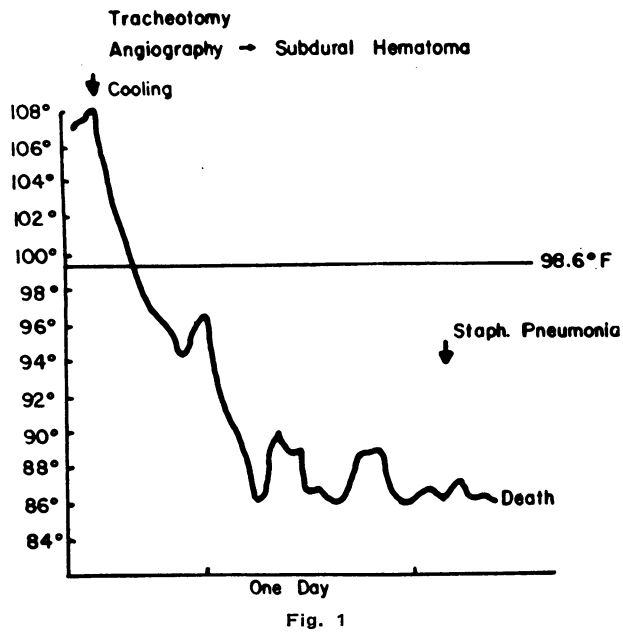

Fig. 1

with a clear-cut history of deterioration of consciousness, but was moribund with a temperature of 108° F., pulse 156, and respirations 56 per min. (Fig. 1). Rapid induction of hypothermia and tracheotomy brought about dramatic improvement. Even though a carotid arteriogram showed a shallow subdural collection, it was felt that an extra few hours of cooling would better the situation, but the patient died rather suddenly early on the morning of the proposed craniotomy. Certainly hypothermia is no substitute for the removal of a clot.

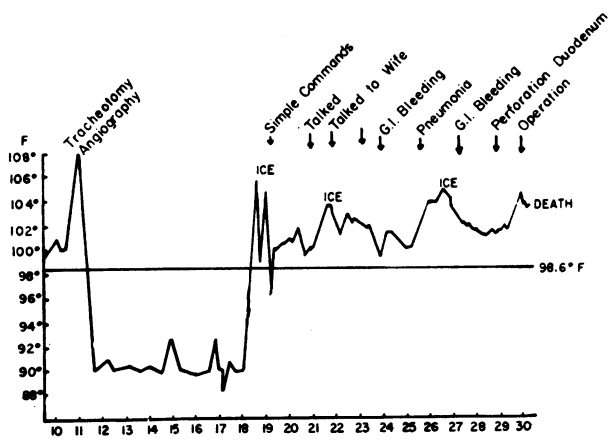

Fig. 2

The other patient was cooled when he deteriorated on the second day with a temperature of 108° F. and decerebrate rigidity (Fig. 2). When his body temperature reached 33° C., improvement in his general condition was dramatic. The rigidity relaxed; by the seventh day he was responding to simple commands; and four days later he was talking to his wife, and joking. But sudden shock followed an episode of gastrointestinal bleeding on the fourteenth day, and two days later he had an established staphylococcal pneumonia. Death oc-

curred after further bleeding and perforation of an acute duodenal ulcer, in spite of laparotomy.

This was the only known example of gastrointestinal ulceration and hemorrhage in this group of cases. Presumably the ulceration could have arisen by one of two separate mechanisms: one related directly to hypothermia, the other to hypothalamic injury (Rokitansky-Cushing). The latter phenomenon has been studied recently in experimental animals by Long *et al.*,[3] who found that anterior hypothalamic lesions caused gastric hemorrhage with acute gastric dilatation, while posterior lesions produced gastric ulceration as well as hemorrhage, the stomach remaining small. Both lesions were associated with a fall in gastric pH. These experiments support the theory that autonomic imbalance causes the erosions, although the local mechanism remains obscure. It is interesting that localized gastric hypothermia seemingly has no effect on ulcers associated with human brain injury,[4] although this form of treatment does have a definite effect on the bleeding and mortality in cases of "functional" peptic ulceration.[5]

