Editorials

A word from the congress president

Welcome to the 8th World Congress of Intensive and Critical Care Medicine and to this special edition of the Australasian critical care medical journal *Critical Care and Resuscitation*. Intensive Care Medicine has been recognised in Australia and New Zealand for a considerable length of time and it was here that the first graduate with a specialist qualification in intensive care medicine was produced. There has been great argument over the years about who should have ownership of 'Intensive Care' and who should have control of the specialty. Perhaps one of the best recommendations for Australia as a venue is that in both Australia and New Zealand, Critical Care Medicine is controlled by intensivists.

An important part of our specialty is the World Federation, which has been established to look beyond our own shores to identify those who we can help. Throughout large parts of the world the provision of simple intensive care techniques would improve outcomes in young members of the population. To develop such practices in many countries must be an important goal of this organisation.

We have tried to make this meeting of interest to people from all lands. The meeting is different from other Intensive Care World Congresses in some uniquely Australian ways: from an opening ceremony where the only people who speak will be patients to the final interactive case discussion session.

The generosity of our sponsors and our invited speakers who have all paid their own fares has enabled us to further fulfil the aims of the World Federation and sponsor attendees from India, Cuba, Venezuela, Argentina, Colombia, Myanmar, Vietnam, Nepal, Western Samoa, Rwanda, Mongolia, Palestine, Brazil, Peru, Columbia, Cuba and Indonesia. This sponsorship has been supported by local chapters of the medical and nursing intensive care societies in Australia and by individual hospitals from funds they have raised themselves, both in the public and the private sector. A strong specialty has a strong World Federation. The World Federation of Intensive and Critical Care is young and its recent progress has been difficult. The most disappointing aspect to members of Council is that the Federation's journal *Intensive Care World* has not been distributed for the past two years and it is hoped that the council can provide initiatives which will enable this to be restored as in many parts of the world this was the only journal that intensive care doctors received.

Enjoy the meeting.

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Monitoring intestinal ischaemia. More problems!

In this issue of *Critical Care and Resuscitation*, Drs Corke and Glenister review some of the methods currently available to the clinician for detecting intestinal ischaemia, and scan the horizon for potential advances in this problematic area.[1] For many years there has been speculation that the gut is a 'motor of multiple organ failure', an 'undrained abscess' which triggers overwhelming host defence responses when its fragile integrity is breached.[2-5] A similar concept is embedded in Fiddian-Green's notion of 'covert compensated shock',[6] in which haemodynamic compromise remains subclinical because of maximally deployed homeostatic responses. A major player in this scenario is occult splanchnic hypoperfusion, which occurs early in low flow states and tends to persist.[7,8] A further important characteristic of the gut is the microcirculatory architecture of its mucosa, with a known predisposition to dysoxia by virtue of plasma skimming and arteriovenous diffusive shunting.[9-11] For these reasons the gastro-intestinal tract has been termed 'the canary of the body'.[12] The problem is to find a signal emanating from all or part of this organ which is both sensitive to and specific for occult dysoxia and can also act as a therapeutic end-point.

As Drs Corke and Glenister point out, at present there are no indices to fit the bill. Fiddian-Green's own contribution of gastric tonometry has come closest,[13-16] but is something of a disappointment so far.[17] Essentially gastric tonometry is tissue capnometry performed in the most accessible part of the gut.[18] The original monitoring end-point was the intramucosal pH or pHi, derived by measuring intramucosal PCO_2 using a saline equilibration medium in a silastic balloon, and then calculating pH by making the incorrect assumption that plasma and mucosal bicarbonate concentrations are the same.[19] Low pHi has been linked with bleeding from stress ulceration,[20] weaning failure,[21]ARDS after blunt trauma,[22] morbidity after liver transplantation,[23] major complications post elective cardiac surgery,[24] and

multiple organ dysfunction syndrome and death.[25-29] However, there is still only limited evidence that titrating therapy to pHi improves outcome.[30-34] It remains to be seen whether changing the monitoring endpoint from pHi to the mucosal-arterial CO_2 gap[35-37] will have any impact. Although current recommendations are to maintain a CO_2 gap < 25 mm Hg,[38] the true dysoxic threshold is uncertain.[39-41] A further refinement has been the introduction of automated air tonometry.[42-45] In this modification PCO_2 is measured by infra-red absorbance, which reduces equilibration time and eliminates the time-based correction factors and inherent inaccuracy of saline equilibration.

