SAJS

D.J. DU PLESSIS LECTURE

# The handless surgeon

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> *'I would like to see the day when somebody would be appointed surgeon somewhere who had no hands, for the operative part is the least of the work.'* (Harvey Cushing, letter to Dr Henry Christian, November 1911)

Cushing was a man of many talents. He was an accomplished artist, illustrating many of his own operations, and was awarded the Pulitzer Prize in 1926 for his biography of Sir William Osler, his friend and mentor. His outstanding contributions to the field of neurosurgery earned him the reputation as the father of that surgical discipline. Osler's aphorism, 'The good physician treats the disease, the great physician treats the patient', undoubtedly influenced his practice. Cushing emphasised the importance of pre- and postoperative care and this, in combination with his meticulous surgical technique, reduced the mortality for intracranial surgery from over 50% to less than 10%.

There can be few more relevant areas for the adoption of Cushing's holistic principles than the management of the critically injured. In fact, with the ever-increasing trend toward selective non-operative management, Cushing's desire expressed in his letter could not be more pertinent. Even if surgery is undertaken, it comprises less than 5% of the total time spent caring for such patients. Resuscitation, imaging and intensive care constitute the vast bulk of the workload, and in each of these aspects enormous advances have been made.

## The machinery of life

One hundred and fifty years ago, shock in whatever form was almost universally fatal. Pessimism pervaded the pathology and prompted John Collins Warren, Professor of Surgery at Harvard, to describe it as 'A momentary pause in the act of death'. Samuel Gross, his contemporary colleague and Professor of Surgery at the Thomas Jefferson University in Philadelphia, viewed shock as 'A rude unhinging of the machinery of life'. Despite our efforts to categorise the shock state, there can be no more exact a definition than that of Gross; for, regardless of cause, shock results in a switch from aerobic to anaerobic metabolism, a pathophysiological situation that disrupts mitochondrial function. These organelles are the machinery of life.

The term shock derives from the description by Henri LeDran in the 18th century and is probably a mistranslation of the French word '*choc*', meaning a blow or severe jolt. The inevitable association of central nervous system dysfunction with profound hypotension led many investigators to conclude that shock was a nervous disorder. At the turn of the 19th century, Riva-Rocci invented the sphygmomanometer, but despite the recognition that hypotension was an invariable component of the shock state, a low blood pressure was believed to be due to 'a great perturbation of the nerves', a misconception that persisted even during the Great War. It was only during the 1930s that the association was made between a low blood pressure and hypovolaemia following severe injury, the essential intervention being the administration of intravenous fluids. This, and the development of blood grouping by Landsteiner, began to oil the components of the machinery of life.

## The meaning of life

Hans Krebs unravelled the intricacies of oxidative phosphorylation and the citric acid cycle in 1937,[1] a feat for which he was belatedly awarded the Nobel Prize in 1953. He showed succinctly, at a time when biochemistry was in its infancy, the difference in adenosine triphosphate (ATP) production between aerobic and anaerobic metabolism. If the mitochondria are the machinery, then ATP is the meaning of life. ATP cannot be stored, and the available amount in the human rarely exceeds 100 grams, yet the daily turnover is around 150 kilograms. The manufacturing process consumes 90% of cellular oxygen consumption, the cell turns over $10^7$ molecules every second, and each molecule is recycled every 20 - 30 seconds. These molecules are responsible for every energy-requiring process from blinking an eyelid to cardiac contractions. There are thousands of mitochondria in each eukaryotic cell, and the human is composed of roughly four quadrillion cells. Switching from aerobic to anaerobic metabolism results in a 95% reduction in ATP production, the effects of which may be irreversible.[2] It is little wonder, therefore, that shock is associated with such a high mortality rate.

The brief description of the basics of cellular biology above emphasises why it is crucial to restore oxygen delivery as soon as possible. Delays in resuscitation result in disruption of intracellular messenger functions and a reperfusion injury at the cellular level.[3] The former concerns toll-like receptor downregulation and the latter the formation of reactive oxygen species (ROS), which cause damage to cellular DNA and proteins, nitric oxide deactivation with resultant endothelial dysfunction, and irreversible mitochondrial wall damage causing cellular apoptosis.[4] There are some intriguing experimental possibilities aimed at maintaining ATP levels or mitochondrial function under anaerobic conditions.[5] The most obvious solution would be to provide exogenous ATP. Unfortunately, ATP binds calcium and magnesium with the detrimental consequence of haemodynamic dysfunction. Administering ATP as a complex of ATP and magnesium chloride ($ATP\text{-}MgCl_2$) has shown promise in animal models of sepsis with a lactic acidosis. Alternative approaches consist of supplying depleted substrates (L-carnitine or succinate), the provision of co-factors (cytochrome-c or caffeine), antioxidants or scavengers to combat

the excessive production of reactive oxygen species (glutathione, N-acetylcysteine, pyruvate), and mitochondrial membrane stabilisers (cyclosporin-A, melatonin). All are currently experimental, but the future of resuscitation is at this microcellular level and, if ATP can be generated under anaerobic conditions, the effect on survival could be profound. Unfortunately, the only strategy to restore cellular oxygenation at present is by fluid resuscitation and blood transfusion.

