Editorials

The teleology of inflammation - doing battle with the selfish gene

Human host-defense systems are calibrated by natural selection against recurrent low-grade tissue incursions by foreign organisms. Without immediate local isolation of tissue invaders and efficient repair of tissue damage, the host becomes dangerously vulnerable. As a consequence, routine host-defense involves explosive, yet contained, and coordinated cellular and humoral responses.

However, the critical end-point here is not individual survival, but rather the best overall chance of successful propagation of the species. In fact it has been argued that we are merely survival machines for our own selfish genes. Certainly host-defense systems are first and foremost products of selection pressure, and less common events lack sufficient evolutionary visibility to have a major impact. From this perspective, overwhelming infection and large-scale tissue damage evidently represent a lesser threat to gene immortality, because responses to these events seem maladaptive, with excessive, prolonged and uncoordinated mediator release. The result is 'malignant intravascular inflammation', which can cause vasodilatory shock, multiple organ dysfunction syndrome and death. The selfish gene may thus allow adverse outcomes for victims of these less common threats, since they are mathematically disadvantaged. As critical care practitioners we find ourselves confronted by the paradox that under certain circumstances, our patients are programmed to die at the hands of what should save them – their own host-defense systems. Trying to rescue victims of evolutionary 'collateral damage' is the more frustrating part of an intensivist’s job description.

In this issue of Critical Care and Resuscitation, Drs Corke, Glenister and Watson look closely at one component of tissue and more particularly splanchnic host-defenses which seems to become maladaptive on major stimulus. Following their recent exploration of the relationship between the gastro-intestinal tract and multiple organ dysfunction syndrome, these authors concentrate specifically on secretory phospholipase type A2 (sPLA2). The sPLA2 enzyme is one of a large group of phospholipases best known for an ability to hydrolyse certain types of phospholipids to produce arachidonic acid, an important precursor in the eicosanoid host-defense pathway. The authors outline the wide variety of sPLA2 subtypes now known, and the various roles attributed to them, ranging from inflammatory mediation to tissue repair and signal transduction. The reasons for their specific interest in sPLA2 can be summarised as follows:

- The sPLA2 enzyme exhibits experimental bacteriocidal activity and promotes phagocytosis.
- The normal substrate is anionic phospholipids, but certain subtypes can act on neutral phospholipids in intact cell membranes, causing tissue damage.
- The gut mucosa is a likely source of most endogenous sPLA2, the expression of which can be up-regulated by endotoxin and platelet activating factor.
- Experimental splanchnic ischaemia-reperfusion releases sufficient gut sPLA2 to cause distant organ injury.
- Administration of sPLA2 to experimental animals causes shock.
- Large quantities of the enzyme are released after cardio-pulmonary bypass, major vascular surgery, sepsis, shock, multi-trauma and pancreatitis.

Because of this profile, the authors suggest that selective inhibition of sPLA2, or one of its sub-types, might be of benefit in critical illness, particularly in situations where there is both inflammatory mediator release and the possibility of occult gut dysxia. They cite some experimental support for this concept.

Such speculation is of course familiar territory. It should not to be discouraged, although prior to the PROWESS study more than fifty novel therapies showing early promise in the treatment of severe sepsis and septic shock generated disappointment, and even adverse outcomes, in Phase II or III trials. There is already speculation that sPLA2 inhibition will go the same way. Possible reasons for the repeated negative findings are many, and have been explored elsewhere along with suggested improvements in the trial process. The very nature of large scale clinical trials of agents such as sPLA2 inhibitors can militate against high quality efficacy data, despite exacting protocols and enthusiastic policing of recruitment criteria by trial coordinators. In particular, one should beware of data originating from units where the prime motivation for patient recruitment is financial.

Just as repeated negative outcomes may reflect the deficiencies of large clinical trials, an isolated positive outcome should also be treated with healthy skepticism. It is not beyond the realms of possibility that the landmark 6% reduction in absolute mortality attributed to the administration of recombinant Activated Protein C was simple type 1 error. In other words, if enough immunomodulation trials with inherent deficiencies are performed, one must eventually produce a false positive
result. Hopefully this was not the case with the PROWESS study, but time will tell.

