

## DISCOVERING THE PATHWAY FOR COOLING THE BRAIN

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### INTRODUCTION

The brain, in spite of extensive research, remains one of the greatest enigmas of human existence. Admittedly, this living organ of only 1500 grams of weight, composed of trillions of cells and fibers formed in a jelly-like matrix, is responsible for all we know as human beings and understand of ourselves and about the universe itself. Since the beginning of human existence the entirety of what man has accomplished, both in a positive and negative way since the beginning of human history, is a result of the activity of this most complex and unique object in the known world. It is within the physical structure of its living fabric that specialized functions that characterize the human mind such as cognition, memory, and intelligence, to name only a few, are all anatomically located in the brain substance. Thus, it can be appropriately argued the theme of this symposium that will deal with the process of creativity and discovery, obviously, must be based on the functioning of the human brain/mind.

This particular presentation will examine the investigative activities undertaken to discover pathways to efficiently cool the brain without causing any measurable alterations in its higher functions. The overall reason for this fundamental form of research is the overwhelming sensitivity of brain tissue at normal temperature (37°C) to any interruption of its intrinsic blood flow. It has been scientifically established that only 5 to 6 minutes of total circulatory arrest to the brain under normal thermal conditions is required to permanently limit or destroy its physiological and psychological performances.

### SENSITIVITY OF CEREBRAL TISSUE TO ISCHEMIA AND WAYS TO PROTECT IT

In recent years, one of the issues raised regarding lengthening this 5 to 6 minute interval was the possibility of developing methods that would provide protection to the cerebral organ during extended periods of circulatory arrest. In actuality, there are two basic problems here that require solutions. First, to find a technique that will offer significant protection during or following cerebral blood flow cessation. Second, to develop a biotechnology that can accomplish this purpose without damaging the brain or its performance capabilities. Obviously, the possibility of a suitable pharmacological agent that would offer these advantages has been extensively explored but, to date, without major success with the possible exception of barbitural compounds which appeared to offer minimal protection.

For some years now, the studies of environmental experience with survival following human cold immersion and hibernating animals has strongly suggested that by purposely alternating the thermal state of the brain, one might confer on the organ an extended time period of survival following the elimination of its somatic circulation but, that still leaves the question: would cooling of the brain be safe? And, could a technique be devised that would effectively cool the organ without being injurious to the cerebrum? Thus, at this point, in our experimental studies we had to discover the effects (be they good or bad) of temperature reduction on the central nervous system. In addition, we would have to create an engineering system that would be highly successful in altering the thermal state of the brain without producing any measurable damage to its intrinsic tissue composition which would cause functional degradation.

### THE ISOLATED BRAIN PREPARATION AND HYPOTHERMIA

Early on, we felt it would be appropriate to develop an isolated brain model in order to document the pure physiological, biochemical, biophysical and reological changes resulting exclusively from vascular cooling of the brain. In this series of experiments, the entire brain including distal brain stem was surgically removed from the cranial vaults of a series of adult subhuman primates (Rhesus monkeys) and maintained in a viable state employing for circulatory purposes either a cross-circulation vascular arrangement utilizing a large Rhesus monkey (Fig. 1) or employing a specially designed miniaturized extracorporeal perfusion circuit (see Fig. 2, page 294). This would be equipped with a small oxygenator unit, a special-

