Tetanus and the evolution of intensive care in Australia

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SUMMARY

- A review of two series of patients with tetanus from the Royal Adelaide Hospital provides a historical perspective on the evolution of intensive care in Australia. Nine consecutive severe cases presenting in 1957 constituted one of the first series published. Four patients died. The second series of 38 severe cases, among a total of 56 cases presenting between 1967 and 1985, included two deaths, comparing favourably with survival in other contemporary series. The specialty of intensive care evolved considerably during this time.
- Neuromuscular blockade introduced in the first series produced radical changes in management. Supportive measures that were not then widely practised, involving intermittent positive pressure ventilation, were used in the second series for up to 46 days and evolved into standard ICU practice. The option of using a tank respirator was rejected. Older patients were susceptible to complications commonly related to respiratory, cardiovascular and diabetic comorbidities, but most returned to their previous lifestyle.
- Severe tetanus often resulted from mild injuries in patients who were incompletely immunised. Four patients developed tetanus following surgical procedures.
- The use of nitrous oxide in the first series was abandoned owing to adverse effects on bone marrow function. Complications reported in early literature, such as fractures and myositis ossificans, presumably related to unrelieved spasm, are no longer seen.
- Clinicians are now likely to see the condition only if working with counter-disaster teams overseas.

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Tetanus has a long history. Hippocrates wrote,[1] "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.[2] 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 J R L,[3] 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 J E G, R R and D C 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. J R L and M S 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

Table 1. Details of first case series*

Case	Age and sex	Incubation period (days)	Time of onset (hours)	Focus of infection: Site	Focus of infection: Treatment	Tracheostomy (hours after admission)	Curarization: Begun after admission	Curarization: Total period	Complications	Result
1	57 M	14	40	Tip of index finger	Amputation of distal phalanx	12	20 hours	15 days	Granulocytopenia	Cured
2	26 M	15	43	Infected ununited compound fracture of tibia and fibula; bone graft	Knee-level amputation	31	2 days	17 days	Surgical emphysema, mediastinitis, hyperglycaemia, lung abscess	
3	16 M	8	30	Nail in sole of foot	Excision of wound	20	2 days	16 days	–	
4	?32 M	14	3	40% full thickness burns of legs and buttocks	Excision of sloughs	6 (after onset of disease)	3 hours (after onset)	4 days	Severe burns 14 days before tetanus occurred†	Death: "toxaemia from burns and tetanus"
5	34 F	14	36	Infected abortion	Hyster-ectomy	4	37 hours	3 days	Thrombophlebitis right leg	Death: "massive pulmonary embolus"
6	5 M	5	20	Splinter in thigh	Excision of wound	20	22 hours	10 days	Hypernatraemic uraemia, hyperglycaemia	Cured
7	32 M		?60		–	3	24 hours	7 days	Anuria, acute tubular necrosis	Death: "uraemia (generalised haemorrhagic tendency)"
8	16 M		30		–	3	24 hours	12 days	Congenital cerebral palsy, granulocytopenia	Cured
9	47 M	5	36	Splinter in paronychia of finger	Amputation of distal phalanx	3	72 hours	10 days	Chronic bronchitis, bilateral basal pneumonia. ?*Ps. pyocyanea* septicaemia	Death: "multiple pulmonary emboli"

M = male. F = female. * Table redrawn from *Lawrence and Sando,*[3] page 114, used with permission. † Severe anaphylaxis after administration of equine antitetanic serum.

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).

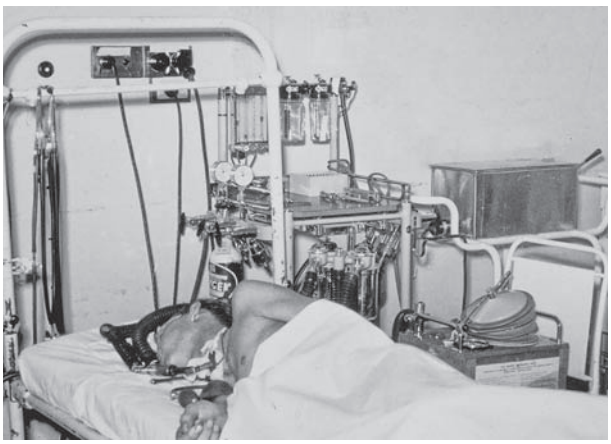
Paralysed patients required continual experienced medical supervision, including titration of medication. Ventilation was assessed clinically and by venous carbon dioxide combining power, assayed twice daily. Daily chest radiography was performed. The FIO_2 was 0.5. Biochemical and other monitoring was 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-

Figure 1. Bear ventilator with anaesthesia machine used in tetanus treatment, Royal Adelaide Hospital, 1959



Photograph courtesy of Royal Adelaide Hospital intensive care unit.

