Tetanus has a long history. Hippocrates wrote, "A convulsion after a wound is lethal . . . In tetanus and opisthotonos it is a fatal sign to sweat and for the body to be relaxed"; and textbooks of the 1950s described devastating spasms, often beginning with risus sardonicus and culminating with opisthotonos — arching of the body between the heels and the head. Death from asphyxia and exhaustion often followed.

The patients included in our review were all admitted to the Royal Adelaide Hospital (RAH); initially, to the specific tetanus ward, and later, to the intensive care unit. The two series cover almost 30 years, preceding the emergence of intensive care in Australia and New Zealand and extending to the mid 1980s when it was well established. Some procedures that were once used hesitantly have become mainstream, while some treatments and clinical problems are no longer seen.

The first series involves nine severe cases that presented in 1957, published in 1959 by JRL, who was then the Barker Research Fellow in Medicine at the RAH. His co-worker was the late Maurice Sando OBE (hereafter "M S"), who in 1957 was a senior registrar in anaesthesia, and later, Director of the Department of Anaesthesia and Intensive Care at RAH and Dean of the Faculty of Anaesthetists of the Royal Australasian College of Surgeons. The second series involves 56 unpublished cases, managed by JEG, RR and DC between July 1967 and August 1985, of which 38 were classified as severe.

Materials and patient management

First case series

In the 1957 case series (Table 1), major spasms were innovatively treated with neuromuscular blockade. The authors instituted early tracheostomy, neuromuscular relaxants and intermittent positive pressure ventilation (IPPV) to ensure effective ventilation. After intravenous (IV) rehydration, penicillin and equine antitetanic serum (ATS; 100 000 units) were administered by IV and intramuscular (IM) routes. To diminish light and sound stimuli that might precipitate spasms, patients were customarily managed in a darkened ward where staff wore tennis shoes. Sedation was initiated with mephenesin (a centrally acting relaxant) or chlorpromazine, with additional promethazine, pethidine, chloral hydrate and oral and IM paraldehyde as necessary.

After debridement of necrotic tissue and suspected foci of tetanus spores, tracheostomy was performed in patients with impaired cough activity less than 24 hours after admission, with one exception of 31 hours. A red rubber cuffed tube sealed the respiratory tract, facilitating IPPV and reducing regurgitation of gastric contents. This now fundamental measure was not universally accepted in the 1950s, when metal tubes had been the norm. JRL and MS were aware of tracheal ulceration from the cuffs and introduced 5 minutes of deflation 2-hourly to allow reperfusion of compressed mucosa.

When sedation did not control spasms, up to 90 mg per injection of tubocurarine was administered, intravenously at
first and subsequently by IM injection. IPPV was undertaken with a Bear ventilator (Figure 1). When these measures did not control cardiovascular hyperactivity, nitrous oxide was introduced via an anaesthesia machine. The option of using relaxants with a tank respirator was rejected, as IPPV techniques allowed better access for patient management (Marshall M G, Director of Anaesthesia, RAH, 1956–1962; correspondence, 1959).

Paralysed patients required continual experienced medical supervision, including titration of medication. Ventilation was assessed clinically and by venous carbon dioxide combining power, assayed twice daily. Daily chest radiography was performed. The FiO₂ was 0.5. Biochemical and other monitoring was limited at this time, unlike in the later series, when early detection of trends by automated biochemistry, bedside spirometry, frequent arterial blood gas studies and advances in organ imaging enabled detection of, for example, venous thromboses.

Nursing care included ventilator monitoring, tracheal and pharyngeal suction, postural changes to help bronchial drainage, and frequent passive movement of paralysed limbs. Additional measures included detailed corneal, oral and skin care and nasogastric nutrition. Expression of urine from the bladder was effected into a penile sheath or by suprapubic pressure into a pan.

### Second case series

Earlier patients among the 56 in the second case series were treated in the postoperative recovery ward, but from 1972 patients were treated in the new ICU. Their immunisa-
tion history was vague and their injury was frequently minor (Table 2). The male:female ratio was 24:32, mean age was 62 years (range, 27–86 years; mode, 65 years), and most patients were aged 60–79 years (Figure 2, A). Thirty-eight patients were classified as having severe tetanus4 (Table 3). The mean duration of ICU admission was 30.6 days (range, 1–64 days), and of neuromuscular blockade was 23.6 days (maximum, 46 days). Treatment included 4000 units of human tetanus immune globulin (except for five patients given equine ATS), tetanus toxoid, and penicillin and other antibiotics as required for intercurrent infections (eg, respiratory). Eighteen patients classified as mild to moderate cases all survived and are not discussed further here.