Hypothermic "stress" ulceration is probably the result of digestion of the mucosa by hydrochloric acid in the face of intense vasoconstriction.[6] The secretory activity of the cold mucosa is vastly reduced and the preformed acid leaks out passively to act on the unprotected mucosa. In the experimental animal this may be prevented by alkaline gastric lavage. This was the probable mechanism in this patient, for at the time of bleeding he was rousing well from his stupor and there was no evidence of hypothalamic injury post mortem.

Eight of the 21 patients in this series developed severe pulmonary complications, chiefly staphylococcal pneumonia, which contributed to all of the deaths, one of which followed nine months in a decerebrate state. This dreaded sequel is prone to occur in these patients, related in part to low body temperature, but assisted by immobility, the inability to raise secretions, and improper tracheotomy care.

Ten patients had significant clots; 11 did not (Table I). The outcome in these two groups was not significantly different. The patients with clots had deteriorated to the same critical state as had those without clots. Four had no "interval" and obviously had severe contusion as well. Surprisingly, all survived, and three are well while one is in poor condition. Of the six with delayed deterioration of consciousness, three are dead and three are in poor condition. This might indicate that brain stem changes and cerebral swelling with prolonged uncal herniation are controlled to a lesser extent than the more diffuse swelling and contusion associated with shallow clots. As an example, one 16-year-old boy had an extradural clot removed in the presence of bilateral fixed and dilated pupils. He is now a permanent resident of the asylum, vicious, incontinent, and with the eating habits of a wolf. We believe that head-injury patients in whom bilateral fixed and dilated pupils occur immediately or shortly after injury should not be treated energetically, for survival is rare and we have never seen useful recovery of cerebral function in such cases. Occasionally the situation will arise where the bilateral pupillary paralysis and coma following a clear-cut "lucid interval" is brief and the midbrain compression can be relieved quickly by administration of urea and rapid evacuation of a clot. In this circumstance a worthwhile result may be obtained with hypothermia.

TABLE I.
PATIENTS REQUIRING URGENT EVACUATION OF CLOTS

	No.	*Dead*	*Alive*	
Extradural	4	1	3	(3 poor)
Subdural	4	2	2	(2 good)
Intracerebral	2		2	(1 good, 1 poor)
Totals	10	3	7	(3 good, 4 poor)

PATIENTS WITHOUT CLOTS

No.	*Dead*	*Alive*	
11	6	5	(3 good, 2 poor)

This sad commentary is brightened only by the fact that six patients recovered reasonably normal mental and physical function, three of them after weeks of stupor, confusion and incontinence. One 12-year-old boy was on the point of death following incomplete evacuation of the subdural hematoma elsewhere. He survived with hypothermia and tracheotomy and another operation, and became lucid five weeks later. He has now passed his high-school entrance examinations with honours.

TABLE II.

	Cases	*Dead*	*Alive*	*Sequelae* *With*	*Without*
Sedzimir	30	13	17	6	11
Lazorthes	47	34	13	4	9
Drake	21	9	12	6	6
Totals	98	56	42	16	26

Two of the larger series[7, 8] in the literature were combined with our own figures (Table II). The total number of cases, 98, is sufficient to permit expression of the totals in terms of approximate percentages. The mortality is over 50%, and although approximately 17% are disabled, one-quarter of the patients treated with hypothermia are now well. This overall figure is encouraging. Walker[9] feels strongly that heroic measures should be reserved for younger persons. Although the overall mortality rate was 60% in his cases, it was 70% in those over the age of 40 years, and 35% among patients under 40 years. Only nine of 66 patients were salvaged for relatively normal lives, and 15 others had such serious neurologic deficits that they were unable to care for themselves.

