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# The safe duration of total circulatory arrest with profound hypothermia*

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## Introduction

Of all the organs of the body, the brain is the most vulnerable to ischaemia and it is generally accepted that a period of circulatory arrest of more than 3 minutes is likely to result in some degree of damage. The brain has no reserves of oxygen so, as soon as the supply in the blood is used up, the high energy phosphates are rapidly depleted and irrecoverable neuronal damage begins. If, however, the patient is a tiny child, who has fallen through the ice of a frozen lake we know from well substantiated case reports that not only is resuscitation possible after an hour or more, but that the child may recover completely.

The protective effect of cooling is probably largely due to the reduction in oxygen consumption of the brain which can be estimated from experimental data, for example that published by Donald Ross in Guy's Hospital Reports *(1)* to fall by a factor (the Q10) of about 2·2 per 10 °C fall in temperature. It seems reasonable to believe that the ischaemic time tolerated, being governed by the availability of oxygen and the rate of its consumption, will be lengthened proportionally as the body temperature is lowered.

This principle was used throughout the 1950s and 60s by Sir Thomas Holmes Sellors, past President of the College, in the surgical treatment of atrial septal defect *(2)*. The method of Bigelow *(3)* was modified at the Middlesex Hospital by Dr Brian Sellick *(4)* and the essential features were anaesthesia using ether and muscle relaxants; surface cooling by blanket and cold bath; a deep tissue temperature of 30 °C during circulatory arrest; and the avoidance of ventricular fibrillation. It was estimated that there might be up to 10 minutes of safe ischaemic time available under these conditions but the majority of the operations were performed with a total circulatory arrest time of 4 to 5 minutes. The results of their experience in 453 cases of ostium secundum atrial septal defect, with an overall mortality of 4.2%, were reported in Holmes Sellors' Bradshaw lecture *(5)*. It is impressive to realise that, by this method, straightforward ASD could be operated on with a risk of under 1% (2 deaths out of 277 'good risk' cases). For quite sometime, even after the development of cardiopulmonary bypass, this method of total circulatory arrest remained safer for the patient and was used for closure of uncomplicated ASD.

The extent of surgery was very limited however, because at 30 °C, the time available under circulatory arrest is very short. To permit a longer period of arrest, attempts were made to lower the temperature even further with right and left heart bypass and extracorporeal cooling *(6)* or more prolonged surface cooling *(7)*. Continuous perfusion on cardiopulmonary bypass with an oxygenator in the circuit gained general acceptance but there remained serious limitations in the use of cardiopulmonary bypass in infants. They tolerated extracorporeal circulation very badly and the presence of venous cannulae passing through the right atrium to drain the venae cavae made accurate repair of tiny hearts extremely difficult. A combination of surface cooling followed by core cooling on bypass and then circulatory arrest at 18–20 °C *(8)* overcame some of these problems and was associated with much improved results. This combination of surface and core cooling has therefore been widely accepted as a means of obtaining much longer periods of total circulatory arrest. In support of this practice, several groups have published IQ data obtained in patients studied some time after surgery. Using these measurements as a basis for their claims they have estimated that a period of 50 minutes *(9)*, 60 minutes *(10)*, or maybe even 70 minutes *(11,12)* of total circulatory arrest at 16–20 °C is 'safe', or at least is not associated with demonstrable functional impairment.

There are several reasons to be concerned about the time estimates based on this IQ data. First of all the measurement of IQ is not an easy or highly reproducible measurement so the influences imposed upon it by the detrimental effects of the heart disease and the beneficial effects of the haemodynamic improvement gained by its surgical cure may swamp any real changes attributable to cerebral damage. Secondly, it has been convincingly demonstrated that structural brain damage and, in particular cortical loss, may be well tolerated and clinically undetectable, perhaps due to the 'plasticity' of the infants nervous system *(13)*. Thirdly, a careful study of the data in these various publications reveals that although it has not been possible to demonstrate a significant and systematic reduction in IQ, the mean tends to be lower, and the standard deviation of the IQ data is larger, in groups of children subjected to circulatory arrest. Furthermore, all these studies are open to criticism on the absence or inadequacy of control groups. More recently, a carefully organised study with sibling controls of children operated upon with and without circulatory arrest has been undertaken by Lincoln and his colleagues *(14)* and the conclusion that arrest times well under an hour may result in damage to the central nervous system is now inescapable.

In spite of the apparent importance of this subject there is a paucity of animal experimental information available. The new experimental work which will be described in this lecture was aimed very specifically at defining the tolerance of the mammalian brain to ischaemia at 18–20 °C and the relationship between structural, biochemical and functional changes.