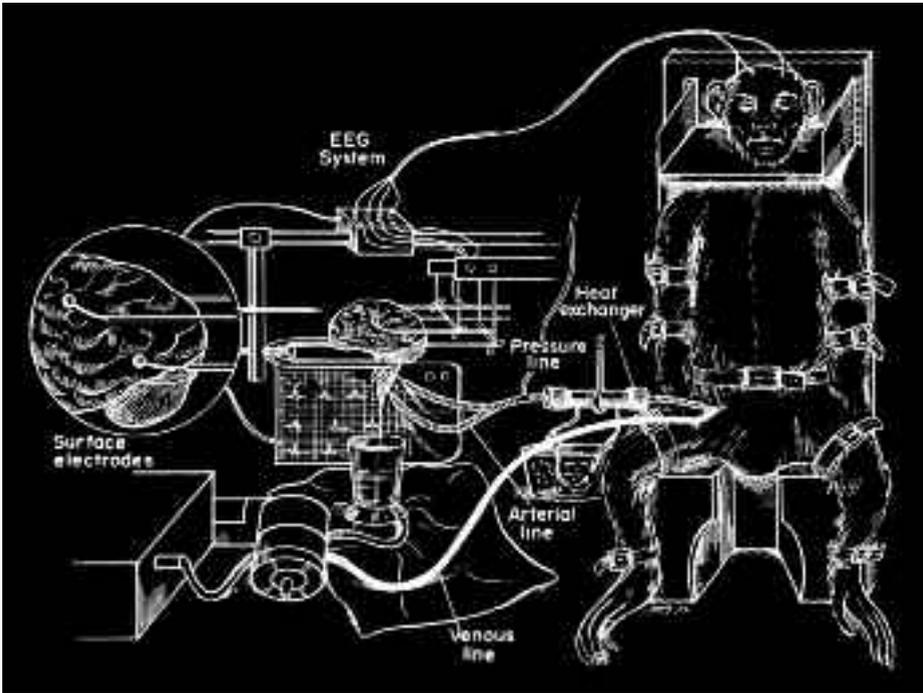


Figure 1. Isolated monkey brain maintained in a viable state employing cross circulation with large donor (note heat exchanger for brain cooling).

ly designed mini-mechanical compression pump, and a miniaturized heat exchanger, all linked together with a plastic tubing arrangement. Individual brains were instrumented (see Fig. 3, page 295) with surface (cortex) and, on occasion, depth electrode systems as well as needle thermometers for continuous intracerebral temperature measurements. From time to time, the isolated brains were submerged in a tank of artificial cerebral spinal fluid (CSF) and often with ventricular draining systems.

With these extremely delicate subhuman living brain modules under conditions of total isolation (available for the first time in medical history), a series of experiments were designed to provide answers to the crucial questions outlined above. In the case of the cross-circulation supported isolated brains, they responded much as a transplanted organ with no evidence of rejection and with normal physiological and biochemical profiles following repeated cooling, arrest of circulation, and re-warming.

As a result of these studies, the significant depression of the electrical and metabolic activities of the total brain at various low temperatures was documented for the first time.

When the isolated brain preparations were supported exclusively by a fully independent extracorporeal perfusion circuit they actually performed very well early on, however, after some time (8 to 10 hours), the brain began to display evidences of failure with decrease of electrical and metabolic activity as well as the development of cerebral edema and subpial bleeding. To some degree, this could be improved by replacing the perfusate (diluted monkey blood with Dextran) entirely with a fresh perfusate. These experiments conclusively demonstrated that, for the first time, the brain could be maintained as a viable isolated organ with a totally mechanized circulation. To significantly extend organ survival, the equipment and perfusate required improvement and this could be appropriately accomplished without too much difficulty.

#### EDUCATED MONKEYS AND DIFFERENTIAL BRAIN COOLING

Finally, we asked ourselves what would be the best experimental design to truly answer the remaining question in these experiments; have there been any significant changes in the behavior of these monkeys that resulted from the cooling technique and global brain ischemia under conditions of profound hypothermia? To address this problem, we felt strongly that we would have to employ highly trained subhuman primates to be completely assured that in the intact animal there were truly no substitutive changes in their mental capacities. As a consequence, a group of monkeys were intensively trained for 6 months to a full year employing cognitive tests (Wisconsin testing device) before they were subjected to differential brain cooling and cerebral circulatory arrest.