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 tetanus[4] (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.

Figure 2. Age distribution (A) and duration of neuromuscular blockade by age group (B) among 38 patients with severe tetanus, July 1967 to August 1985, Royal Adelaide Hospital

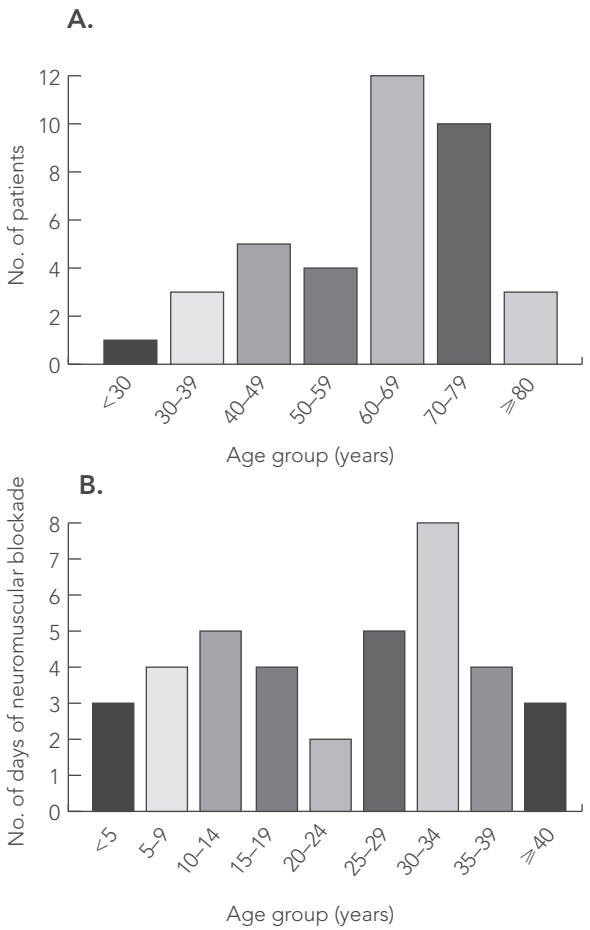


Table 2. Apparent sites of *Clostridium tetani* infection in 56 patients, 1967–1985, Royal Adelaide Hospital

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

* One infection was from a below-knee amputation site.

The severe cases (Grade III, as per Ablett's classification[4]) 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 thiopentone 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 3. Severity of tetanus in 56 patients (based on Ablett's classification[4]), 1967–1985, Royal Adelaide Hospital

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

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)[5,6] 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[7] and was possibly cephalic tetanus[8] 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[9] was found. Raised small plaques adherent to the caecal, colonic and rectal mucosa were shown histologically to be pseudomembranous colitis,[10] either antibiotic related[11] 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.[12]

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-

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

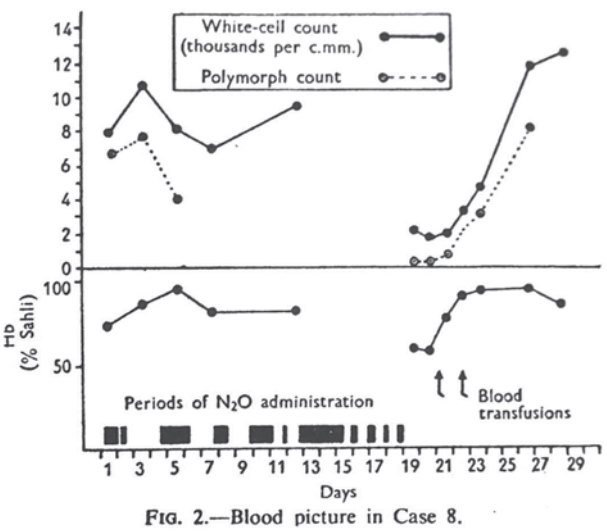


Figure reproduced from Lawrence and Sando,[3] page 115, with permission.

Table 4. Principal adverse events during management of 38 patients with severe (Grade III) tetanus, 1967–1985, Royal Adelaide Hospital

Event	No. of patients	Outcome
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

ICU = intensive care unit.