## Methods

The 'experimental model' used for these experiments was developed specifically to study the cerebral consequences of hypothermic circulatory arrest and a need was seen for measurements of functional, structural and biochemical

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*The Editor would welcome comment on this paper by readers*

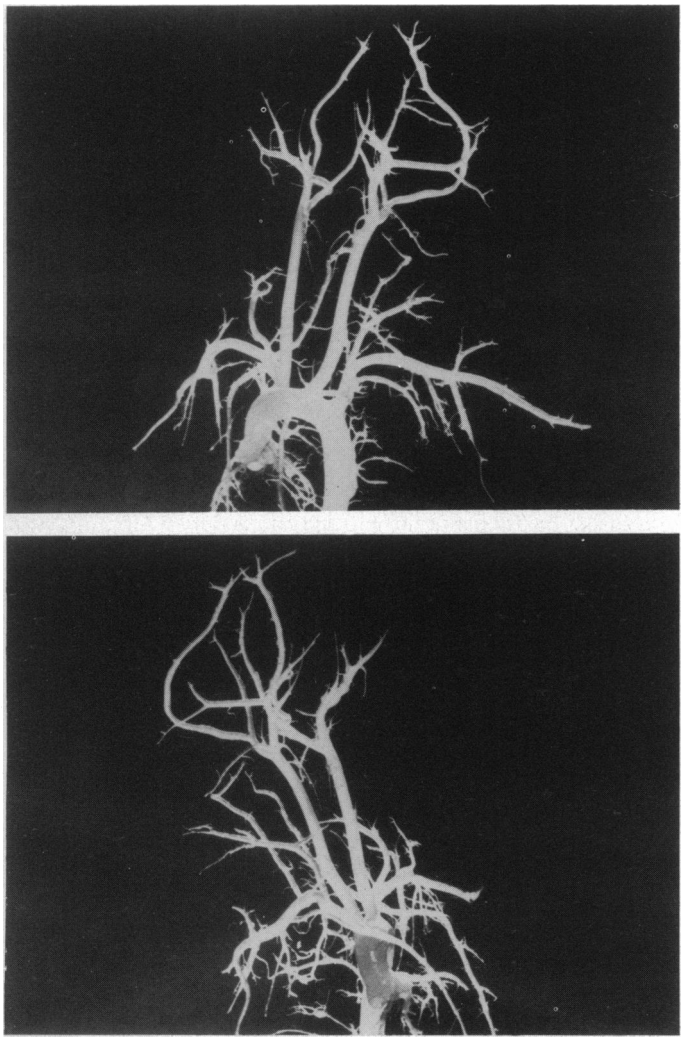

FIG. 1 A corrosion cast (Yate's flash acrylic) of the gerbil arterial system. The aortic arch and the branches to the forelimbs, and the head and neck are illustrated. There are no posterior communicating arteries and therefore no circle of Willis.

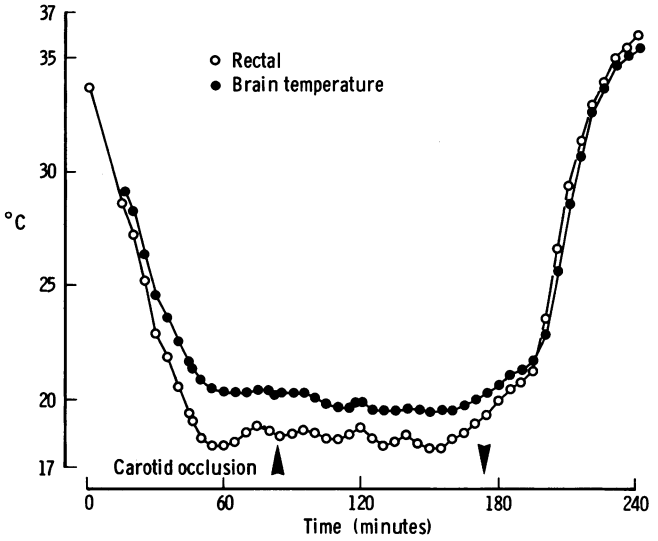


FIG. 2 The rectal temperature (open circles) and brain temperature (closed circles) during surface cooling and rewarming of a gerbil anaesthetised with chloral hydrate. The brain temperature is below 20 °C while the cerebral circulation is arrested.