Careful consideration must be given to the decision to use hypothermia. The hazards have been

emphasized, but of more concern is the selection of cases, for it would seem from our experience that patients with otherwise irretrievable brain injury may survive as a burden to their families and their community. In this series, six of the 12 survivors are crippled, with continuing stupor or dementia.

The cause of these sequelae has been attributed to bruising and laceration of the hemispheres and brain stem, or to mid-brain and pontine injury consequent to temporal coning. Sabina Strich of Oxford has shown in two very important reports[10, 11] a new feature of the pathology of human brain injury; namely, that diffuse severe degeneration of the white matter of the brain may follow a closed and apparently uncomplicated head injury, leaving the patient permanently incapacitated and more or less demented. She presented evidence that the extensive white-matter lesions, both of the hemisphere and brain stem, represent a secondary degeneration of nerve fibres which have been stretched or torn by the sheer stresses and strains set during rotation acceleration of the head at the time of injury.

How are we to recognize patients with such diffuse injury of white matter or those with irretrievable deep contusion and laceration, for it would be futile to cool these patients? It may be that secondary swelling furthers such changes and that hypothermia may alter the degree of final injury. Ideally, only those patients with massive swelling but mild or moderate contusion or laceration should be treated, as resolution of this process can be followed by recovery of function. As yet, no strict criteria are available, for analysis of these case histories has failed to reveal any clinical finding which might indicate the potential for survival, or for satisfactory recovery of cerebral function. Youth was the only common factor in the six successful cases, yet these patients were in the same desperate clinical state as the patients in the older age group. Walker[9] has also commented on the factor of youth. Perhaps it is related to our clinical impression that children are more prone to develop cerebral swelling than are adults. This impression has been gained from a considerable number of younger cases admitted because of delayed deterioration of consciousness but without focal disturbance of brain function. These children seem to improve in a day or two without specific treatment. If there is any truth in this surmise, it is conceivable that young people could develop a critical state in which edema plays a large part. In the absence of an underlying grave injury to the brain, resolution of the brain swelling would favour excellent recovery.

Often posed is the question, how deep and for how long should hypothermia be applied? It has not been fully answered. The experimental evidence would suggest that the level be deep, but of short duration, for Rosomoff was able to influence profoundly the character of the inflammatory response by cooling to 25° C. for only one hour. However, in clinical practice shallow levels are used for longer periods, usually a few days to a week. As the likelihood of cardiac irritability and fibrillation increases greatly at body temperatures below 28° C., the experimental levels are, in fact, dangerous and not practical for clinical use.

Our early cases were cooled to levels between 28° and 33° C., whereas latterly levels between 33° and 36° C. have been used. These higher levels seem to improve the critical clinical state to the same degree, but experimental evidence is lacking whether the same alteration of the pathological process occurs. Of 15 patients kept at the deeper levels of hypothermia, only two patients (aged 12 and 21) did well. Eight died and six are chronic invalids with dementia. Six more recently treated patients under the age of 20 years were kept above 33° C. Four became well, one died, and the other is completely disabled. The unplanned factor of youth rather than the level of hypothermia was probably the determining factor in the more favourable results in this group.

The time interval between injury and induction of hypothermia is undoubtedly very important. Bouzarth,[12] in Philadelphia, has had the opportunity of inducing hypothermia early in a series of 10 critical brain injuries. In most instances the cooling was begun within an hour after the injury and was carried to 90° F. (32° C.). Angiography, tracheotomy, and, if necessary, craniotomy followed. Seven of the 10 patients had intracranial clots evacuated. Only one patient died, one has a persisting hemiplegia and another has a severe aphasia. The remaining seven patients are well. This is remarkable evidence of the importance of early cooling, particularly in patients with acute intracranial bleeding.

