Can doctors make the dead walk again?

Death has always been seen as final. In fact its finality defines it. The Oxford English Dictionary's definition of death reads:

"The end of life; the final cessation of the vital functions of an animal or plant."

Identifying a dead person used to be easy. When a person's heart stopped beating they were done for. Without blood being pumped round their body life was impossible. But as biological and medical knowledge has improved we have learnt about CPR, we have invented the defibrillator. Now when a person suffers a heart attack they can be up and about in days. And so we have had to redefine death.

But doing so isn't easy. Getting an agreed definition of when someone is beyond any possible resuscitation seems impossible.

Dr. Norman Frost, a professor at Princeton University, puts it like this: "'Beethoven is clearly dead. You and I are alive. But between us and Beethoven, there is no medical or scientific way of saying what is the point in the process by which you are actually dead.''

What was once death, the failure of the heart and circulatory system, is now given the technical term "clinical death" because to call it actual "death" would be to imply a finality it no longer has. "Death" itself has moved back to a vague term of varying definitions.

But most people would agree that someone starved of oxygen for an hour is almost certainly dead.

At least for now.

A new discovery

After a few minutes without oxygen a person's brain shuts down. A few minutes later all their vital functions have come to a complete halt. The conventional understanding of these processes has been that cells in the body die, starved of their life giving oxygen.

But this idea has been thrown into turmoil by new research carried out by Dr. Lance Becker at the University of Pennsylvania. He starved heart cells of oxygen and then observed them under a microscope. The results were extraordinary. As time progressed the cells still appeared to be alive. After an hour of oxygen starvation just 4% of cells were dead. After 4 hours the figure was still just 16%, remarkably low. A lack of oxygen hardly seemed dangerous to the cells at all, contrary to all medical knowledge.

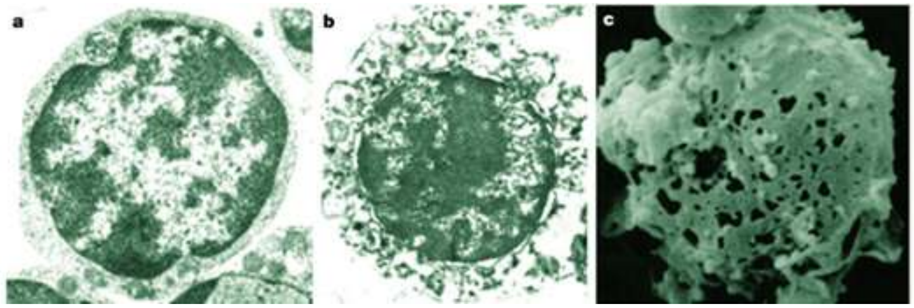

Figure 1 - Electron Micrographs of: (A) a normal cell, (B) a cell undergoing cell-death, (C) a dead cell

There was a catch though, or the dead might already be walking, when the oxygen supply was resumed the cells suddenly died. Life giving oxygen, vital for respiration, made them all die within seconds.

It has emerged that the vast majority of cells that die after heart failure occur not during the ischemic period when the cells are deprived of oxygen but in the few seconds after the oxygen supply is resumed. Once a cell has been deprived of oxygen for five minutes it will almost certainly die when oxygen enters it again.

Reperfusion injury

Mitochondria are known mostly for their fundamental role in respiration. But they also have a darker side. Mitochondria initiate the caspase cascade that results in apoptosis, the digestion of the cell from within.

Normally apoptosis occurs because the breaking down of a particular cell is for the good of the organism as a whole. It is part of intentional 'programmed cell death'. In a developing foetus the cells that connect the digits together break down by apoptosis to form separate fingers. The process also helps to prevent cancer.

However it can be triggered in circumstances in which it is not desirable. Becker's theory is that cell's cannot tell the difference between cancerous cells and cells being reperfused with oxygen.

The theory is that when the oxygen supply is restored reperfusion, results in an accidental trigger of apoptosis. The cell commits suicide at the moment of its salvation.

Reperfusion injury is a major cause of damage in strokes, another circumstance where blood supply is cut off for a time.