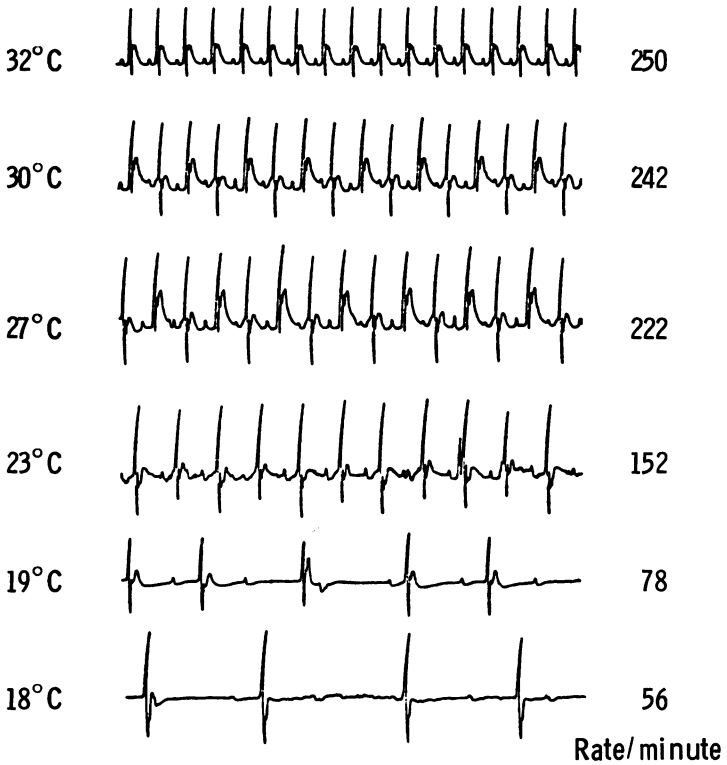


FIG. 3 The electrocardiogram (lead 2) of a gerbil during cooling to a deep body temperature of 18 °C. There is progressive slowing of the heart rate, conduction abnormality and eventually, complete heart block. Ventricular fibrillation did not occur, but below about 17 °C there was asystole.

impairment. A small mammal has the advantage that a large number of experiments can be performed without the problems of inordinate use of time and money yet the well known difficulties involved in getting small animals to survive bypass, if we had attempted it, might well have precluded any interpretation of the cerebral consequences of circulatory arrest. We had to use a different approach. The Mongolian gerbil (*Meriones unguiculatus*) was therefore chosen because of the unique organisation of its cerebral circulation in that it does not have posterior communicating arteries (Fig. 1). This absence of a circle of Willis means that, unlike all the other small animals usually used in research, its cerebrum can be made completely, uniformly and reliably ischaemic by occlusion of the carotid arteries in the neck while the brain stem, supplied by the vertebro-basilar system, continues to function. This unusual anatomical arrangement has been used to advantage by those interested in stroke and accidental circulatory arrest but always at normothermia. By careful surface cooling we lowered the animal's body temperature until, measured in the rectum, it was below 18 °C while the brain temperature was about 20 °C (Fig. 2, 3). At that temperature the carotid arteries were occluded in the neck thus imitating the situation in patients undergoing surgery during hypothermic circulatory arrest. Details of this experimental method have been published *(15, 16)*.

In the series of experiments described here 64 animals were each subjected to a single period of ischaemia and then, after cerebral circulation was restored, were rewarmed. They were in 16 groups of 4 with ischaemic times of from 0 to 180 minutes at 12 minute increments (the '0' minutes ischaemia indicating a control group where sham dissection only was performed without carotid occlusion).

After completion of the ischaemic period, the animals were rewarmed. Half of them were allowed to recover and were then kept for a week during which time daily neurological examinations were performed. On the seventh day, they were reanaesthetised and, through a cannula in the left ventricle, perfused with a glutaraldehyde solution so that the brain could be examined histologically. The other animals

were quick frozen in liquid nitrogen after 90 minutes and the brains saved for biochemical analysis. Functional, structural and biochemical changes were thus examined.

The assessment of functional changes consisted of a set of 9 tests which were used to score the animals motor, visual, auditory and social behaviour as objectively as possible. All examinations were made by a single observer. The assessment was made without knowledge of the animals ischaemic time as were the morphological and biochemical examinations. The brains, perfusion fixed in glutaraldehyde, were sectioned and searched for any pathological changes. The hippocampus which is readily identifiable, has palisades of easily counted cells and is known to be particularly vulnerable to ischaemia, was used to compare the animals objectively. Four counts of 100 cells each were made in each animal and every cell categorised. Analysis of cortical ATP, ADP, creatine phosphate, glucose, lactate, pyruvate, alanine, glutamate and a number of other metabolites was performed on the deep frozen brains.

## Results

### BIOCHEMISTRY

Preliminary experiments had shown that the cerebral ATP falls to very low levels soon after occlusion of the carotids but restoration begins very quickly with reperfusion *(16)*. In this series of experiments we see that the ATP is incompletely replenished even after 90 minutes of reperfusion and that it has an inverse, linear relationship to the duration of ischaemia ($p<0.0001$) (Fig. 4) with a strong correlation ($r=-0.84$). There is thus no evidence of a 'safe' period of circulatory arrest, however short, which is not associated with some depletion of the high energy phosphates. Other experiments where profound hypothermia was used for up to three hours without arrest of the cerebral circulation showed that cooling alone was not associated with loss of ATP.