Lastly, in another vein, we must not forget the less severe injuries: those patients whom we expect to survive with good nursing care. One can find no reference to radical treatment of this group. The rather dramatic modification of experimental brain injury by hypothermia may lessen greatly the final morbidity in such cases. Some form of anesthesia would be necessary and whether the hazards of prolonged narcosis and cold will be worth the risk remains to be seen.

SUMMARY

From the evidence available, early induction of hypothermia has a profound and beneficial influence on the character and mortality of *experimental* brain injury.

Hypothermia used in the treatment of 21 patients, critically ill with severe brain injury, was followed by recovery in five and by death in nine. Six of the 12 survivors are chronic nursing problems with severe dementia.

Older patients and those with fixed or irregular pupils did not fare well. Youth was the only factor that seemed to favour survival and return to a reasonably normal state.

Delay in the induction of hypothermia occasioned by transport and preparation may have accounted for a few of the poor results. However, a large proportion of these patients have such gross or microscopic tearing of deep cerebral and brain stem structures that in the event of survival there are severe mental and physical handicaps.

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The XXXXY Sex Chromosome Abnormality

M. L. BARR, M.D., D. H. CARR, M.B., Ch.B. and J. POZSONYI, M.D.,
London, Ont., and
R. A. WILSON, M.D., M.R.C.P., F.R.C.P.[C],
H. G. DUNN, M.B., M.R.C.P., D.C.H., T. S. JACOBSON, B.Sc. and
J. R. MILLER, Ph.D., *Vancouver, B.C.*
(with an Appendix by MARION LEWIS, B.A. and BRUCE CHOWN, M.D.
Winnipeg, Man.)

A CONSIDERABLE number of sex chromosome abnormalities have been discovered in man; they were reviewed in this Journal in 1960[1] and have since been fully summarized by Sohval.[2] In brief, abnormal sex chromosome complexes have less or more chromosome material than the XY and XX of normal males and females, respectively. In a sex chromosome deficiency, all or part of a sex chromosome is missing. This is likely to interfere with embryological maturation of the gonads; the best example is the XO condition which causes variable abnormalities of the gonads (usually aplasia) in Turner's syndrome.[3] Sex chromosome excess may occur in a variety of forms. When one or more X chromosomes are added to the normal female complement, development proceeds along female lines, as shown by the reports of XXX[4] and the rarer XXXX[5] patients. Similarly, judging from the single case on record,[6] the XYY abnormality is consistent with normal male development.

It is now known that several enlarged complexes (XXY, XXYY, XXXY and XXXXY) may occur, which have in common the presence of at least two

ABSTRACT

The most common sex chromosome complex in sex chromatin-positive males with Klinefelter's syndrome is XXY. When the complex is XXYY or XXXY, the clinical findings do not seem to differ materially from those seen in XXY subjects, although more patients with these intersexual chromosome complements need to be studied to establish possible phenotypical expressions of the chromosomal variants.

Two male children with an XXXXY sex chromosome abnormality are described. The data obtained from the study of these cases and five others described in the literature suggest that the XXXXY patient is likely to have congenital defects not usually seen in the common form of the Klinefelter syndrome. These include a triad of (1) skeletal anomalies (including radioulnar synostosis), (2) hypogenitalism (hypoplasia of penis and scrotum, incomplete descent of testes and defective prepubertal development of seminiferous tubules), and (3) greater risk of severe mental deficiency.

That the conclusions are based on data from a small number of patients is emphasized, together with the need for a cytogenetic survey of a large control or unselected population.

From the Department of Microscopic Anatomy, University of Western Ontario, and the Children's Psychiatric Research Institute, London, Ont., the Department of Pediatrics, University of British Columbia, Vancouver, B.C., and the Rh Laboratory, Winnipeg, Man.
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For a glossary of cytogenetic terms, see Sergovich, F. R., Soltan, H. C. and Carr, D. H.: *Canad. Med. Ass. J.*, 86: 852, 1962.