The severe cases (Grade III, as per Ablett’s classification4) presented with a consistent pattern of dysphagia, trismus and neck stiffness, followed by lumbar and abdominal rigidity and generalised hyperreflexia. Progression to opisthotonos and respiratory arrest occurred in three patients presenting to the emergency department in extremis. Emergency control of spasms was achieved by IV thioptepone or diazepam with suxamethonium and rapid sequence endotracheal intubation, followed by IPPV with an ongoing regimen of sedation, neuromuscular blockade and intensive supportive measures. Hypotension with tubocurarine was not troublesome, perhaps modifying autonomic effects; circulatory volume expansion was required on occasion. Later in the series, pancuronium replaced d-tubocurarine, with occasional tachycardia. A trial suspension of neuromuscular blockade was performed, usually weekly, to assess spasms. Weaning from ventilatory support often extended several days beyond cessation of

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limbs</td>
<td></td>
</tr>
<tr>
<td>Arm injury (usually minor)</td>
<td>15</td>
</tr>
<tr>
<td>Leg injury (usually minor)</td>
<td>30</td>
</tr>
<tr>
<td>Areas of chronic vascular insufficiency (leg)</td>
<td>2*</td>
</tr>
<tr>
<td>Head and neck (carious teeth)</td>
<td>1</td>
</tr>
<tr>
<td>Abdomen</td>
<td></td>
</tr>
<tr>
<td>Gut: (a) Gangrenous bowel (b) Gut strangulation</td>
<td>2</td>
</tr>
<tr>
<td>Uterus: (a) Caesarean section (b) Illicit abortion</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
</tr>
</tbody>
</table>

* One infection was from a below-knee amputation site.
relaxants, because of the effects of sedation and residual neuromuscular blockade.

Because of the infrequent presentation of patients with tetanus, initial misdiagnoses included hysteria, masseteric spasm from dental sepsis, phenothiazine dystonic reactions and the abdominal rigidity of peritonitis.

**Patient outcomes**

Five patients in the first case series survived. Four patients died with major comorbidities (Table 1); one, with 40% full-thickness burns, also suffered severe anaphylaxis associated with equine ATS; another, with an abortion site infected with *Clostridium tetani*, required a hysterectomy and apparently also developed a septic syndrome; and a third was dehydrated and in renal failure on admission when dialysis and venous pressure assessment of rehydration were not yet used at RAH.

In the second case series, 36 survivors of 38 severe cases were discharged from hospital. Major problems encountered in their management are listed in Table 4. Episodes of acute respiratory distress syndrome (ARDS) followed inhalation of gastric content from tracheostomy cuff leakage. These resolved with continued IPPV, positive end-expiratory pressure, antibiotics and mild dehydration measures. One patient developed a residual restrictive ventilatory defect, prompting lung function tests on a random selection of six other patients, which were normal. One tracheostomy-related stricture was associated with an older design of tube (1969). A second was in a patient whose tracheostomy was necessarily repeated at the site used previously during an acute exacerbation of chronic respiratory failure. Both strictures responded to tracheal dilation. Tracheal computed tomography performed on six other asymptomatic patients showed no significant narrowing. Skin tethering and stomal granulations were relieved by minor surgery and silver nitrate cautery, respectively.

Respiratory failure of central origin occurred in a woman aged 30 years. After severe tetanus she developed uncoordinated intercostal and diaphragmatic action, unrelated to persistent drug effects. Her limb power was normal and there was no Babinski response. This syndrome was not consistent with polyneuropathy of the critically ill and was possibly cephalic tetanus or a brainstem vascular accident. Reinstituted ventilatory support was gradually withdrawn over 5 weeks.

Of the two deaths, one 74-year-old male patient with diabetes, transferred from ICU after 41 days of IPPV, succumbed on a general ward. Autopsy revealed extensive peripheral arterial disease and coronary atheroma. A large recent myocardial infarction involved the anterior wall of the left ventricle, confirmed histologically, but no evidence of myocardial lesions ascribed to tetanus was found. Raised small plaques adherent to the caecal, colonic and rectal mucosa were shown histologically to be pseudomembranous colitis, either antibiotic related or ischaemic in origin, which had not been suspected while the patient was alive. The second death involved a woman aged 86 years, who had been on IPPV for 20 days. She developed ARDS and died before abdominal exploration could be performed (this was the pre-laparoscopic era). Autopsy revealed a perforated acute duodenal ulcer and peritonitis, confirming the difficulty in diagnosing the acute abdomen in such patients.