With simplification of the perfusion circuitry (elimination of the oxygenator and mechanical pump) to an arterial circulatory system utilizing the animal's own heart to pump the blood through the system, it now contained only a miniaturized heat-exchanger to alter the blood's temperature as it entered the brain. The vascular arrangement required not only surgical exposure of the carotid and vertebral arteries in the monkey's neck, but frequently the femoral artery in the groin was also surgically exposed to provide an alternative site for arterial outflow. As a result of this arterial arrangement, blood flow into the brain could be limited to the carotid arter-

ies and at the time of circulatory arrest all four arteries (carotid and vertebral) were occluded to provide global brain ischemia. Following periods of purposeful interruption of brain perfusion (1/2 hr. to 1 hr.), the animal's brain was allowed to be re-warmed by the somatic circulation itself. Following a day or two of post-operative recovery, these subhuman primates were submitted for re-testing and demonstrated no evidence of intellectual decline. Thus, with the successful demonstration of cognitive performance in these highly educated animals after profound cooling and total ischemia of the brain, it was now believed to be time to examine the possibilities of creating a similar technology for the human being.

#### THE HUMAN BRAIN AND ITS THERMAL RELATIONSHIP

As a result of its intracranial location, the brain is superbly protected against thermal variations in the environment. The brain is literally immersed and floating in fluid (thus, its normal weight of 1500 grams is reduced to approximately 47 grams in accordance with Archimedes principle). In turn, it is surrounded by its bony skull, whose inner surface is lined by a non-elastic, thin, tensel strong membrane – the dura. Finally, the tissues of the scalp, including muscles, skin, and fat offer excellent insulation to preserve appropriate intracranial temperatures and prevent the development of wide variations within the thermal environment of the brain. As a consequence, cooling the brain via convection methods would appear to be extremely difficult unless, of course, the entire surface of the body was also cooled. This has been done on numerous occasions including to date, but has been found to be laborious, inefficient, and time consuming.

Thus, the problem before us was obvious; how to reduce the brain's temperature safely, rapidly, and efficiently. The solution, as far as we were concerned, would be fashioned after the technique developed in the monkey and would require using the body's own vascular system which, of course, was primarily responsible for homeostatically maintaining the thermal relationship of the entire body. We were also committed to examining the issue of brain hypothermia in an isolated state. In other words, we were determined to cool only the brain while the rest of the body's organs were kept at, or near, their normal temperatures. Obviously, to successfully accomplish our mission we would have to create a modified extracorporeal unit, similar in design to the circuit utilized in the subhuman primate, which would allow us to exclusively perfuse only the brain *in situ* while the somatic circulation remained intact and responsible for the rest of the body (see Fig. 4, page 296).

### THE DEVELOPMENT OF DIFFERENTIAL COOLING OF THE HUMAN BRAIN

We were well aware of the great success that extracorporeal engineering systems (the heart-lung machine) had accomplished for cardiac surgery. Often, they were additionally equipped with instrumentation that offered the capability of rapidly reducing brain temperature to 10° or below, especially in infants undergoing congenital heart surgery. We were also knowledgeable in regard to the neurological complications which frequently developed with the use of extracorporeal circulation during surgery especially when body (and brain) cooling was utilized. These unfortunate cerebral events were often, in the beginning, believed to result from the employment of profound cooling. In time, however, it was established to be an embolitic phenomena caused by the interaction of blood and the surfaces of the tubing and machinery. In order to minimize this possibility, we eliminated the pumping element and the oxygenator from our cerebral perfusion unit. As a consequence, our artificial circulation became an arterial-to-arterial perfusion system, not requiring artificial propulsion. In this vascular design, the individual's own heart provided the circulatory force to propel the blood through the system. Also, since the vascular circuit is totally arterized, no oxygenating equipment was necessary (see Fig. 5, page 297). While this has seen only limited employment in human brain surgery, there has been no evidence of neurological damage.

### THE PATHWAY FOR BRAIN COOLING: DISCOVERY AND RESULTS

Thus, we come to the end of our discovery pathway which has led us to a safe, rapid and efficient technique for providing profound hypothermia of the brain to provide protection under conditions of staged total cerebral circulatory arrest. It is almost unimaginable to think that one can duplicate the same conditions in the human brain that were proven to be so successful in the subhuman primate brain, where deep hypothermic temperatures were produced followed by prolonged periods of total cerebral circulatory arrest without producing evidence of structural or functional damage, it has been achieved. However, the question remains; how does a biophysical substance which possesses memory and cognition retain and preserve these unique properties as well as many other special functions following this dramatic neurological and thermal distortion? If one looks at its tissue morphology under the electron microscope and examines its intrinsic electrical activity and its mental capabilities, we have no scientific explanation as to why the

