

## NEUROLOGICAL ASPECTS OF TROPICAL DISEASE

## Tetanus

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Received 21 September 1999  
and in revised form  
9 November 1999  
Accepted 26 November 1999

**General description**

Tetanus was first described in Egypt over 3000 years ago and was prevalent throughout the ancient world. Despite the availability of passive immunisation since 1893 and an effective active vaccination since 1923, tetanus remains a major health problem in the developing world and is still encountered in the developed world. There are between 800 000 and 1 million deaths due to tetanus each year, of which about 400 000 are due to neonatal tetanus.<sup>1</sup> Eighty per cent of these deaths occur in Africa and south east Asia and it remains endemic in 90 countries world wide.<sup>2</sup> Incomplete vaccine deployment among the population at risk is the major factor, but the quality of the tetanus toxoid and how it is stored is also important. Fifteen lots, in use from eight manufacturers in seven countries, had potency values below World Health Organisation (WHO) requirements.<sup>1</sup>

In this decade 12–15 cases have been reported per year in Britain<sup>3</sup> and between 40–60 in the United States.<sup>4,5</sup> Mortality varies with patients' age. In the United States mortality in adults younger than 30 may be as low as zero. However, in those aged over 60, who account for 75% of tetanus deaths, mortality is above 50%.<sup>4,6</sup> In Portugal between 1986 and 1990 all age mortality varied between 32% and 59%.<sup>7</sup> In neonatal cases mortality without ventilation was reported as 82% in 1960 and 63%–79% in 1991.<sup>8,9</sup> With ventilation this may be reduced to as low as 11%.<sup>10</sup>

The facilities available to manage severe tetanus have a major impact on the therapeutic options and mortality. In the United Kingdom intensive care costs \$1500–2500/patient/day; such costs are clearly unrealistic in most of the world where tetanus is a major problem.<sup>11</sup> Without the facility to artificially ventilate patients, airways obstruction, respiratory failure, and renal failure are the major contributory factors. Availability of artificial ventilation should prevent most deaths caused directly by acute respiratory failure even in very severe cases. However, autonomic disturbances then become a major problem. Sudden cardiac death and the complications of prolonged critical illness (nosocomial infections, particularly ventilator associated pneumonia, generalised sepsis, thromboembolism, and gastrointestinal haemorrhage) become the major causes of death. The clinical course of tetanus is often unpredictable and patients should be closely monitored throughout their illness.

**Causative agent: *Clostridium tetani***

The clostridia genus is a diverse group of anaerobic spore forming gram positive bacilli. They are widely distributed in the environment, and are found in the intestinal flora of domestic animals, horses, chickens, and humans. Endospores are produced which are wider than the bacillus, giving rise to the characteristic drumstick shape (fig 1). The most noteworthy toxin mediated diseases associated with infection by this genus are tetanus (*C tetani*), and botulism (*C botulinum*). *C tetani* is a gram positive, obligate anaerobic bacillus, older organisms lose their flagella after the development of a spore.<sup>12</sup> The spores are extremely stable, and although boiling for 15 minutes kills most, some will survive unless autoclaved at 120°C, 1.5 bar, for 15 minutes, which ensures sterility.

In routine practice few attempts are made to culture *C tetani*; it is difficult to culture, a positive result does not indicate whether the organism contains the toxin producing plasmid, and *C tetani* may be present without disease in patients with protective immunity. There is very little recent information on the antimicrobial sensitivity of *C tetani*. Similarly, there have been very few attempts to quantify the toxin load and assess the prognostic relevance of this. If large amounts are produced the toxin may be transported by blood and the lymphatics as well as by direct entry into nerve fibres, hence more rapid and wider dissemination of the effects of the toxin. Tiny amounts of the toxin are thought to be present in a typical infection. Rethy and Rethy estimated the human lethal dose to be approximately 500 pg/kg—that is, 25 ng/70 kg adult.<sup>13</sup>

**Tetanus toxin and pathogenesis**

The toxin gene is encoded on a 75 kb plasmid and synthesised as a single polypeptide with a molecular weight of 150 000. The complete amino acid sequence of the toxin is known from gene cloning.<sup>14–16</sup> The polypeptide undergoes post-translational cleavage into two disulfide linked fragments, the light (L) and heavy (H) chains (fig 2). The carboxyl terminal portion of the H chain, termed H<sub>C</sub>, mediates attachment to gangliosides (GD<sub>1b</sub> and GT<sub>1b</sub>) on peripheral nerves, and subsequently the toxin is internalised.<sup>17</sup> It is then moved from the peripheral to the central nervous system by retrograde axonal transport and trans-synaptic spread. The entire toxin molecule is internalised into presynaptic cells and, in a process