*C. tetani* was cultured from wounds in 21 of the 56 patients (37.5%), but the diagnosis is essentially clinical — cultures from many of the patients with severe tetanus did not grow the organism. Tetanus followed surgical condi-

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**Table 3. Severity of tetanus in 56 patients (based on Ablett’s classification), 1967–1985, Royal Adelaide Hospital**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Features</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Mild, no dysphagia or respiratory difficulty</td>
<td>16</td>
</tr>
<tr>
<td>II</td>
<td>Moderate, dysphagia and increasing rigidity</td>
<td>2</td>
</tr>
<tr>
<td>IIIa</td>
<td>Severe, requiring neuromuscular blockade, relaxants and sedatives</td>
<td>12</td>
</tr>
<tr>
<td>IIIb</td>
<td>As for Grade IIIa, plus autonomic disturbances</td>
<td>26</td>
</tr>
</tbody>
</table>

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Figure 3: Effects of treatment with nitrous oxide on haemoglobin and polymorph count in a patient with severe tetanus

Figure reproduced from Lawrence and Sando, page 115, with permission.
tions in three patients: in one woman the organism was cultured from the vagina following caesarean section. Two patients developed peritonitis after strangulated ischaemic gut — a reminder that \textit{C. tetani} can be found in human faeces.\cite{13}

\section*{Discussion}

Comparison of the two case series produces several points of interest. Neuromuscular blockade and IPPV had been described in earlier case reports\cite{14,15} but Lawrence and Sando's series\cite{3} illustrating management of severe tetanic spasms using muscle relaxants with IPPV confirmed a major change in treatment, radically affecting the outcome of the disease by preventing death from asphyxia during spasms. They eschewed the option of using a tank respirator as too cumbersome.

They emphasised the advantages of relaxants over their previous protocol of sedation in a quiet, darkened room:

\begin{quote}
[Neuromuscular blockade] eliminates the exhausting painful spasms and rigidity, making the patient more comfortable and less apprehensive. It allows nursing procedures … to be done more effectively by eliminating the strain of working as silently as possible in a darkened room … physiotherapy and adequate tracheal aspiration can be performed without precipitating further spasms.\cite{3}
\end{quote}

\ldots

we feel that the technique of paralysis and mechanical artificial ventilation has a real place in the management of tetanus \ldots in the fulminating case or in the severe case when sedation and other relaxant agents fail to control reflex spasms and thoracic rigidity \ldots it should not be left until \ldots the patient is in extremis.\cite{3}

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|}
\hline
Event & No. of patients & Outcome \\
\hline
Respiratory & & \\
Acute respiratory distress syndrome & 4 & Resolved \\
Atelectasis, respiratory infection (clinical and radiological) & Several & Resolved \\
Restrictive ventilatory defect & 1 & No change. Mobile \\
Tracheal stricture & 2 & Resolved with repeated dilatations or dilations \\
Tracheostomy site skin tethering & 1 & Successfully resected \\
Tracheostomy site stomal granulations & 2 & Resolved, silver nitrate cautery \\
Neurological & & \\
Central respiratory failure (cephalic tetanus?) & 1 & Resolved \\
Right facial nerve weakness (cephalic tetanus?) & 1 & No data \\
Hemiparesis from cerebrovascular accident & 1 & Resolved \\
Sciatic nerve injury (intramuscular injection?) & 1 & Slow progress at discharge \\
Lateral popliteal nerve injury (pressure effect?) & 2 & Slow progress at discharge \\
Circulatory & & \\
Cardiac arrest (on presentation) & 3 & Recovered \\
Myocardial infarction & 2 & 1 recovered; 1 died (post ICU) \\
Atrial fibrillation, arterial embolism, foot gangrene & 1 & Below-knee amputation \\
Pulmonary embolism & 2 & Resolved \\
Deep venous thrombosis (leg) & 1 & Resolved \\
Venous thromboses (arm) & & \\
Subclavian venous thrombosis, carpal tunnel syndrome & 1 & Improved with anticoagulants \\
Superficial major thrombophlebitis at intravenous insertion site & 1 & Resolved \\
Other & & \\
Joint stiffness & 8 & Resolved \\
Depression & 3 & Resolved \\
Pseudomembranous colitis & 1 & Autopsy diagnosis (died: myocardial infarction) \\
Perforated duodenum & 1 & Autopsy diagnosis \\
\hline
\end{tabular}
\caption{Principal adverse events during management of 38 patients with severe (Grade III) tetanus, 1967–1985, Royal Adelaide Hospital}
\end{table}

\begin{quote}
ICU = intensive care unit.
\end{quote}

In the 1950s, the first steps towards the use of relaxants in tetanus had been taken. However, the discussion in major textbooks at the time on their use in combating skeletal muscle spasm was hesitant and confused:

Curare and curare-like compounds \ldots probably represent the agents of choice if they are intelligently and carefully administered \ldots D-tubocurarine chloride may be used as a repository preparation in oil and wax \ldots Succinylcholine \ldots [is] contraindicated in the treatment of tetanus because of the possible dangers that attend prolonged depolarisation of the motor endplate \ldots In some cases a mechanical respirator will be necessary \ldots\cite{5}\n
Lawrence and Sando\cite{3} emphasised continuous attendance in such unstable patients along with early tracheostomy, relaxants, IPPV plus meticulous airway care, including measures to limit the effect of cuff pressure on tracheal mucosa. Damage from cuffs still remains a cause for concern, although developments such as polyvinyl chloride construc-
tion and large-volume, low-pressure cuffs have reduced the problem.

Lawrence and Sando\textsuperscript{16} found nitrous oxide useful as an additional sedating agent for conscious and paralysed patients, supplementing their regimen of basal sedation and neuromuscular blockade. Administered via an anaesthesia machine, it reduced cardiovascular hyperactivity, but they encountered dramatic falls in polymorph and reticulo- cyte counts, which rapidly recovered upon its withdrawal (Figure 3). Lassen and colleagues\textsuperscript{17} described similar findings. Career pressures deflected Lawrence and Sando from further exploration of these observations, which antedated by many years what we now know as the limitations of this agent in anaesthesia, considering current knowledge of its role in human biology.\textsuperscript{18}

By the time of the second case series, ICU educational programs had enabled registered nurses to undertake greater responsibilities with critically ill patients. Intravascular and electrocardiogram monitoring enabled early attention to be given to circulatory disturbances. The safe management of paralysed ventilated patients for prolonged periods, tentatively developed during the time of the 1957 series, became well established (Figure 2, B) — a key development. While prolonged endotracheal intubation was used in other conditions, early tracheostomy was preferred for the commonly extended period of IPPV in tetanus. The Bjork flap was used initially; later, a window technique was used,\textsuperscript{19} usually performed at the time of wound exploration. The Griggs dilational technique,\textsuperscript{20} developed at ICU RAH to obviate moving ventilated patients over distances to operating theatres, was to come later.

Standard use of central venous lines markedly reduced painful IM injections and multiple peripheral thrombophlebitides, which were problematic in the first case series. They facilitated hydration, administration of medication, venous pressure measurement and IV nutrition during periods of gut stasis, although nasogastric intubation was preferred for nutrition and for much medication. Enteral nutrition may have accounted for the infrequency of significant gastrointestinal bleeding\textsuperscript{21} in an era when prophylaxis was not widespread.

Autonomic hyperactivity\textsuperscript{22,23} produced bouts of hypertension, hypotension, and ventricular and atrial tachyarrhythmias in 13 of our patients. They responded to combinations of alpha and beta blockade, antiarrhythmics, preload adjustment and judicious infusion of inotropes. Chlorpromazine, with combined alpha-adrenergic blockade and anxiolytic effects, was especially useful. Thermodilution studies during brief periods of autonomic hyperactivity in sedated, paralysed patients typically returned a mildly elevated cardiac output of around 9 L/min with blood pressure 220/110 mmHg. One patient required total alpha and beta sympathetic blockade and titrated fluid and inotrope infusion to achieve circulatory stability. With adequate sedation, analgesia and control of tetanic spasms, asystole and recurrent circulatory arrest\textsuperscript{24} described in patients receiving beta-blockers and labetolol\textsuperscript{25} were not encountered, and it is conceivable that vigorous beta blockade in the face of high systemic vascular resistance may have produced left ventricular failure in reported cases. There were reports of epidural placement of local anaesthetic agents successfully reducing circulatory hyperdynamic effects by sympathetic blockade,\textsuperscript{26} but the duration of such techniques is necessarily limited.