However, other problems with the technique include signal degradation by luminal blood [46] and to a lesser extent by feeds, [47]doubt concerning the reliability with which luminal PCO_2 reflects mucosal PCO_2, [48] and the probability that in the absence of hypoperfusion, regional PCO_2 is insensitive to tissue dysoxia. [49,38] Finally, gastric tonometry suffers from the major disadvantage that it samples only one small region of a very large organ. This criticism can also be leveled at some newer techniques not discussed by Drs Corke and Glenister. For example orthogonal polarisation spectroscopy (OPS) is an imaging tool for the real-time *in vivo* assessment of microcirculatory blood flow, [50] but tissue beds visualized routinely in intensive care patients are necessarily restricted to the sublingual, rectal and oral microcirculations. Only when a stoma is in place can the ileal or colonic mucosa be monitored. Another example of a gut monitoring tool with limited sampling potential is laser Doppler flowmetry. [51,52]

Accordingly, much attention has been directed towards developing markers of ischaemia which scan larger sections of the gastro-intestinal tract. Drs Corke and Glenister outline some of the progress here. They touch on clinical and radiological markers of severely ischaemic or infarcted gut, which are more relevant in surgical conditions and of little value in 'covert' ischaemia. Faecal enzyme markers are rightly dismissed as unreliable and often unavailable. The authors point out that standard plasma enzyme profiles lack sensitivity and specificity, even when splanchnic ischaemia has gone on to produce infarction. The iso-enzymes alpha glutathione S-transferase and creatinine kinase-BB may be more reliable, although by the time of diagnosis the situation may still have deteriorated to a point where gut resection is the only appropriate intervention. More interesting from the critical care aspect are intestinal fatty acid binding protein (1-FABP), which is showing promise in animal models of reversible small intestinal ischaemia, and a sub-variant of phospholipase A2 (sPLA2), which may be a specific indicator of intestinal ischaemia-reperfusion.

For completeness it is worth mentioning some further indices of splanchnic well-being not covered by these two authors, although they are largely research tools. These include hepatosplanchnic measurements of blood flow, [53] oxygen delivery, oxygen consumption and lactate dynamics, [54,55] and hepatic near-infrared or ^{31}P NMR spectroscopy. [56-59] Finally, the original proposition that the splanchnic circulation is the only one with genuine 'canary' status has come under question. Researchers are turning their attention to other microcirculations which might also emit warning signals of occult haemodynamic compromise. Examples include the tongue, [60] oesophagus, [61]muscle, [62,63] bladder [64,65] and subcutaneous tissue. [66,67] In the end multi-pronged surveillance using simultaneous inputs from many tissue beds may provide the most complete picture.

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Written guidelines for laboratory testing

A laboratory test is often performed to rule in or rule out a diagnosis, assess the severity of an illness, prognosticate, monitor disease or therapy, confirm an abnormal result, screen, educate, satisfy medico-legal requirements, carry out research, obtain a baseline, or reassure patients.[1] However, laboratory tests may also be ordered inappropriately. For example, to satisfy idle curiosity, because of ready availability, habit (i.e. 'to be complete', 'what have *we* got to lose'),[2] or even due to non-availability of a previous result.[3] In general, if there is no clinical indication for a test or if an abnormal finding will not influence therapy or outcome of the patient, then the test should not be performed.