ATP is not necessarily a good indicator of irrecoverable damage however. It is possible that after reperfusion, chemical processes may return temporarily, even though the cells are irrecoverably damaged. On the other hand, depletion of ATP due to slow recovery of adenylate would not be worrying if the cells subsequently recovered completely. More reliable information can be obtained about mitochondrial damage, and hence inevitable cell death, by studying other metabolites. The glycolytic pathway results in an accumulation of pyruvate (Fig. 5) which cannot be cleared in the Krebs cycle in the absence of oxygen. The accumulated pyruvate is metabolised to lactate anaerobically, a reaction which reaches a rapid equilibrium in the presence of LDH. There was significant elevation of both cerebral pyruvate ($p=0.001$) and lactate ($p=0.01$) which were also linearly related to the ischaemic time although less well correlated than ATP ($r=0.46$ and 0.56 respectively). Removal of lactate cannot occur during ischaemia and, even with reperfusion, is rate limited across the blood–brain barrier. There is an alternative, slower, reaction which clears pyruvate; catalysed by the transaminase GPT, it yields the amino acid, alanine (Fig. 6). After the ischaemic insult it remains as an integrator of mitochondrial dysfunction and in these experiments was significantly correlated with the ischaemic time ($p<0.001$, $r=0.82$).

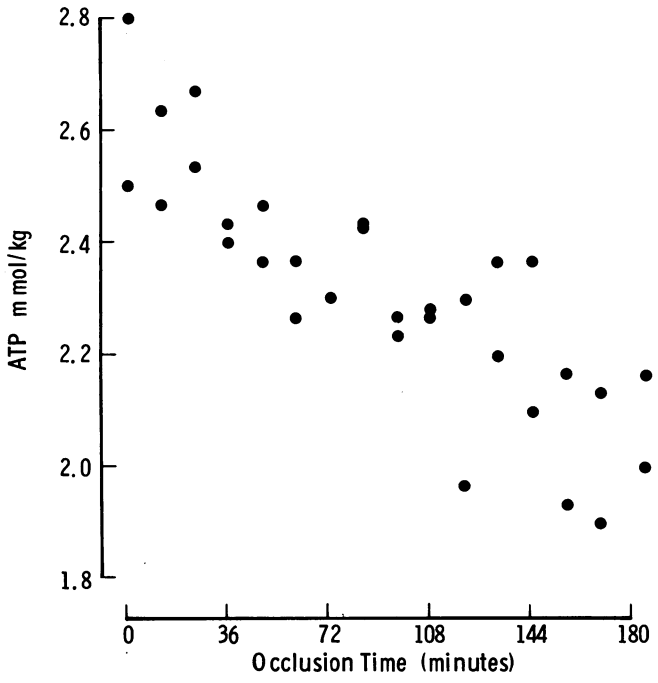


FIG. 4 The cerebral ATP content in 32 gerbils rewarmed to 37 °C after 0–180 minutes of ischaemia at 18 °C.

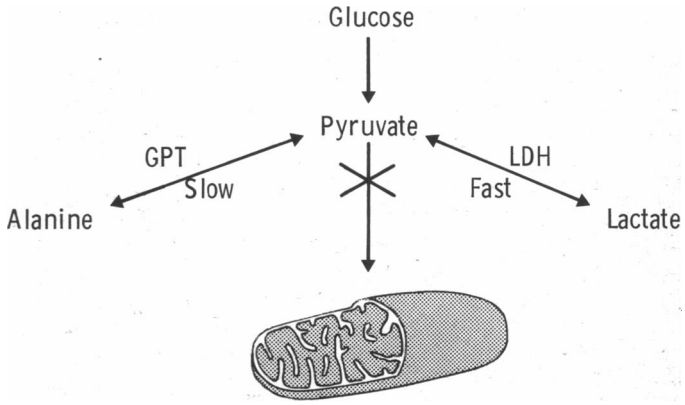


FIG. 5 Pyruvate, the end point of the glycolytic pathway, accumulates in the brain during ischaemia because it cannot be cleared through the Krebs' cycle. It equilibrates rapidly with lactate and more slowly with alanine. All three are elevated after ischaemia.