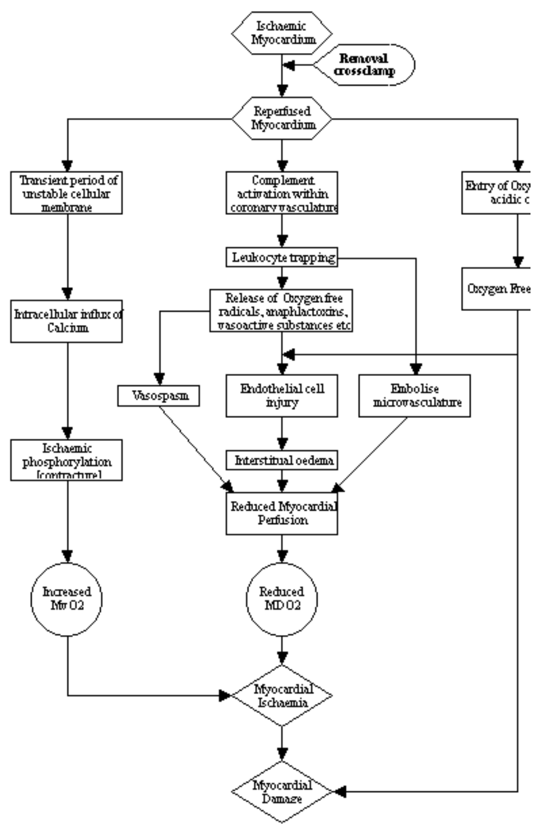

Figure 2 - Pathophysiology of reperfusion Injury

http://www.perfusion.com.au/CCP/Details%20in%20perfusion%20technique/plegia.htm

There are a number of mechanisms by which reperfusion causes damage. The sudden influx of oxygen is converted into oxygen free radicals. These are oxygen atoms with a lone electron. When they react in redox reactions with other molecules they destroy them and tend in the process to form a new free radical. The process continues until eventually all the free radicals react with each other in their termination step.

Oxygen radicals are also often released by the enzyme NADPH oxidase[i] and by electrons leaking from the electron transport chain in mitochondria.

A revolution in medicine?

When this process is fully understood it may lead to a revolution in medical practice. The realisation is just being made that current methods of treating victims of cardiac arrest may in some cases be resulting in their death. If someone collapses in the street, by the time they get to hospital their cells will have gone ten minutes without oxygen. And then, says Becker "We give them oxygen. We jolt the heart with the paddles, we pump in epinephrine to force it to beat, so it's taking up more oxygen." This is precisely what is seen in the laboratory to cause cells to die.

But what’s the alternative? Ultimately the patient needs to eventually get oxygen into their blood if they are going to be revived.

Potential Treatment

Cardioplegics

A study has been carried out in which victims of heart attacks were given cardioplegics which stopped the heart and their blood passed through a heart bypass machine. The survival rate was 80%, but the study was only carried out on 34 patients.

Ice Slurry

Becker’s proposal is to induce hypothermia, significantly slowing down the chemical reactions that result in reperfusion injury. In the west open heart surgery is carried out by first bypassing the heart, sending blood instead through an artificial pump and oxygenator, and then operating on it. In Russia, however, another technique is used. The patient is surrounded by an ice filled blanket and his head placed in an ice helmet. The rate of metabolism slows and the brain stops requiring oxygen. The patient’s heart is then stopped and the surgery carried out.

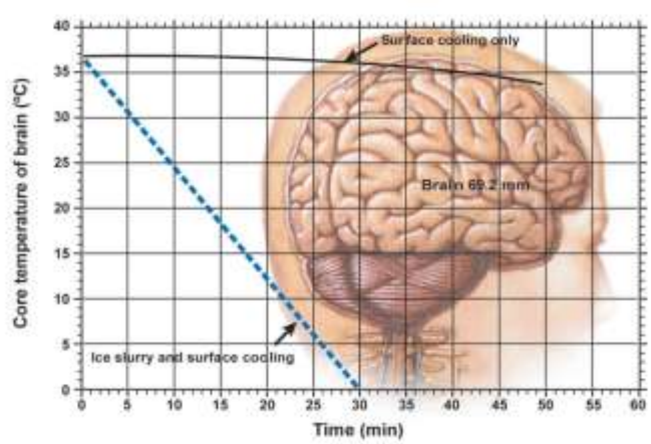

Figure 3 - Comparison between cooling skin surface with blankets and injecting ice slurry

In a case of cardiac arrest the heart would already have stopped. To avoid some cells dying during ischemia it would be necessary to cool all of the organs of the body, and most importantly the brain, very quickly. This involves the development of a new technology as conventional ways of cooling the body such as cooling blankets take a very long time to achieve significant cooling deep inside the body.

Becker's team is investigating an ice slurry that could be injected either into the stomach and lungs or directly into the blood stream. The temperature change would need to be distributed around the body by using chest compressions to artificially create a heartbeat, circulating the blood.

In the case of injecting the slurry into the organs the organs are acting as a heat exchange, blood is cooled as it flows through and around them. When it is directed into the blood stream it is circulated and directly cools the body itself. The slurry reduces ischemic injury and when reperfusion occurs when the body is cooled many less dangerous oxidants are created.[ii]

The slurry is of the same consistency of saline solution used in hospital drips, but frozen. This means that once it melts it is entirely harmless and that it does not affect the osmotic potential of the blood as it has a similar solute potential. The slurry was initially designed for use in air conditioning systems, it has small globular crystals which can flow through narrow pipes (capillaries) more easily than normal rough ice crystals which form a more viscous slurry.