In an attempt to reduce the number of inappropriate tests and thereby address the important issues of cost, blood loss, contamination and nursing workload, Mehari and Havill report in this issue of the journal, a second study[4] which follows an earlier report[5] which assesses the impact of developing and implementing guidelines for laboratory testing in an intensive care unit in terms of the number of blood tests and arterial blood gases performed in the general and the post-cardiac surgery intensive care wards. In the earlier study a decrease in testing varying between 16% and 25% and potential

savings of $80,000 (NZ) per year were identified.[5] The follow-up study performed three years later and reported in this issue, confirmed that the level of testing remained at/or below the level achieved after the introduction of the guidelines.[4]

However, the designs of both the original and follow-up study raise more questions than they answer. For example, there was no control group in the original study to allow for the well known "Hawthorne effect" where observation of a practice improves its performance without any other intervention. Any apparent improvement in practice in the original study may be partly or completely attributable to this effect. The follow-up study did not allow for any changes in work-load, patient case mix or work practice that might affect patterns of laboratory testing. Any or all of these factors could have changed during the three years following the original study. Once again there was no control group where guidelines were not implemented to see whether patterns of laboratory testing showed the same trends over time. It was also not clear in either study that the quality of care or the workload were assessed to ensure that patient care, patient outcomes or nursing workload were not affected by any changes in laboratory testing. In both studies the study outcome measures relate to the frequency of tests and adherence to the introduced guidelines was not assessed. If the apparent reduction in laboratory testing were indeed attributable to the introduction of guidelines, one might expect that it was adherence to the guidelines that achieved the reduction.

The investigators have addressed an important topic for critical care medicine but unfortunately have not clearly demonstrated to the dissenter that developing and implementing guidelines can reduce laboratory testing without adversely affecting quality of care, patient outcomes or staff workload.

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Clinical features of an increase in intracranial pressure

If the intracranial pressure is raised gradually and the structures within the skull maintain their normal anatomical relationships with no obstruction to the flow of cerebrospinal fluid (CSF), the intracranial pressure (ICP) may approach the mean arterial pressure (e.g. 40 mmHg) and the patient remain asymptomatic.[1]

However, if the ICP is increased rapidly and the intracranial structures are compressed or there is blockage to the CSF flow, then the characteristic symptoms and signs associated with an increase in ICP will often occur.[2] Symptoms include severe headache (worse with coughing), anorexia and nausea. Signs include, projectile vomiting, high pitched cry or scream, lethargy, disorientation, drowsiness, strabismus, loss of upward gaze ('sun setting'), papilloedema (which takes 36 hours to develop with an acute elevation of ICP), absence of retinal venous pulsation and an ability to obliterate retinal arterioles before obliterating the retinal veins with orbital pressure.[3] Late signs include the Cushing reflex (e.g. bradycardia, hypertension, irregularity of respiratory rhythm),[4] pulmonary oedema, bilateral extensor plantar responses, stupor, coma, fixed dilated pupils (uncal herniation) and brain death.[2]

Rarely, other signs may occur. For example, a transient cutaneous flush of the face, shoulders, upper arms, upper chest or abdomen that lasts for 5 - 15 minutes has been described in paediatric patients with a sudden rise in ICP.[5,6] The flush may be patchy or confluent and pink or cyanotic. Paediatric patients may also develop a tense anterior fontanelle, splayed cranial sutures and an increase in head circumference.

In this issue of *Critical Care and Resuscitation*, Hill and Sleigh describe a similar flush during stimulation in an adult patient with head injury and postulate a central neurogenic mechanism similar to that postulated for the paediatric patients. [7]

Vasogenic flushing is caused by a transient vasodilation of the epidermal vasculature and is usually controlled by autonomic nerves. As the autonomic nerves also control eccrine sweat glands the erythema may be associated with sweating (i.e. 'wet' flush). However, most of the reported cases of neurological

flushing associated with an increased ICP occurred without sweating (i.e. 'dry' flush) indicating that the epidermal flush in these cases was not under the exclusive control of a normal autonomic system.