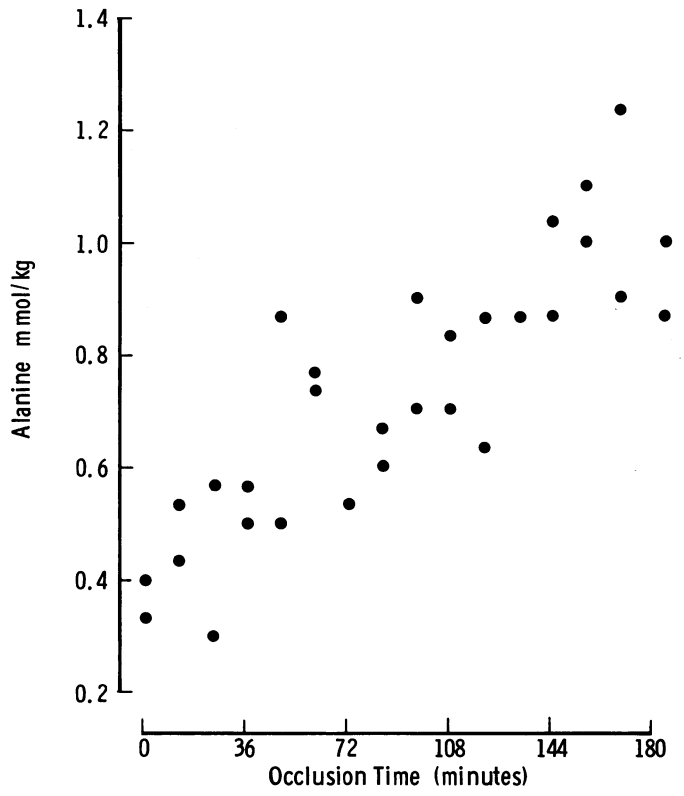


FIG. 6 The amino acid, alanine, accumulates in the brain after ischaemia as an integrator of pyruvate concentration and hence mitochondrial dysfunction.

MORPHOLOGICAL CHANGES

The normal gerbil hippocampus includes a majority (90%) of even sized cells with a round, homogeneous nucleus which stains pale blue with Lee's methylene blue/basic fuchsin stain. There are a smaller number of shrunken dark staining cells, generally accepted as dead neurones which represented 8% of the total count in normal animals. The remaining 2% include cells with abnormal red staining cytoplasm or with scalloped margins, believed to represent accumulation of water within the cell membrane. These are believed to be damaged neurones. All animals with up to 24 minutes of ischaemia had a normal proportion of healthy hippocampal cells on all of the four counts. With ischaemia of 36 minutes or more the proportion of abnormal cells increased (Fig. 7) and in animals subjected to 120 minutes of ischaemia there were no normal counts. Not only did the proportion of dead and damaged cells increase but, beyond 48 minutes of ischaemia, some of the cells were completely destroyed and only a 'ghost' of nuclear staining material was left. The loss of normal cells with increasing ischaemic time was highly significant ($p<0.0001$); the relationship is described by a logistic equation:

$$\log(n)\ \langle P/(100-P)\rangle = 2.4 - 0.28 \times \text{ischaemic time (minutes)}$$

FUNCTIONAL RESULTS

One animal in the series of 64 died during cooling and was replaced. Of the 32 animals in the recovery group, 4 died before completion of the experiment, 2 of them within hours and both of these had been subjected to ischaemia for over two and a half hours. Their function was therefore scored as 0%. In general, the gerbils tolerated the surgery well and there was no wound infection although some animals apparently had paralytic ileus. The 9 part neurological examination was performed daily, the animal was weighed and the nesting ability assessed on each of 5 consecutive days so an enormous amount of data was collected in an attempt to arrive at a truly objective measure of the degree of functional impairment. Details of this are to be found elsewhere (*15,16*) but the results are summarised in Fig. 8, expressed as a nomogram drawn from the logistic equation relating the integrity of neurological function to the length of ischaemia:

$$\log(n)\ \langle P/(100-P)\rangle = 3.4 - 0.025 \times \text{ischaemic time (minutes)}$$

There is a highly significant loss of function with increasing ischaemic time ($p=0.0005$).

**Summary of results**

The biochemical, histological and functional damage are all related to increasing ischaemic time but while in the case of the biochemical changes the relationship is linear, as far as cell death and functional impairment are concerned the relationship is curved. There is a time when the risk although present, remains small and later the risk increases rapidly. To help decision making in surgical practice it is important to try and estimate the time at which the risk is obviously increasing. If we take the ischaemic time at which the 70% confidence limits (1 standard deviation) for the measurement of interest no longer overlaps the confidence limits at zero occlusion time we can say that the change has become 'evident' (p-value about 0.1). In these terms, cerebral damage is evident in biochemical terms at 30 minutes, as judged by cell loss at 37 minutes and by functional impairment at 45 minutes. Individual animals were severely damaged within those times while others were spared at longer times.

**Discussion**

Whenever data from animal experiments is used to guide us in clinical practice an act of faith is made in the existence of general biological laws which govern biochemical and cellular phenomena, independent of species, and which permit