Figure 4 – Ice particles pictured through a microscope. (Left) Ice crystals formed from simply freezing water, they are rough and tend to clump. (Center) Ice particles formed from ice which has been shaved or crushed, rounder but still rough. (Right) Smoother ice crystals, as used in the slurry, formed by adding warm water to melt ice roughness or by adding a freezing point depressant.[iii]

It is hoped that an injector device for the slurry can be created, simple enough for those not trained as medics to use. Once someone was fully cooled and in hospital, their body would be very slowly reperfused to avoid as much cell damage as possible.

Reasons for hope

There's an old saying medicine that nobody is dead until they are both cold and dead. In 2000 Anna Bagenholm was skiing down a waterfall valley in northern Norway when she fell head first into an icy river. She was wedged under thick ice and could not move. After forty minutes struggling to stay in an air pocket she fell still and was submerged, her body temperature dropping to just 13.7° C. After another forty minutes her friends were able to cut the ice to free her and she was taken to hospital where her blood was warmed in a heart bypass machine. After 35 days on a ventilator and more time in intensive care she was left with the only effect a tingling in her hands.

There have also been numerous reported cases of young children surviving after exposure to severe cold as well as cardiac arrest. This is because children have a much smaller surface are to volume ratio and so their bodies are cooled more quickly.

In 1997 an experiment was carried out on 6 groups of 13 rats[iv]. They were anaesthetised and cooled to cranial temperatures of 34, 30, 27, 24, or 22 °C depending on their group. Additionally, one group was not cooled, remaining at 37° C. After cooling an 11-minute cardiac arrest was created by temporarily compressing the rats' chests. After this period CPR was performed on the rats and they were rewarmed. 5 days later the effect on the rats' brain was measured.

The results conclusively showed that protective hypothermia increased survival rate. None of the rats in the group kept at normal cranial temperature survived and neurological damage to those cooled to 30°C was lower than that to those cooled to 34°C. However it was found that, for rats, cooling to below 30°C had a negligible effect. Similar results have been noted for rabbits[v].

Throughout history the protective properties of hypothermia have been noted. Hippocrates, the Father of Medicine, suggested packing patients with haemorrhages in snow and ice. Baron de Lerrey, Napoleon's chief battlefield surgeon noted that injured soldiers would die more quickly if they sat near the fire. Bazzett noticed that soldiers left in the snow survived better than those treated with warm blankets and hot drinks.[vi]

Applications

Ischemia (the restriction of the blood supply) is dangerous because it creates hypoxia (the lack of an adequate oxygen supply to tissues). Ischemia is a feature of many medical issues, but particularly heart attacks (myocardial infarctions) and other cardiac arrest. If it was possible to allow people to survive prolonged ischemia many medical conditions would be much more survivable. Ultimately almost all death results from oxygen failing to reach the brain. If people could be revived after this ischemia then many causes of death could be prevented. Another medical issue to which the ice slurry technique could be applied is the stroke. 80% of strokes are ischemic and in these cases the ice slurry technique would also be effective.

It would be a fundamental change to medicine. Many people for whom an ambulance is called might routinely be injected with slurry to ensure their brain and heart is safe on the way to the hospital and then slowly warmed when they arrive.

Conclusions

Death is impossible to define, but as human knowledge of science and technology has progressed it has been pushed back further and further. New knowledge of protective hypothermia may allow us to push it back further still and revive people whose cells have been ischemic for a long time without them suffering reperfusion injury. The discovery that such a significant proportion of cells that die due to ischemia are killed not during ischemia but at the time of reperfusion and may lead to very different resuscitation techniques and a revolution in medicine.

Bibliography

To Treat the Dead. (2007, May 7). Jerry Adler. Newsweek. http://www.msnbc.msn.com/id/18368186/site/newsweek

Reperfusion Injury in Stroke. Wayne (January 17, 2007). M Clark, MD. eMedicine http://www.emedicine.com/neuro/topic602.htm

The New Science of Saving Lives**.** April 2, 2007. Penn University Press Release. http://www.uphs.upenn.edu/news/News_Releases/apr07/resuscitation-center.html

When the heart stops beating. Yuduit Bhattacharjee. University of Chicago Hospitals. http://www.uchospitals.edu/pdf/uch_003646.pdf

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[i] http://circ.ahajournals.org/cgi/content/full/95/4/787
[ii] http://www.aemj.org/cgi/content/abstract/12/5_suppl_1/68-b
[iii] http://www.anl.gov/techtransfer/Available_Technologies/Biosciences/Ice_Slurry.html
[iv] http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=Retrieve&db=PubMed&list_uids=9150781&dopt=Abstract
[v] http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0102-86502002000400006
[vi] http://www.swsahs.nsw.gov.au/livTrauma/education/newsletters/Mar99.pdf