Autonomic functions are complex and the neurotransmitter substances released into the circulation with central nervous stimulation involve many vasoactive agents,[8] some of which are reviewed in the report by Hill and Sleigh.[7] While the pathophysiological mechanisms for flushing remain speculative, a sudden erythematous skin reaction may now be added as one of the clinical signs associated with severe head injury.

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Reporting of clinical trials using group sequential methods

Two multi-centre trials reporting positive outcomes for interventions in critically-ill patients have recently been reported.[1,2] Both were large scale studies and used group sequential trial methods to allow the possibility of early study termination: i) in the Prowess trial[1] "O'Brien-Fleming spending function according to the method of Lan & DeMets", with initial enrolment of up to 2280 patients and two planned interim analyses at 760 and 1520 patients, and ii) in the ARDS Network trial [2] "interim analyses…after each successive group of approximately 200 patients. Stopping boundaries (with two-sided α level of 0.05) were designed to allow early termination of the study if the use of lower tidal volumes was found to be either efficacious or ineffective" No initial enrolment estimate was provided. Patient recruitment was, in fact, prematurely ceased in both studies due to a positive treatment effect, after the second and fourth interim analyses, respectively. In the Prowess trial, primary statistical analysis was based upon the Cochran-Mantel-Haenszel test; in the ARDS Network trial, primary analysis was based upon the 180-day cumulative mortality. Both trials demonstrated modest treatment effects (6.5% and 9% absolute risk reduction) and both had similar lower 95% limits for the risk reduction (2.2 and 2.5% respectively).

However, the physician who considers changing practice based upon the actual magnitude of these risk reductions must be circumspect, to the extent that these estimates are overly optimistic. Although little recognised in the clinical literature, it has been demonstrated for some time that early trial stopping based on group sequential designs results in inflated estimates of treatment effect and inappropriately narrow and incorrectly centred confidence intervals. Such bias(es) are also a function of the number of interim analyses.[3-5] As Demets and Lan observed, "Naïve estimates are biased after a sequentially designed trial has been completed, and appropriate adjustments for unbiased point estimates involve parameters whose values are typically unknown.".[6] Hughes and Pocock, addressed the question of exaggerated magnitude of the treatment effect and proposed a Bayesian solution,[7,8] Emerson and Fleming[9] and Pinheiro and DeMets,[5] reported methods for estimating and reducing the bias of treatment differences. Emerson[10] and Kim,[11] both derived unbiased estimators following a group sequential trial and Liu *et al*, investigated appropriate adjustments for secondary hypotheses to control inflated Type I error and reduced power of conventional likelihood-based testing procedures.[12] Two recent software packages EaST 2000,[13] and S+SEQTrial,[14] provide facility for use of these unbiased estimators (of Kim[11] and Emerson[10] respectively).

Group sequential methods have an established place in trial methodology[15] and a review of randomised trials reported in the *New England Journal of Medicine* over the time spanned by the above two trials (January 2000 to March 2001) revealed a total of 16 randomised trials conducting interim analyses. Of these, 10 used formal O'Brien-Fleming stopping rules; one used Pocock

stopping rules and two mentioned "formal" stopping boundaries. A positive treatment effect was established in 10 trials, all but one (using no formal stopping rules) being stopped early. Trial statistical methodology statements were variously detailed, but none specifically identified group sequential methods as a potential source of bias and no "positive" trial adjusted (downward) the primary outcome estimate(s).

It is appropriate for the reports of such trials to include at least some statement of, or actual adjustment for, the expected bias in outcome estimates. These concerns are legitimate, especially in the context of potential extrapolation from an estimate of risk reduction to, say, a number needed to treat.[16] That these adjustments were not used may reflect the lag phenomenon of statistical method transfer into the medical literature.[17]

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