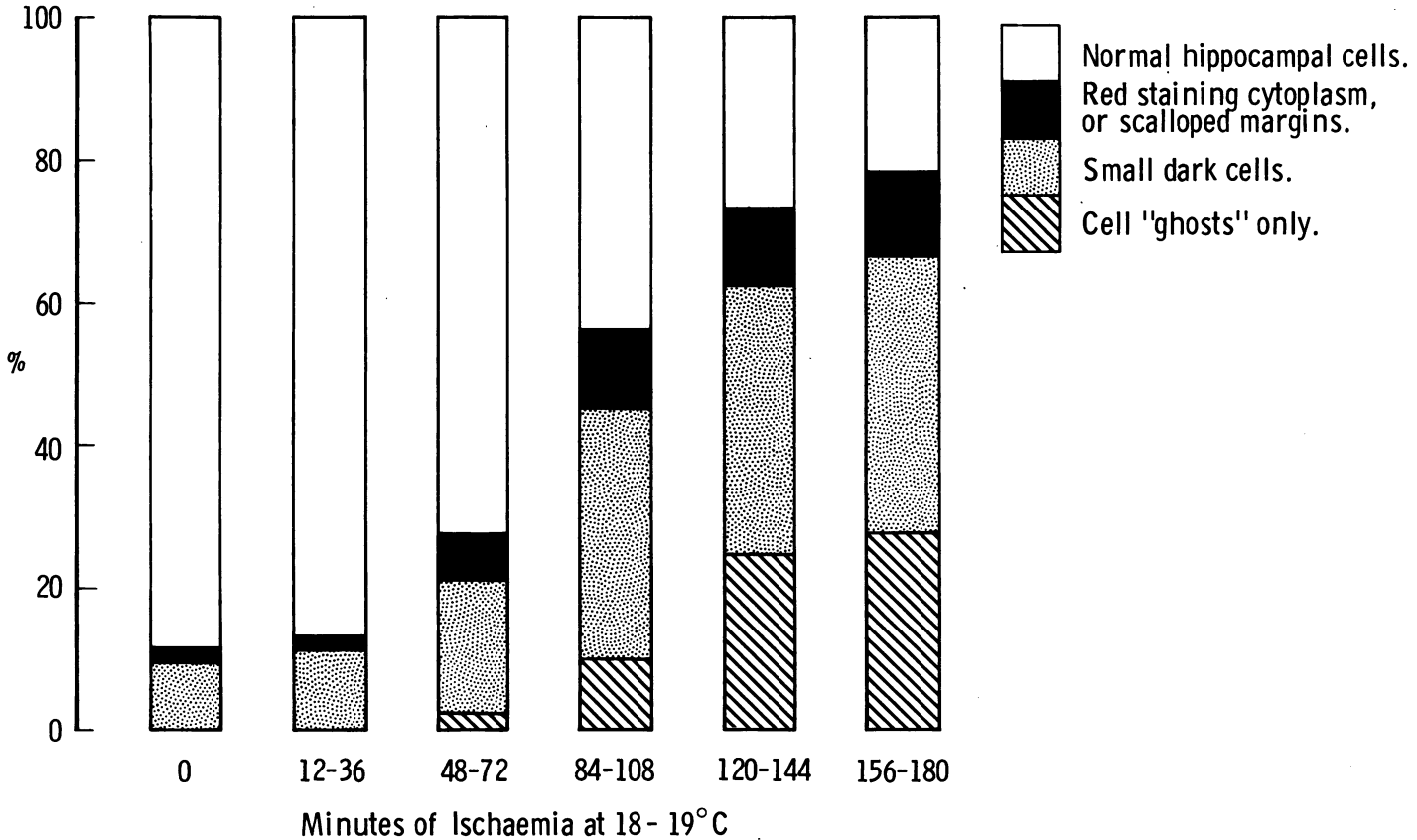


FIG. 7 The proportion of damaged, dead and completely destroyed hippocampal neurones increases with ischaemic time but no loss of cells was evident with less than 36 minutes of ischaemia.

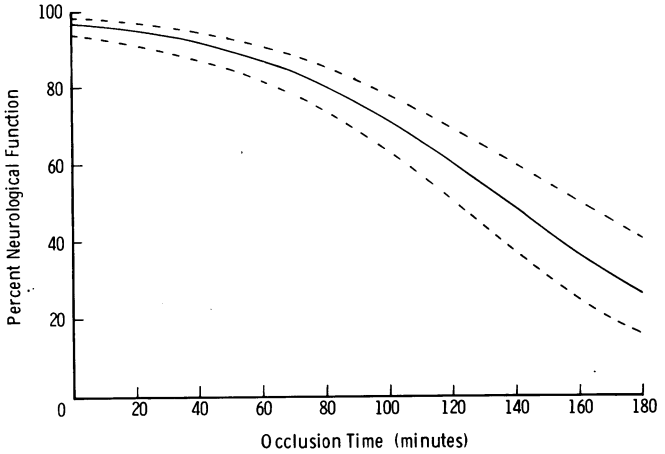


FIG. 8 The logistic equation for the relationship between increasing ischaemic time and worsening neurological function based on functional assessment in 32 gerbils. Probability = $[1+e^{-(a+bx)}]^{-1}$ where a = 3.4 and b = 0.025.