What seems certain is that there will be no single magic bullet capable on its own of protecting our patients from maladaptive responses to intense inflammatory triggers. In the end, incremental benefits from individual agents such as recombinant activated Protein C will need to be pooled to counteract the legacy of the selfish gene.

Dr. T. J. Morgan
Intensive Care Facility
Royal Brisbane Hospital
QUEENSLAND 4029

REFERENCES

Treatment options for refractory intracranial hypertension: the evidence-based cupboard is bare

The management of patients with refractory posttraumatic intracranial hypertension remains a difficult and often frustrating clinical problem. This typically occurs in young patients with moderate to severe diffuse axonal injuries, frequently associated with traumatic subarachnoid haemorrhage, occurring 3-5 days following injury. The natural progression of this "hyperaemic" or "vasogenic" phase of brain injury is variable and depends on the elas tant reserve of the brain. Put simply, if the patient has adequate intracranial volume to absorb increases in intracranial pressure without further compromising cerebral blood flow, then associated neuronal loss should be minimised. The mortality in these patients is high; survivors are frequently left with significant disabilities.

By applying a pathophysiological approach to exhaustion of elas tant reserve, it would appear that mechanical therapies such as cerebrospinal fluid (CSF) drainage or decompressive craniectomy would be successful in improving intracranial pressure/volume relationships. Many experienced neurosurgeons have anecdotes of "remarkable" recoveries in patients with apparent refractory intracranial hypertension following decompressive craniectomy. Medical therapies such as cerebral volume regulation ("Lund" therapy), or "optimised" hyperventilation, have theoretical merit. However, the plural of anecdote is not data: none of these therapies have been subjected to an adequately powered, outcome based, randomised and controlled trial.

Current management guidelines offer little in terms of providing evidence-based strategies for such patients. Drainage of CSF via an intraventricular catheter is recommended both as an intracranial pressure monitor and as a "first line" method of reducing intracranial pressure. Medical therapies to reduce intracranial hypertension such as hyperventilation, hypothermia, or barbiturates are considered as "second tier" therapies, whilst surgical decompression is mentioned as an option.

The logistics of conducting a randomised trial to assess whether any of these treatments improve outcome are formidable. Traumatic brain injury is a heterogenous process. Outcomes are markedly influenced by primary injury and secondary ischaemic/hypoxic insults; ICU management strategies vary widely between centres, and surgical interventions such as decompressive craniectomy are applied with various levels of enthusiasm. Quantification of outcome is problematic - the extended Glasgow Outcome Score is the most widely used tool, but opinion is inconsistent about the optimal follow up period and the sensitivity and specificity of functional survival.

These logistic hurdles do not however mean that future studies are impossible. Recent interest in revisiting the role of decompressive craniectomy has increased around the world, particularly in Europe.
following a specific survey conducted by the European Brain Injury Consortium and in Australia following a positive study in children. Decompressive craniectomy is an inconsistently and infrequently performed procedure, largely influenced by surgical preference. To demonstrate an absolute reduction of mortality by 10 - 15% from baseline mortality of 30%, a sample size of 350 patients would be required. This would mandate a multicentred, probably multinational, trial requiring a standardised management approach.

Patient selection is an interesting issue as the role of decompressive craniectomy in patients with raised intracranial pressure due to extra-axial or intradural haematomas is different to those with primary diffuse axonal injury. Consequently, patients would need to be identified, or stratified according to underlying cerebral pathology determined by CT scan. Treatment thresholds could be determined by the degree of intracranial hypertension, assessed using a standardised method of intracranial pressure measurement, such as ventricular drainage. Thereafter, surgical methods of decompressive craniectomy (unilateral vs bilateral) and medical therapy will need to be standardised. Finally, mortality and functional outcomes will need to be assessed at six and 12 months using a standardised method. Such a study would require an adequately funded, cohesive and committed study group.

The allocation of funding and research resources directed at a high mortality and morbidity condition such as traumatic brain injury have been questioned by some. Studies directed at injury prevention and early quantification of functional outcome are considered to be better cost-effective research initiatives. Concerns have been expressed that such “aggressive” interventions such as decompressive craniectomy, or cerebral volume regulation may reduce mortality, but increase vegetative survivors. These are valid comments particularly when the significant funding, design, coordination and conduct of such a trial may provide an answer for only one question.