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 *C. tetani* can be found in human faeces.[13]

Discussion

Comparison of the two case series produces several points of interest. Neuromuscular blockade and IPPV had been described in earlier case reports[14,15] but Lawrence and Sando's series[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:

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

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 ... probably represent the agents of choice if they are intelligently and carefully administered ... D-tubocurarine chloride may be used as a repository preparation in oil and wax ... Succinylcholine ... [is] contraindicated in the treatment of tetanus because of the possible dangers that attend prolonged depolarisation of the motor endplate ... In some cases a mechanical respirator will be necessary ...[5]

Lawrence and Sando[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[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 reticulocyte counts, which rapidly recovered upon its withdrawal (Figure 3). Lassen and colleagues[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.[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,[19] usually performed at the time of wound exploration. The Griggs dilational technique,[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[21] in an era when prophylaxis was not widespread.

Autonomic hyperactivity[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[24] described in patients receiving beta-blockers and labetolol[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,[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.[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[29] and vertebral crush fractures,[30] presumably related to sustained tetanic spasms. Myositis ossificans,[31] a slow passive deposition of calcium salts maturing into bone formation in tendons,[32] ligaments and joint capsules in tetanus, has been noted in other central nervous conditions such as poliomyelitis and musculoskeletal trauma.[33] Gunn and Young[34] noted that physiotherapy in such conditions could involve joint movements conducted against muscle spasm and contended 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[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[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.[37]

Medication via the intrathecal route was an interesting innovation. Miranda-Filho et al,[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.[39] The intrathecal route for medication is worthy of consideration, but antispasmodic agents such as baclofen used intrathecally[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[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,[43] mainly among the incompletely immunised,[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.

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Competing interests

None declared.

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References

1 Potter P (editor and translator). Hippocrates. Volume IX. Coan prenotions. New York: Loeb Classical Library, 2010: 187.
2 Rose HM. Neurotoxic infections – tetanus. In: Cecil RLF, Loeb RF, editors. A textbook of medicine. 9th ed. Philadelphia: WB Saunders Company, 1955: 214-21.
3 Lawrence JR, Sando MJW. Treatment of severe tetanus. *Brit Med J* 1959; 2: 113-7.
4 Ablett JJL. Analysis and main experiences in 82 patients treated in the Leeds Tetanus Unit. In: Ellis M, ed. Proceedings of the symposium on tetanus in Great Britain; 1967 Apr 7-8; Leeds: 1-10.
5 Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967; 290: 319-23.
6 Walker L, Eiseman B. The changing pattern of post traumatic respiratory distress syndrome. *Ann Surg* 1975; 181: 693-7.
7 Bolton CF, Gilbert JJ, Hahn AF, Sibbald WJ. Polyneuropathy in critically ill patients. *J Neurol Neurosurg Psychiatry* 1984; 47: 1223-31.
8 Park DM. Cranial nerve palsies in tetanus: cephalic tetanus. *J Neurol Neurosurg Psychiatry* 1970; 33: 212-5.
9 Rose AG. Catecholamine-induced myocardial damage associated with phaeochromocytomas and tetanus. *S Afr Med J* 1974; 48: 1285-9.
10 Price AB, Davies DR. Pseudomembranous colitis. *J Clin Path* 1977; 30: 1-12.
11 Larson HE, Price AB, Honour P, Borriello SP. *Clostridium difficile* and the aetiology of pseudomembranous colitis. *Lancet* 1978; 1: 1063-6.
12 Worthley L. Acute abdominal disorders in the paralysed patient. *Anaesth Intensive Care* 1985; 13: 263-71.
13 Fleshner PR, Hunter JG, Rudick J. Tetanus after gastrointestinal surgery. *Am J Gastroenterol* 1988; 83: 298-300.

14 Honey BM, Dwyer BE, Crampton Smith A, Spalding JMK. Tetanus treated with curare and intermittent positive pressure ventilation. *Brit Med J* 1954; 2: 442-3.

15 Gunner BW, Cumming WJ, Schalit I. The employment of anaesthetic principles in the management of a severe case of tetanus. *Med J Aust* 1956; 43: 404-6.

16 Sando MJW, Lawrence JR. Bone marrow depression following treatment of tetanus with protracted nitrous oxide anaesthesia. *Lancet* 1958; 271: 588.

17 Lassen HC, Henriksen E, Neukirch F, Kristensen HS. Treatment of tetanus; severe bone marrow depression after prolonged nitrous-oxide anaesthesia. *Lancet* 1956; 270: 527-30.

18 Kano Y, Sakamoto S, Sakuraya K, et al. Effect of nitrous oxide on human bone marrow cells and its synergistic effect with methionine and methotrexate on functional folate deficiency. *Cancer Res* 1981; 41: 4698-701.