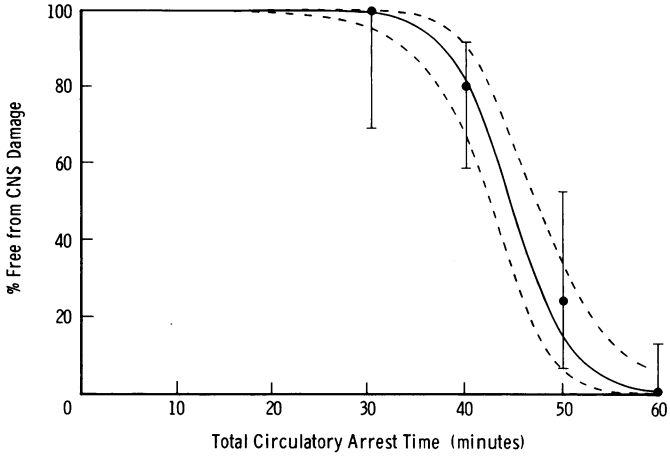


FIG. 9 An analysis of data published in 1968 by Mohri and colleagues *(7)*. Dogs were subjected to surface cooling and circulatory arrest for 30 to 60 minutes at 16–18 °C. The points (with bars representing the 70% confidence limits on the proportions) indicate the occurrence of a 'high stepping gait' in a series of 31 dogs (0/5, 2/10, 3/4 and 12/12) as the arrest time increased. The logistic equation derived from the data permits further interpretation of the findings.

extrapolation from what is observed in the animal to what pertains in man. It is therefore very reassuring when we compare results from one animal to another to find close agreement. The only animal work found in which cerebral biochemistry was examined after profound hypothermic circulatory arrest was that of Kramer and colleagues *(17)*. In the profoundly hypothermic dog they found the cerebral ATP to be 2.42 mmol/kg (SD, 0.16), identical to our value of 2.42 mmol/kg (SD, 0.10) in gerbils. After 60 minutes of ischaemia and rewarming to 37 °C the results were again statistically indistinguishable at 2.17 mmol/kg (SD, 0.24) and 2.05 (SD, 0.16) respectively. The metabolism of the profoundly hypothermic, ischaemic gerbil brain subjected to carotid occlusion is thus remarkably similar to that of the dog subjected to profound hypothermic total circulatory arrest. Under normothermic conditions, the biochemistry of the gerbil brain is generally accepted in neuroscience as being representative of that in other mammalian species so the biochemical results obtained in these gerbil experiments are probably an indication of what occurs in man.

The histological changes resulting from periods of circulatory arrest have, in the past, been difficult to identify because they tend to be swamped by the postmortem ischaemic changes which are unavoidable in most methods of preparation. The techniques used in the present study effectively fixed the brain in vivo and produced easily identifiable and, even more important, quantifiable histology. The work of Folkerth *et al. (18)* on puppies revealed that circulatory arrest at 20 °C for 45 minutes caused cell damage in all animals, most readily identified in the hippocampus; Fisk and colleagues *(19)* found hippocampal damage in all their infant pigs at 60 minutes under similar experimental circumstances. The limited information given about the extent of the damage makes comparison difficult and the use of only one ischaemic time precludes estimation of a 'safe' duration of ischaemia or any calculation of the time of increasing risk. Nevertheless, a careful analysis of the data available from those experiments in puppies and infant pigs reveals that the results, although limited, are statistically similar to our own results in gerbils *(15)*.

Information on functional recovery in animals is similarly sparse but there were large numbers of experiments performed on dogs by the group in Seattle who advocated the use of surface cooling alone to below 20 °C. While they believed functional recovery of the dogs to be good with up to an hour of circulatory arrest at this temperature, they did note the occurrence of a 'high stepping gait' although they failed to identify any organic basis for it *(20)*. Although, at the time, they regarded this neurological change as a benign, recoverable lesion, their own observation that 20% of animals retained this abnormality 2 full years after the