However, given the persistently high mortality and morbidity associated with traumatic brain injury, research at all facets of this global epidemic is a priority. Evidence-based guidelines, such as those promulgated by the Brain Trauma Foundation, highlighted the paucity of evidence upon which many units base their practice. In many ways, these guidelines have laid the foundation to address future questions, rather than provide definitive answers. The next challenge is to answer them.

Dr. J. A. Myburgh
Intensive Care Unit
St George Hospital
NEW SOUTH WALES 2217

REFERENCES

Rare and emerging infections

Most intensive care specialists are aware of the emergence of antibiotic resistant bacteria in critical care units and the risks of cross infection via hands of hospital personnel or contaminated equipment, of resistant gram positive and gram negative bacteria and even Candida. Methicillin resistant S. aureus, vancomycin resistant enterococcus, extended spectrum β lactamase (ESBL) producing Klebsiella sp., multi-resistant Pseudomonas sp. and, most recently, vancomycin intermediate S. aureus all represent major therapeutic challenges in critically ill patients.

However in this months Journal, Hore describes the
‘hazards outside’ – an eclectic collection of rare but potentially devastating infectious diseases that may require critical care management. Many other emerging or severe and unusual infections such as Hendra (equine morbillivirus) and the related Nipah virus, Aeromonas, Melioidosis, Flinders Island spotted fever and new strains of influenza virus could have been described, but those selected are illustrative of a number of points.

Firstly, all the infections discussed are associated with exposure to either marine or soil environments, arthropods or vertebrate hosts and are thus often associated with travel or leisure activities. More adventurous travel, environmental and climate changes may change the frequency at which these emerging and re-emerging infections occur. Thus an accurate history of potential exposure remains the key to diagnosis. This may be problematic when patients are critically ill or if the incubation period, as is the case for Lyssavirus infection, may extend for several years. A further difficulty is that a history of arthropod or other exposure may never be obtained. For example, a recent analysis of the epidemiology of rabies acquired in the USA found that 80% had no definite history of an event associated with transmission.

Secondly, most physicians will be unaware of these infections and their virulence potential. If acquired and established, infection with marine Vibrios and Capnocytophaga sp. may present in the fulminant manner normally associated with overwhelming meningococcal infection.

Thirdly, diagnostic difficulties (even if the infection is considered) arise because of the fastidious nature of the bacteria or limited availability of reliable serological assays. When exposure is common and severe symptomatic disease unusual, positive serological responses may be misleading. For example, almost 20% of healthy dairy farmers in the Gippsland have leptospirosis antibody titres by microagglutination of $\geq 1:50$.4

Finally, these infections may require antibiotics not generally considered for empirical regimens in hospitalised patients. The best example of this is rickettsial infection, which is refractory to penicillin and cephalosporins but responds promptly to oral tetracycline. *Chromobacterium violaceum* also has an unusual antibiotic profile, with resistance to penicillins and cephalosporins common.

It is inevitable that the infections discussed by Hore and other new, or reemerging diseases, will continue to appear or their geographical distribution will change as a result of behavioural and environmental changes. Detection of these diseases requires continuing clinical and laboratory vigilance and close liaison between intensive care and infectious diseases specialists and diagnostic laboratories.

The Infectious Diseases Society of America has established an Emerging Infections Network (http://www.idsociety.org/EIN/AboutEIN.htm#Purposes &Functions) for the reporting of rare infections and unusual clinical events that may indicate the presence of new infectious diseases. The establishment of a similar network in Australia should be considered.

Assoc. Professor D. Gordon
Department of Microbiology and Infectious Diseases
Flinders Medical Centre
SOUTH AUSTRALIA 5042

REFERENCES

**Is endotracheal suctioning an art or a science?**

Tracheobronchial suctioning 2 - 4-hourly (or when large airway sounds are heard) is performed in intubated intensive care patients to remove airway secretions and reduce the incidence of atelectasis, lung collapse and pneumonia. Generally, it is performed by two people, with the patient monitored using an ECG recording and pulse oximetry. One person ventilates the patient manually using 100% oxygen, a reservoir bag and assembly, increasing the patient’s tidal volume by 1.0 - 1.5 L for 3 - 6 breaths, before removing the endotracheal tube connector for suctioning (i.e. ‘open’ system suction technique). Pre-suction saline instillation is also used by some, particularly in paediatric practice. A sterile suction catheter (usually a 12 - 14 French gauge catheter in an adult) is inserted, by the other person, into the airway until a resistance is felt, it is then withdrawn 2 - 3 cm before suction is applied. The catheter is then withdrawn completely with negative pressure interrupted momentarily throughout.
the 15 second suctioning interval. A minimum of one minute is usually required between suctioning episodes.2