Interestingly, we encountered no overt polyneuropathy, despite the use of repeated boluses of relaxants, considered by some to be contributory.\textsuperscript{27,28} A sciatic nerve palsy was thought to be the result of a misplaced intramuscular injection. No obvious cause existed for the other neural lesions (Table 4). Comorbidities common in the elderly, particularly vascular and respiratory diseases, contributed both to causation and some adverse events. For example, a 73-year-old man developed tetanus after below-knee amputation, performed when atrial fibrillation produced embolic dry gangrene of a digit; and an 81-year-old man sustained an anterior myocardial infarction during IPPV, requiring several days’ inotropic support before recovery. Nonetheless, elderly patients commonly returned to acceptable lifestyles: review of hospital records and questionnaires sent to GPs regarding the 38 severe cases in our second series indicated that 20 (53%) returned to a quality of life similar to that enjoyed previously.

Earlier literature described kyphotic spinal deformities\textsuperscript{29} and vertebral crush fractures,\textsuperscript{30} presumably related to sustained tetanic spasms. Myositis ossificans,\textsuperscript{31} a slow passive deposition of calcium salts maturing into bone formation in tendons,\textsuperscript{32} ligaments and joint capsules in tetanus, has been noted in other central nervous conditions such as poliomyelitis and musculoskeletal trauma.\textsuperscript{33} Gunn and Young\textsuperscript{34} noted that physiotherapy in such conditions could involve joint movements conducted against muscle spasm and contained excessive force could produce local damage to muscles and ligaments, resulting in the deposits. However, such problems were not noted in the two series we reviewed and are uncommon in recent publications. Conceivably, the abolition of the effects of severe spasm on tendons and ligaments by neuromuscular blockade and maintenance of the normal range of joint movements with relaxed muscles may have reduced these phenomena.

Two other Australian groups grappling with tetanus produced significant reports during the period of the two series discussed. Newton-John\textsuperscript{35} (1957–1980) described 106 cases with a fatality rate of 26% in an infectious diseases hospital. In the severe group he progressed from
using tank ventilators and uncuffed metal tracheostomy tubes to IPPV using relaxants and cuffed tubes, though he seemed cautious, awaiting “chest fixation” before using such measures. Saady and Torda\textsuperscript{36} (1961–1972) managed 37 patients with conventional intensive care techniques. Twenty-four severe cases treated with relaxants, tracheostomy, cuffed tubes and IPPV returned a mortality of 23%. These involved a death during tracheostomy, one from sepsis, three from cardiomyopathy and three associated with gastrointestinal bleeding. Two of the latter were given steroids, advocated at the time for tetanus.\textsuperscript{37}

Medication via the intrathecal route was an interesting innovation. Miranda-Filho et al.\textsuperscript{38} in a Brazilian randomised controlled trial, compared the outcomes of intrathecal versus intramuscular antitetanus immunoglobulin in 120 patients, claiming “improved clinical progression”. It appeared to reduce severity and fewer required mechanical ventilation, although the difference was not significant. Mortality, reduced from 35% to 18%, still exceeded other recent ICU figures. Reports of paraplegia following the technique encourage caution.\textsuperscript{39} The intrathecal route for medication is worthy of consideration, but antispasmodic agents such as baclofen used intrathecally\textsuperscript{40,41} seem best confined to locations where conventional intensive care is unavailable. Evidence suggests the only technique likely to relieve life-threatening spasms involves the use of relaxants and IPPV.

Tetanus incidence and mortality in Australia following World War II was high, especially in older adults with incomplete immunity. Effective immunisation\textsuperscript{42} has corrected this, with one death reported from 2003 to 2005. Recently, from 2001–2008, the larger body of United States data indicated a case fatality rate of 13.2% and, for 1998–2000, 31% among severe patients who required mechanical ventilation,\textsuperscript{43} mainly among the incompletely immunised,\textsuperscript{44} intravenous drug users, the elderly and those with comorbidities such as diabetes. Similar figures are quoted from Brazil.

However, as shown in our limited series, an overall death rate of 3.6% (5.3% for severe cases) is achievable. Mortality remains high in developing countries, and the current generation of health professionals is likely to encounter the disease only when working in medical teams attending less developed nations in disasters such as floods, earthquakes and civil disturbances (Cornish BL, Orthopaedic Surgeon, Vung-Tau Field Hospital, Vietnam, 1978, personal communication).

The 53 years since the first series was published saw a considerable improvement in tetanus outcomes, coinciding with the evolution of intensive care. This disease, now eminently treatable but requiring major resources, is fortunately now rare. Its response to neuromuscular blockade and effective supportive therapy can be considered a model for intensive therapy. It may have prompted the more widespread use of relaxants in various conditions requiring IPPV, but the pros and cons of that debate are for another forum.

Acknowledgement
Permission to publish this review was provided by the Medical Staff Society, RAH.

Competing interests
None declared.

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