physical structure of this living material can be reduced to an extremely low temperature (5°C.), where all evidence of neuroelectricity has ceased and metabolism reduced to a minimum and, yet, when vascularly re-warmed to normothermia will demonstrate normal neuroelectrical, neurochemical and retain behavior-appropriate behavioral performance. What has been so conclusively achieved in animal studies should be applicable to the human central nervous system as well. We must not forget that in both animal and human investigations significant periods of total brain ischemia from 30 to 60 minutes (10 times the possible time frame for survival of the brain as a functioning organ at normothermia) were imposed with complete neurological and psychological recovery as a result of the brain being maintained in a deep hypothermic state.

#### IN THE END, THE HUMAN BRAIN STUDIED THE BRAIN

One of the difficulties that arises when studying the brain/mind is that one is actually investigating the organ with itself – thus, to create pathways to discover and unravel the mysteries and activities of the brain/mind provides an interesting paradox – could the brain fool the brain itself? Or, could it purposely, or even unwillingly, mislead the human brain/mind in terms of the creative and discovery process? Nevertheless, we must acknowledge that *all* creative activity and the origin and design of all pathways of discovery exclusively originate in the human brain.

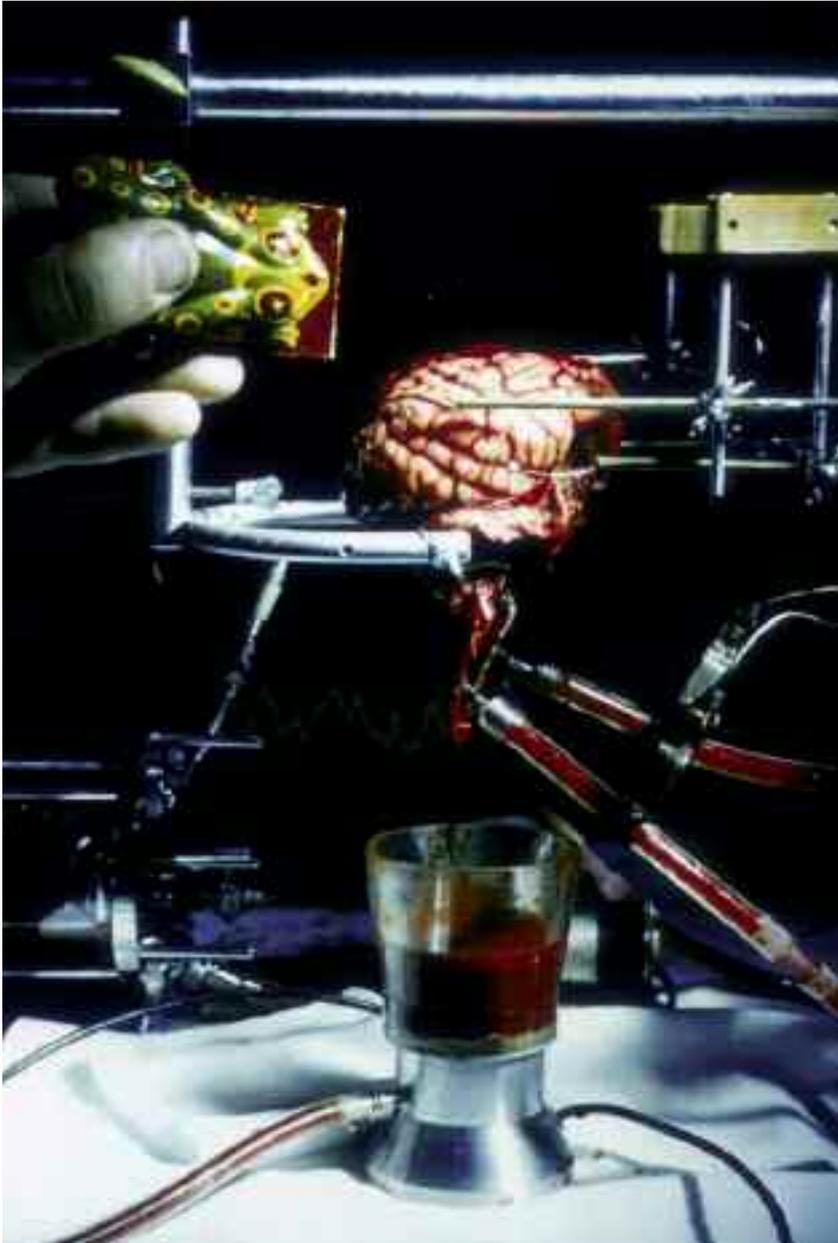


Figure 2. Isolated monkey brain without reservoir on mechanical perfusion. The preparation can record 'clicking' sound in the cortical auditory areas of the brain.



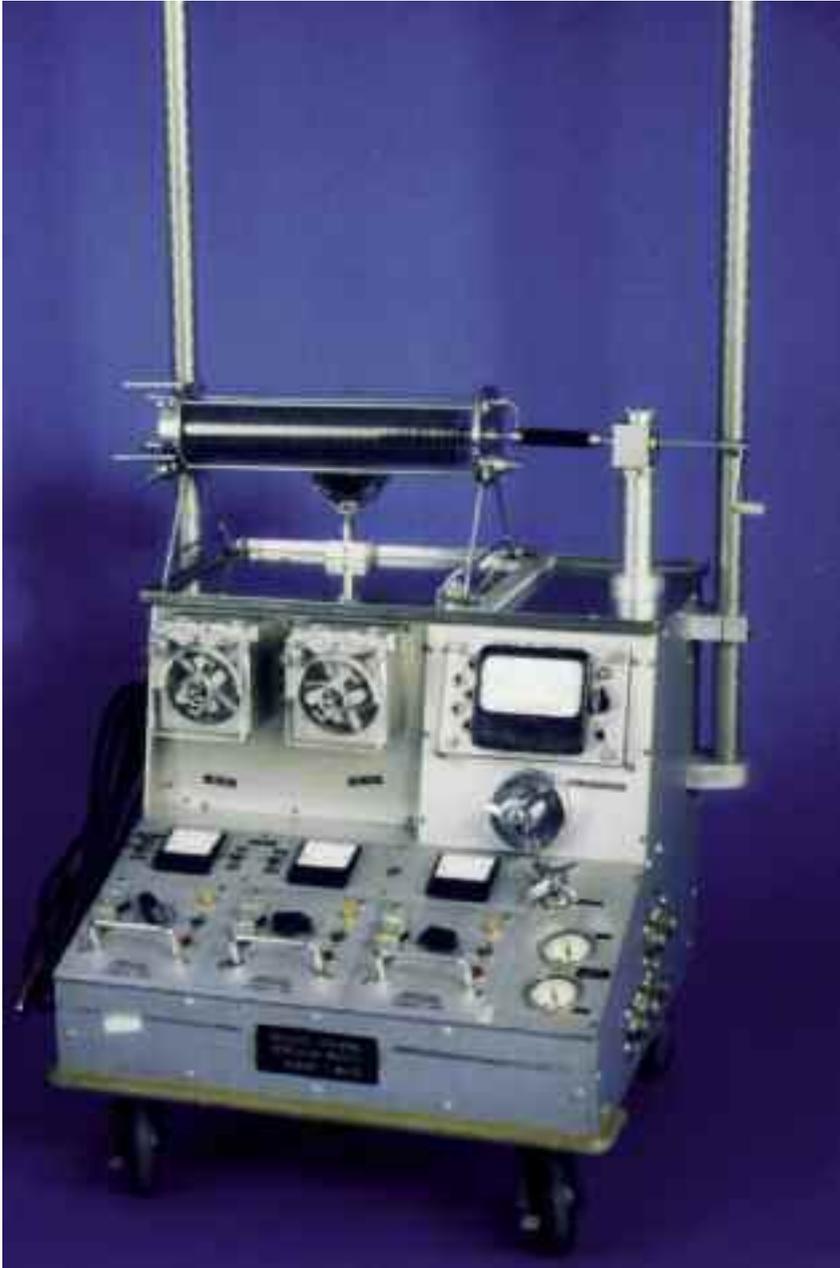


Figure 4. Mechanical heart-lung machine to keep human brain alive.