## Repaying the oxygen debt

Crucial to the understanding of oxygen delivery during resuscitation are the concepts of oxygen deficit and oxygen debt.[6] The former reflects the discrepancy in oxygen delivery at any single point in time, whereas the latter describes the total amount that is required to be repaid before resuscitation is complete. During a shock episode, both oxygen deficit and debt will increase until the commencement of resuscitation. Although re-establishing oxygen delivery may prove successful in restoring vital haemodynamic signs and oxygen consumption to normal (no oxygen deficit), there remains an unpaid amount (oxygen debt) that must be settled, akin to repaying the interest on a financial loan. Until such time as the total debt is eradicated, ongoing resuscitation is required. Failure to appreciate this situation may result in a complicated intra- and postoperative course if surgery is undertaken too early. This is the concept of sub-clinical occult hypoperfusion.[7] The means of determining the end-points of resuscitation have been hotly debated and numerous techniques have been proposed, a sure sign that no single parameter is reliable. The most convenient and practical measurements are lactate and base deficit.[8] If both remain elevated despite normal vital signs, the loan has not been repaid and the patient is in the phase of compensated shock.

The proposed techniques of resuscitation are almost as numerous as the means of identifying the end-point. The initial concept of restoring normal pre-injury haemodynamic values was challenged by Shoemaker *et al*., who enthused about supranormal levels of oxygen delivery and consumption.[9] This was followed by Bickell *et al*. suggesting that permissive hypotension was preferable for penetrating trauma.[10] Both have been challenged and found wanting. There is no benefit in driving delivery and consumption to excessive levels, and hypotension is only appropriate if access to theatre can be guaranteed within a maximum of 60 minutes of injury. The thrust has changed to maximising oxygen delivery using vasopressors, blood and blood products early and limiting the amount of crystalloids or colloids. Vasopressors reduce the vascular capacitance while enhancing the perfusion of vital organs and clear fluids are not good oxygen carriers. This, and the recent recognition of the specific entity of the acute coagulopathy of trauma (ACoT), has led to the development of massive transfusion protocols and an attempt to define the optimal ratio of blood and component therapy.[11]

As with many developments concerning surgery for trauma, the lessons have been learnt from the casualties of war. Recent conflicts in the Middle East combined with sophisticated delivery of blood and blood products to the front line have led to the proposal of a ratio of 1:1:1 for packed red blood cells (PRBCs), plasma and platelets. This has been extrapolated to the civilian environment, with strong evidence for a distinct survival advantage if a massive transfusion protocol is established and similar ratios are employed.[12] The optimal ratio remains to be determined, but it would appear that PRBCs and platelets should be infused in a 1:1 ratio, whereas the ratio for PRBCs and plasma should be 2:1. The rationale is to maximise oxygen delivery while minimising blood loss from a coagulopathy. At least one objective end-point has been established in this setting, and that is the use of thromboelastography. The South African contribution of Professor Franz to this modality has long been under-recognised in the international arena.[13]

## Selective non-operative management

Non-therapeutic surgery, especially for suspected abdominal trauma, is associated with an increase in morbidity and even mortality rates.[14] This realisation, in combination with modern imaging techniques, has been the driving force behind the concept of selective non-operative management (SNOM). Initially proposed for blunt trauma, the same approach was later adopted for penetrating stab wounds[15] and has recently been extended to include gunshot injuries. Although driven partly by necessity due to an overwhelming patient load, South African research has made a major contribution in this field.[16,17] While clinical assessment remains the cornerstone for penetrating trauma, the computed tomography (CT) scanner has revolutionised the management of blunt injury. Once again, South Africa figured prominently in this radiological revolution.

Allan Cormack received his BSc in physics from the University of Cape Town in 1944 and subsequently gained a Master's in crystallography. Two papers he published in the mid 1960s addressed the theoretical technology applicable to CT scanning. In 1971, Godfrey Hounsfield built the first scanner using Cormack's calculations. Both scientists were awarded the Nobel Prize in 1979, with Hounsfield being knighted in 1981. Cormack was subsequently honoured posthumously, the gold Order of Mapungubwe, South Africa's highest honour, being bestowed upon him in 1992, the same year that Nelson Mandela received a similar platinum award. Technology advanced exponentially with the fourth-generation scanners appearing within 6 years of Hounsfield's original design. High-resolution images illustrate and quantify injuries, a prerequisite for SNOM. Management decisions based on CT scanning have stood the test of time, and spared many patients unnecessary surgery and many surgeons a sleepless night. Although areas of diagnostic doubt remain, especially regarding hollow visceral abdominal injury, the combination of the latest generation scanners, an astute radiologist and a sceptical surgeon have reduced the non-therapeutic laparotomy rate to almost zero.