The suction catheter is connected by a large diameter extension tube to a collection bottle and a vacuum system. The apparatus provides a free air flow rate of no less than 40 L/min at the end at which the catheter is attached.3 While negative pressures of 100 - 170 mmHg are suggested as safe suctioning pressures (particularly in paediatric patients),4 the Australian Standards for suction systems require suction units that can generate negative pressures of 450 mmHg or greater when occluded.5

In an adult, the catheter normally extends up to 10 cm beyond the end of the endotracheal tube and is 45 - 50 cm long to enable the correct length of insertion. The catheter should be free of sharp edges, contain an end hole and two or more side holes. There is an air entrainment hole at the other end of the catheter to allow intermittent suctioning. If an angled tip is used, one of the side holes should be placed at the convex side of the angle,6 and an external marker should indicate the direction of the tip.

As flow is proportional to the pressure difference, viscosity of the fluid being removed, and length and 4th power of the internal radius of the catheter, it is clear that the internal radius of the catheter (which should be as large as possible) has the greatest effect on efficiency of suction. However, to allow gas to return to the airway during suctioning, the outer catheter diameter should be no greater 0.6 times the inner diameter of the endotracheal tube (e.g. 14 French gauge for an 8 - 9 mm tube).6

A ‘closed’ system has also been used for tracheobronchial suctioning, with the postulated advantages including a multiple-use single-catheter system (changed every 24 hr), reduction in environmental contamination7 and allowing continuous mechanical ventilation during suctioning to reduce hypoxia and hypercapnoea.8-11 However, the benefits of a ‘closed’ system suction technique have been disputed, as hand contamination from showering of the condensate from the flush port, pooling of the catheter irrigation saline within the connectors, difficulty in cleansing the inner tube after use, ineffective secretion removal, catheter infection and sticking of the suction catheter in the endotracheal tube have all been reported.12,13

In this edition of the journal, Frengley et al.,14 report the effect of a closed tracheal suction system in adults (using a 14 French gauge catheter inserted for 5 seconds in an 8.0 mm internal diameter endotracheal tube and a negative pressure of 368 mmHg) on mechanical ventilation. They found that the effect varied depending on the ventilatory mode used. For example, in volume control ventilation the end expiratory pressure increased following catheter insertion and subatmospheric airway pressures were recorded during suctioning. During continuous positive airway pressure/pressure support ventilation, the ‘closed’ suction system had no effect on end-expiratory pressure following catheter insertion and subatmospheric airway pressures were largely avoided during suctioning.14

In general, suctioning is an art, particularly as surveys of techniques used by nurses, physiotherapists and respiratory therapists reveal that the techniques used vary widely.15,16 There are no prospective, randomised controlled studies that have demonstrated an advantage of any technique (e.g. presuction hyperventilation, saline instillation, angle tip catheters, suctioning only on the way up, etc) in reducing the incidence of atelectasis, lung collapse and pneumonia, while minimising the adverse effects of airway trauma, hypoxia, hypercapnoea and haemodynamic instability. Indeed, many of these techniques continue to be used even though some have been shown to be hazardous (e.g. a five fold increase in bacterial contamination of the lower airway has been reported when presuction saline instillation is used, compared with standard suctioning techniques).17

The ‘closed’ system suction techniques that have emerged as an alternative to the conventional ‘open’ system suction techniques are another ‘art’ form, and as disadvantages of this technique are now being reported, they must also undergo rigorous investigation before being accepted into clinical practice.