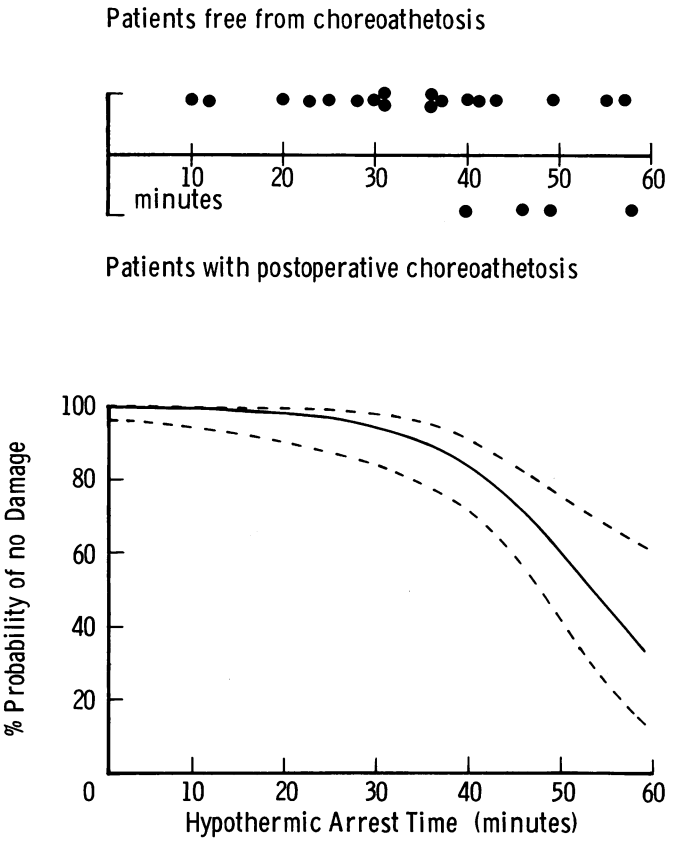


FIG. 10 The circulatory arrest times for a series of 22 patients under 2 years from Brunberg, Reilly and Doty *(21)*. The four cases with choreoathetosis are seen to be in grouped between 40 and 60 minutes. The logistic equation derived from this data shows decreasing probability of freedom from damage (i.e. increasing risk) with time.

experiment makes the conclusion that this is, in fact an organic lesion, unavoidable. The data available in that publication has been reanalysed and a logistic equation fitted to it (D C N). From this analysis (Fig. 9) we conclude that the animals had a 10% risk of developing the neurological abnormality after 38 minutes of circulatory arrest, a figure remarkably similar to the gerbil data.

In the analysis of the outcome in patients, the problems associated with collection and interpretation of IQ data has already been outlined and although the evidence now seems to be that times of up to an hour are certainly not 'safe', it has not been possible to prove it statistically with the available IQ data. There is another approach. A proportion of infants and small children subjected to circulatory arrest develop a neurological abnormality, choreoathetosis, which presents with writhing movements of the head and shoulders within the first few days after surgery and may persist for several weeks. Although the abnormality disappears in time with apparent full recovery, the fact that it persists well into the convalescent period, when the haemodynamic and metabolic consequences of surgery are past, suggests that there is underlying structural damage, to the brain, probably the basal ganglia. Brunberg and colleagues *(21)* observed an incidence of 4 out of 22 cases. The arrest times in all the cases are given in their paper and it is easily seen that the lesion occurred in those with longer arrest times, the mean being 48 minutes (SE, 3.8) in those with choreoathetosis and 34 minutes (SE, 3.1) in those without ($p=0.04$). Analysis by a logistic model (Fig. 10) suggests that the risk of choreoathetosis is 10% at 36 minutes, again in close agreement with estimates from other sources.

Dr John Kirklin and his colleagues undertook a retrospective analysis of their experience in 219 infant and small children operated upon in The University of Alabama using circulatory arrest and profound hypothermia. This revealed 5 cases of choreoathetosis and 3 other cases of more severe neurological damage. The difference between the arrest time in the neurologically normal (45 minutes) and impaired groups (59 minutes) was significant ($p<0.001$) and clinically obvious damage could occur with ischaemic times of under an hour.

## Conclusions

The combined weight of the evidence from this series of 64 experiments and the factual information gleaned from a careful reanalysis of the published clinical and experimental data suggests that it is 'safe' to use circulatory arrest with a cerebral temperature of less than 20 °C but that the time available is substantially less than the hour generally quoted in the literature. Even with very short periods the risk is never absent so, if circulatory arrest must be used, the maxim should be to keep it as short as possible. If the arrest time is kept within 20 minutes the risk of structural brain damage is extremely small at this temperature. The time to an 'evident' difference ($p<0.1$) for hippocampal damage in our gerbils, neurological abnormalities in the Seattle dogs and choreoathetosis in children was between 35 and 40 minutes in each case. Therefore, we must conclude, by 40 minutes the probability is that irreversible cerebral damage has occurred. The fact that it is difficult to identify, some years later in children, only serves to demonstrate that function can be preserved or restored in spite of a degree of neuronal loss. Recognition of the risk does not mean that the technique should be dropped from the armamentarium of the cardiac surgeon but its use should be selective and carefully controlled. Although its most frequent use is in intracardiac repair in infants there are occasions in adult surgery where knowledge of this method is life saving. The emergency management of the dissecting or infected ascending aorta remains one of the most dangerous of problems and is associated with much higher mortality than is familiar in modern cardiac surgery. Femoral cannulation, cooling to 18 °C and a 20 to 30 minute period of circulatory arrest permits these otherwise lethal conditions to be treated.

This work was carried out while the lecturer was Cardiovascular Research Fellow to Dr John Kirklin at The University of Alabama during tenure of a British American Research Fellowship from The British Heart Foundation and The American Heart Association. I am also deeply indebted to the following members of The University of Alabama, doctors, scientists and technicians, who helped me with various parts of this work: Eugene Blackstone, Lafayette Briggs, Karl Conger, Mark Farrington, Julio Garcia, James Halsey, David Naftel, Ralph Roseman and Bill Tracey.

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