The uncertainty of CT scanning in identifying hollow visceral injury made its use for penetrating abdominal trauma circumspect and for many years clinical assessment remained the cornerstone for management decisions. Although the new generation scanners allow superb visualisation of the missile tract, many surgeons revert to the time-honoured hands-on principle. SNOM of abdominal stab wounds evolved in the 1980s with large patient cohorts from both South Africa and the USA appearing in the literature.[16-18] For abdominal gunshot wounds, mandatory laparotomy was the gold standard until the first publications documenting the safety of SNOM in selected cases; the first two publications emanated from South Africa.[16,17] Other anatomical areas involving hollow visceral injury were subjected to similar scrutiny. At a

time when routine neck exploration was advocated for all wounds penetrating the platysma, evidence emerged from South African centres that this was not justifiable, and a selective policy based on imaging became the standard approach.[19] This was taken further by studies demonstrating that, even in the presence of oesophageal penetration, surgery was not always necessary.[20] The South African surgical fraternity can be justifiably proud of the contributions made in the management of civilian trauma, and many of the recommendations which now represent standards of care internationally were developed within our shores.

## SIRS – past, present and future

Traditionally, intensive care was the domain of the anaesthetist, the surgeon being relegated to the role of technician. Times have changed, and many surgeons, especially those interested in trauma, have developed an interest in the management of the critically ill or injured, some committing full-time to this discipline. This, I resolutely believe, is not only advantageous but essential, and history reflects the insight of surgeons into critical illness. In 1794, John Hunter, the prodigal surgical son of Glasgow, described the metabolic response to injury based on his observations on gunshot wounds during the Napoleonic wars, when he wrote, 'There is a circumstance attending accidental injury that does not belong to disease, namely that the injury done has in all cases the tendency to produce both the disposition and the means of cure.' By so saying he surmised that a physiological degree of inflammation is a prerequisite for recovery. He also noted that 'Inflammation is not in itself considered to be a disease but a salutary operation, but when it cannot accomplish that salutary purpose it does mischief.' Despite our attempts to categorise the systemic inflammatory response syndrome (SIRS), as with Gross's description of shock, Hunter's definition of a pathological inflammatory response has yet to be surpassed, and even in the modern arena of intensive care it continues to do mischief.

Much effort has been devoted to unravelling the cellular response to inflammation and in the field of sepsis the doors are beginning to open, hence the current definitions of sepsis, severe sepsis and septic shock. It has now been established that a pathological inflammatory response to infection stems from the activation of the innate immune system in response to foreign antigens in the form of the organism cell wall. But what of patients without a focus of infection, especially those sustaining major injury, who behave in an identical fashion to their septic counterparts with an overwhelming inflammatory response, the need for aggressive intravascular volume loading and vasopressor support? An analysis of the SIRS criteria in major trauma suggested the terms 'severe SIRS' and 'sterile shock' as analogous to 'severe sepsis' and 'septic shock'.[21] The outcomes in the septic and non-septic patients were identical in all categories of the SIRS, and although it was explicable in those with sepsis, the reasons why the non-septic patients should behave likewise was elusive and remained so until recently. Although the explanation is amazingly simple, the management is a major challenge. Yet again, the role of the mitochondrion is pivotal.

The human innate immune system recognises foreign antigens such as bacteria, viruses and fungi via pathogen-associated molecular patterns and pattern-recognition receptors on various cells of the immunological system without priming by prior exposure. This subsequently induces an inflammatory response. The prokaryotic mitochondrion is now believed to have evolved from α-proteobacteria, and there is substantial evidence to support this. Mitochondria have their own genome, and DNA resembles that in bacteria as a circular chromosome; proteins synthesised by mitochondria have the same configuration as bacterial proteins; protein synthesis can be blocked by antimicrobials.[3,4] Given this evolutionary theory, in the presence of major tissue injury these foreign antigens also invoke an inflammatory response via damage-associated molecular patterns and the same pattern-recognition receptors.[4] Indeed, concentrations of mitochondrial DNA several thousand times greater than normal can be found in the plasma of victims of major trauma.[22] This explains the identical nature of septic and non-septic shock after major trauma, and begs the obvious question – what can we do about it?

## On the shoulders of giants

Although dexterity (or sinistery for my left-handed colleagues) remains of paramount importance to operative success, the surgeon is not merely a technician or handyman. In all surgical disciplines, but especially when managing major trauma, not only time but also effort consumes a far greater proportion of patient care than the actual surgical component. Advances in molecular biology and immunology have opened new doors for therapeutic intervention. We are moving from the macroscopic to the microcellular level, and it is in the latter that the secrets of success lie. The research path to cellular manipulation has been rough and frustrating but I have no doubt that not far beyond the horizon lie new avenues. Young researchers of today need encouragement to see beyond our line of sight.

There can be no greater accolade, no higher pinnacle to climb, in a surgical academic career, than to be asked to deliver this lecture. I have been fortunate indeed to work with a number of the giants of South African surgery who have not only encouraged me in my research but have been generous in their praise. Without their support I would not be standing here and the words of Bernard of Chartres of the 12th century ring true: '… we can see more than they and things at a greater distance, not by virtue of any sharpness of sight on our part, or any physical distinction, but because we are carried high and raised up by their giant size'.

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