Dr. L. I. G. Worthley
Department of Critical Care Medicine
Flinders Medical Centre
SOUTH AUSTRALIA 5042

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EDITORIALS

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Further reflections on clinical trials in critical care

In a recent editorial in this Journal, we drew attention to some potential problems of the reporting of trials involving group sequential methods. In particular, i) we cited evidence from the statistical literature that, as a consequence of group sequential methodology, point estimates of treatment effects of such trials are inflated and confidence intervals are inappropriately narrow, and ii) in a hand-search of 16 trials in the New England Journal of Medicine from January 2000 to March 2001, using group sequential methods, no trial was found to include a statement of, or actual adjustment for, these biases in treatment estimates.

It is now of some interest to review the results of a trial by Van den Berghe and co-workers in a recent edition of the New England Journal of Medicine. The trial involved 1548 patients in a prospective randomised controlled protocol investigating the utility of intensive versus conventional insulin therapy (targeted to blood glucose concentration), with the primary outcome measure as death from any cause during the intensive care stay. The 4.6% intensive care mortality in the intensive-treatment group vs the 8% in the conventional-treatment group represented an apparent risk reduction of 42% (95% CI: 22-62%). The final treatment-effect estimate was subsequently adjusted for the four interim analyses undertaken in the study: the median unbiased estimate giving a value of 32% reduction in mortality with adjusted 95% CI of 2-55%.

Obviously a substantial inflation of the treatment-effect had occurred as a result of the use of sequential group methodology and the trial by Van den Berghe et al is one of the few reports in the literature where an appropriate adjustment has been made.

Such adjustments are not post-hoc but derive from the trial structure and the number of interim analyses. All the reader may infer, in the absence of these adjustments, is that the trial treatment estimates are not as good (or as bad) as presented. There are three other recent trials in the literature reporting positive intensive care unit (ICU) treatment interventions where interim analyses have been performed and no adjustment of treatment estimates have been made. We note that in recent updates to site-information on the two software packages providing facility for use of unbiased estimators (EaST 2000 and S+SEQTrial) that the United States FDA has acquired both these packages. Such may herald, in the future, more regulatory attention to these matters.

At this time, when a number of positive trials of ICU interventions are appearing in the medical literature, it is perhaps relevant to canvas some other issues of trial methodology. The accompanying editorial to the Van den Berghe et al and Rivers et al papers points to problems of interpretation of unblinded and single-institution trials. With respect to: a) the impact of “unblindedness”: we may assess the effects of this on treatment efficacy by use of the Mann-Whitney statistic, as an alternative to the more traditional estimates such as risk ratio or risk difference. The Mann-Whitney statistic estimates the probability (0 to 1.0) that a randomly selected patient given an innovative therapy will respond better than a randomly selected patient given “standard” treatment. That is, for a value of the statistic of say 0.6, the interpretation is that there is a 60% probability that the (next) randomly selected patient (or, more correctly, one of a pair of patients) on therapy will improve compared with no therapy. In the presence of non-blinded randomised studies, it
is suggested that the statistic be decreased by 0.1 to 0.15. In the current context, two of the ICU trials were non-blinded and a third was partially blinded. Table 1 shows the Mann-Whitney statistic for the 4 trials mentioned previously (i.e. ARDS, PROWESS, Van den Berghe and Rivers) and the positive, but non-blinded trial of Amato et al which reported a protective-ventilation strategy in ARDS. What is apparent is the increased unadjusted probability of better response in the smallest study (Amato et al11) and the non-blinded studies compared with the large blinded PROWESS study; but, after “adjustment”, the response probabilities, at least for the larger 4 studies, are reasonably comparable. This comparability of responsiveness may say something of future expectations of therapeutic success in the ICU.

<table>
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<th>MWstat, adj</th>
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<td>0.58 b</td>
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</table>

Total n = total study patient number, MW stat = Mann-Whitney statistic, MW stat, adj = adjusted Mann-Whitney statistic, a = MW stat, adj related to 28 day mortality, b = MW stat, adj related to hospital discharge mortality.