19 Dukes HM. Tracheostomy. *Thorax* 1970; 25: 573-6.

20 Griggs WM, Worthley LIG, Gilligan JE, et al. A simple percutaneous tracheostomy technique. *Surg Gynecol Obstet* 1990; 170: 543-5.

21 Pingleton SK, Hadzima SK. Enteral alimentation and gastrointestinal bleeding in mechanically ventilated patients. *Crit Care Med* 1983; 11: 13-6.

22 Corbett JL, Kerr JH, Prys-Roberts C, et al. Cardiovascular disturbances in severe tetanus due to overactivity of the sympathetic nervous system. *Anaesthesia* 1969; 24: 198-212.

23 Tsueda K, Oliver PB, Richter RW. Cardiovascular manifestations of tetanus. *Anesthesiology* 1974; 40: 588-92.

24 Tsueda K, Jean-Francois J, Richter RW. Cardiac standstill in tetanus: review of seven consecutive cases. *Int Surg* 1973; 58: 599-603.

25 Wesley AG, Hariparsad D, Pather M, Rocke DA. Labetolol in tetanus. The treatment of sympathetic nervous system overactivity. *Anaesthesia* 1983; 38: 243-9.

26 Lindahl SG, Dahlgren N, Lundberg D, Nordén N. Adrenergic hyperactivity and epidural block in severe tetanus. *Acta Anaesthesiol Scand* 1985; 29: 87-9.

27 Meistelman C, Plaud B. Neuromuscular blockade: is it still useful in the ICU? *Eur J Anaesthesiol Suppl* 1997; 15: 53-6.

28 Hund E. Neurological complications of sepsis: critical illness polyneuropathy and myopathy. *J Neurol* 2001; 248: 929-34.

29 Roberg OT. Spinal deformity following tetanus and its relation to juvenile kyphosis. *J Bone Joint Surg Am* 1937; 19: 603-29.

30 Bohrer SP. Spinal fractures in tetanus. *Radiology* 1965; 85: 1111-6.

31 Mitra M, Sen AK, Deb HK. Myositis ossificans traumatica: a complication of tetanus. Report of a case and review of the literature. *J Bone Joint Surg Am* 1976; 58: 885-6.

32 Femi-Pearse D, Oluwu A. Myositis ossificans — a complication of tetanus. *Clin Radiol* 1971; 22: 89-92.

33 Costello FV, Brown A. Myositis ossificans complicating anterior poliomyelitis. *J Bone Joint Surg Br* 1951; 33-B: 594-7.

34 Gunn DR, Young WB. Myositis ossificans as a complication of tetanus. *J Bone Joint Surg Br* 1959; 41-B: 535-40.

35 Newton-John HF. Tetanus in Victoria, 1957-1980. Review of 106 patients managed in one hospital. *Med J Aust* 1984; 140: 194-200.

36 Saady A, Torda TA. Tetanus: principles of management and review of 37 cases. *Anaesth Intensive Care* 1973; 1: 226-31.

37 Sanders RKM. Betamethasone in tetanus. *Lancet* 1966; 288: 1467-8.

38 Miranda-Filho D de B, Ximenes RA, Barone AA, et al. Randomised controlled trial of tetanus treatment with antitetanus immunoglobulin by the intrathecal or intramuscular route. *BMJ* 2004; 328: 615.

39 Robert R, Rouffineau J, Cremault A, et al. [Reversible paraplegia following intrathecal injection of high doses of human gammaglobulins in the treatment of low-grade tetanus. 4 cases] [French]. *Presse Med* 1984; 13: 1947-9.

40 Saissy JM, Demazière J, Vitris M, et al. Treatment of severe tetanus by intrathecal injections of baclofen without artificial ventilation. *Intensive Care Med* 1992; 18: 241-4.

41 Engrand N, Guerot E, Rouamba A, Vilain G. The efficacy of intrathecal baclofen in severe tetanus. *Anesthesiology* 1999; 90: 1773-6.

42 Brotherton J, Wang H, Schaffer A, et al. Vaccine preventable diseases and vaccination coverage in Australia, 2003 to 2005. *Commun Dis Intell* 2007; 31 Suppl: S80.

43 Pascual FB, McGinley EL, Zanardi LR, et al. Tetanus surveillance — United States, 1998-2000. *MMWR Surveill Summ* 2003; 52: 1-8.

44 Centers for Disease Control and Prevention. Tetanus surveillance, United States 20012008. *MMWR Morb Mortal Wkly Rep* 2011; 60: 365-9.

45 Brauner JS, Veira SR, Bleck TP. Changes in severe accidental tetanus mortality in the ICU during two decades in Brazil. *Intensive Care Med* 2002; 28: 930-5. ❑