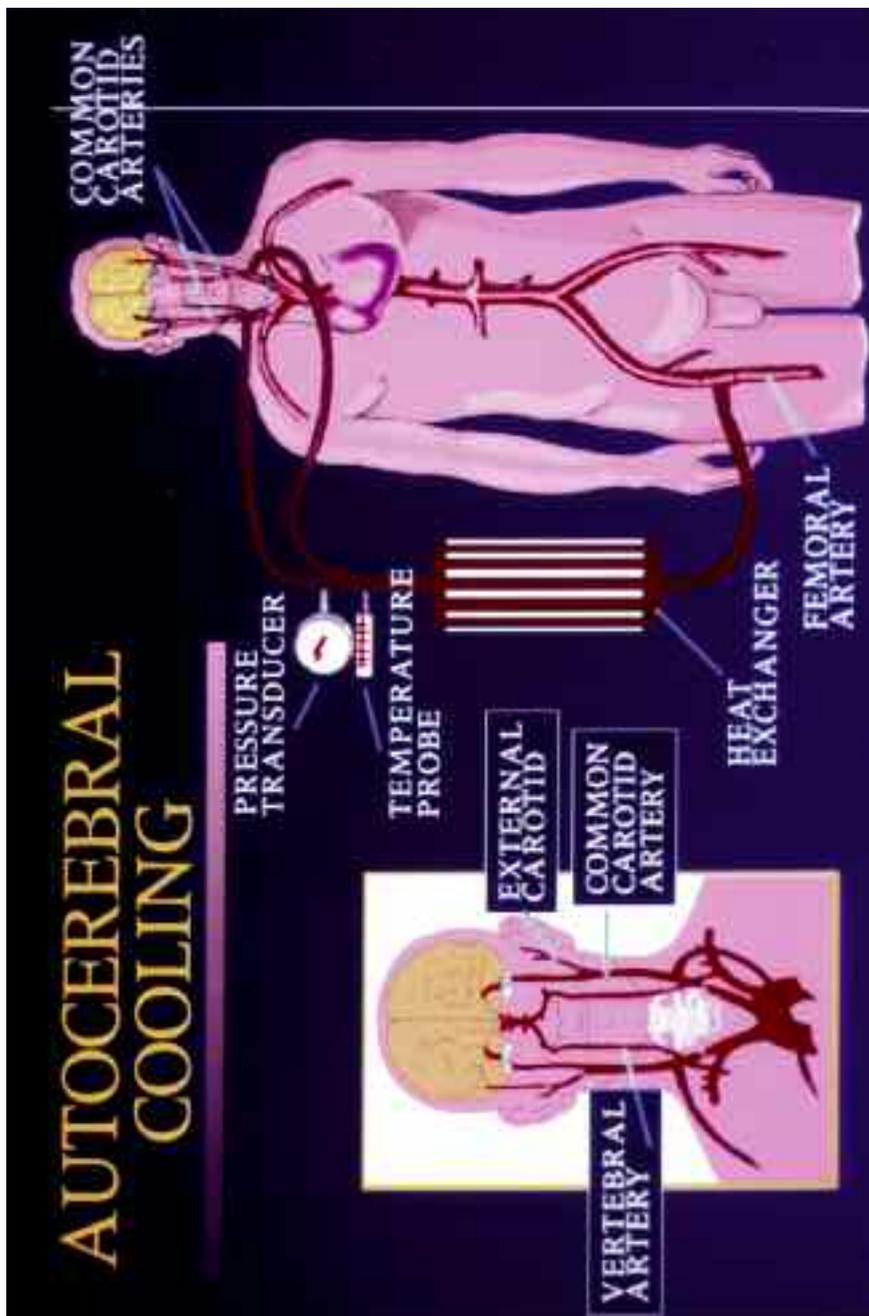


Figure 5. Autocerebral cooling – Patient cools his own brain without pump or oxygenation