b) single versus multi-institutional trials: that the results of a single-institution trial may reflect, uniquely, the local structure of care has been previously attested to12 but the interpretations(s) of the results of multi-institutional trials may also be a cause for some controversy, if we are to believe the exchanges in current mailing lists. What we are concerned about here is the recurrent debate on the implications of heterogeneity at the patient,14,15 institutional,16 or analytic level17,18. That is, will “dissimilar” patient and site characteristics and numbers vitiate the results of a trial which reports an overall treatment effect. However, the problems of multi-institutional trials are not uniquely different from those of the single institution, although the preponderance of multi-institutional trials may force us, rather, to seek solutions to these problems and not ignore them. In particular, we note recent recommendations for individualisation of patient therapy19,20 and debates on the appropriate form of site-weighting and site-treatment interactions (the so-called type II vs type III model),21-23 the use of random-effects approaches to model site-effects24,25 and Bayesian methods as an alternative to traditional ANOVA analysis26. These questions are, of course, pertinent to another paradigm, that of meta-analysis and the close comparisons, at least at the analytic level, between meta-analysis and multi-centred trials has been commented upon.27,28 This close relation has seen changes in clinical trials mandated by meta-analysis29 and the meta-analysis of individual patient data has been suggested as being at the top of the hierarchy of strength of evidence concerning efficacy of treatment.30

Two other aspects of trial methodology deserve further attention:

i) the problem of “optimal” cut points in the evaluation of (and implementation in subsequent trials) prognostic factors. There has been extensive discussion of the problems of this approach in the cancer31-33 and statistical literature34,35. The problems are those of increased Type I error, inflated estimates of effect and increased variance of these estimates and decrease in the efficiency of analysis. Appropriate adjustment of p-values may be made for this form of exploratory analysis.32,36 That this may effect the outcome of trials may be indicated by recent research into the effect of anti-tumor necrosis antibodies (MAK 195F) in sepsis and septic shock. In a preliminary assessment of safety and efficacy of MAK 195F,37 the prognostic value of IL-6 concentrations of greater than 1000 pg/mL was established by retrospective cut-point analysis with no adjustment of the p-value. Although in the subsequent randomised placebo-controlled RAMSES38 study of MAK 195F, a difference in mortality rates was observed between patient groups with IL-6 levels above and below 1000 pg/mL (40% vs 50%, p < 0.001), this did not translate into a mortality difference between treatment and placebo groups with IL-6 levels > 1000 pg/mL (p = 0.36). The recently completed MONARCS trial39 is reported to have demonstrated a mortality difference based upon the same criteria, but this study has yet to be published. Similar prognostic cut-point classification occurred in the recent investigation of cortisol levels and cortisol response to corticotrophin in septic shock.40 Subsequent reports of improved mortality41 based upon this rationale will, again, await review of the published trial.

(ii) the problem of “responsiveness” in assessing therapeutic interventions: this rather subtle problem was first given prominence in the cancer literature. It involves the responsiveness of patients to chemotherapy in terms of a “remission” or rate of favourable response, being interpreted as evidence
that the effect of treatment was to prolong overall survival. At the most, this is trivially true (patients who survive longer have a better outcome), but when differences in survival time (responders vs non-responders) are subjected to formal test (for example log rank test), bias in favour of responders may occur because these patients are being counted at risk of failure (death) before the time of response. As response to treatment and survival are both outcome variables, the use of testing to compare responder and non-responder survival distributions merely serves to confirm or deny the association between response and survival; it does not necessarily invoke a causal pathway. We may think of a number of reasons why this scenario may occur: early deaths are counted as non-responders, by definition response involves a “guarantee time” before the response occurs, “response” may be a surrogate for the selection a particular patient subset not previously identified at initial randomisation (that is the distribution of frailties [an “unobservable” prognostic index] between responders and non-responders, differs) and the failure to appropriately operationalise the notion of response.

The translation of these analytic principles to the critically-ill context may not be straightforward, given the obvious different time scales and problems of definition of response. For instance, in the observational studies and trials looking at the effectiveness of increases in oxygen delivery in septic patients, responsiveness was usually defined as an increase in cardiac output, but this may be an insensitive criteria. Such responsiveness was located in particular patient subsets in the trials addressing the question of goal-oriented therapy. This may not be surprising, but it serves to caution us in our interpretations of what a response actually means (did it select out a group of patients with “better” (or worse) prognosis) and how it should be appropriately analysed. We may also speculate that where no improvement in mortality has been observed, but there are improvements in other endpoints (rates of infection, length of stay), the same mechanisms may be operative.

Dr J. L. Moran
Dr. S. L. Peake
Intensive Care Unit
Queen Elizabeth Hospital
SOUTH AUSTRALIA 5011

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