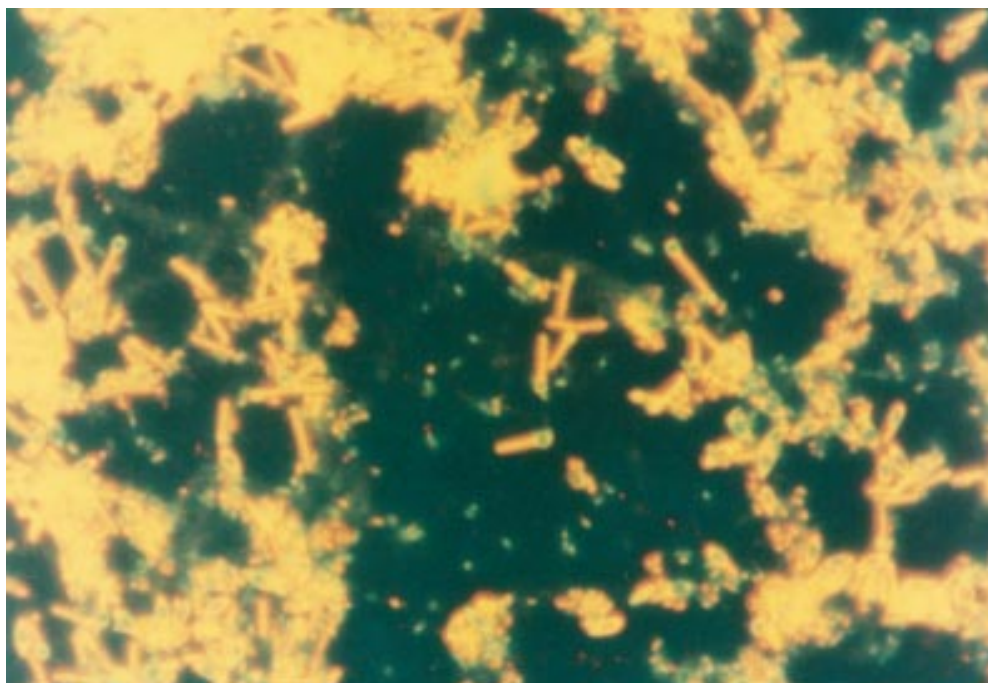


Figure 1 Acridine orange stain of characteristic *C tetani* with endospores wider than the characteristic drumstick shape.

requiring the  $H_N$  fragment, the L chain is released from the endosome. The L chain is a zinc metalloprotease, which cleaves synaptobrevin.<sup>18</sup> A single base pair mutation in the light chain abolishes this proteolytic activity.<sup>19</sup> Synaptobrevin is an integral membrane component of synaptic vesicles and is essential for the fusion of synaptic vesicles with the presynaptic membrane. Cleavage by tetanus toxin L chain prevents release of their contents, the inhibitory neurotransmitter  $\gamma$ -aminobutyric acid (GABA), into the synaptic cleft. The  $\alpha$  motor neurons are therefore under no inhibitory control and undergo sustained excitatory discharge causing the characteristic motor spasms of tetanus. The toxin exerts its effects on the spinal cord, the brain stem, peripheral nerves, at neuromuscular junctions, and directly on muscles. To what extent cortical and subcortical structures are involved remains unknown. Certainly the toxin is a potent convulsant when injected into the cortex of experimental animals.

Tetanus toxin is highly homologous in amino acid sequence to the family of botulinum neurotoxins, which like tetanus toxin, inhibit neurotransmitter release by cleavage of proteins involved in vesicle fusion.<sup>20</sup> The distinct differ-

ence in clinical symptoms between botulism and tetanus is due to the location of toxin action. Botulinum toxin is not transported to the CNS and remains at the periphery where it inhibits the release of acetylcholine. This results in an acute flaccid paralysis.

$x$  Ray crystallographic studies have shown the three dimensional structure of the tetanus toxin  $H_C$  chain responsible for binding of gangliosides.<sup>21</sup> The  $H_C$  fragment, which can undergo retrograde transport in the absence of the remainder of the toxin molecule, is composed of two dissimilar structural domains (fig 3). These domains, which in other systems are involved in recognition of saccharides and proteins respectively, exhibit structural homology to legume lectins and to proteins such as interleukin (IL)- $1\alpha$  and IL- $1\beta$  and may reflect the ability of the  $H_C$  fragment to bind to receptors. Reflecting high sequence homology, the overall three dimensional structure of tetanus toxin  $H_C$  is remarkably similar to  $H_C$  of botulinum toxin A.<sup>22</sup> Thus the binding and transport activities of these two toxin families, which lead to distinct clinical symptoms, could be due to subtle differences in sequence within the  $H_C$  chains, which result in binding to distinct receptors. Site directed mutagenesis of the Hc

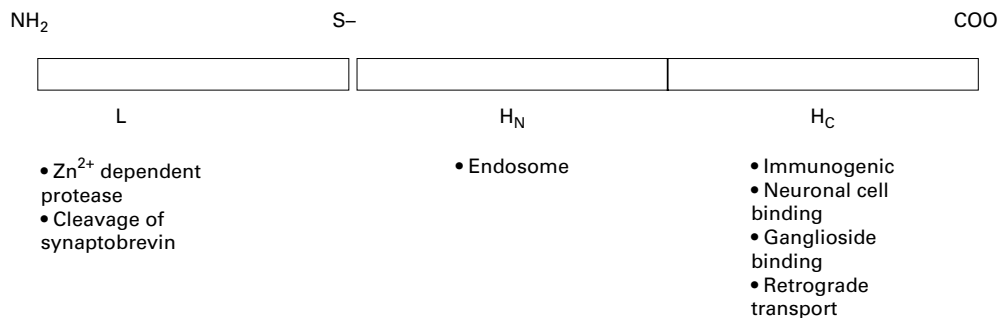


Figure 2 Linear representation of tetanus toxin showing the functions of the L,  $H_N$ , and  $H_C$  chains. Each chain is 50 kDa.

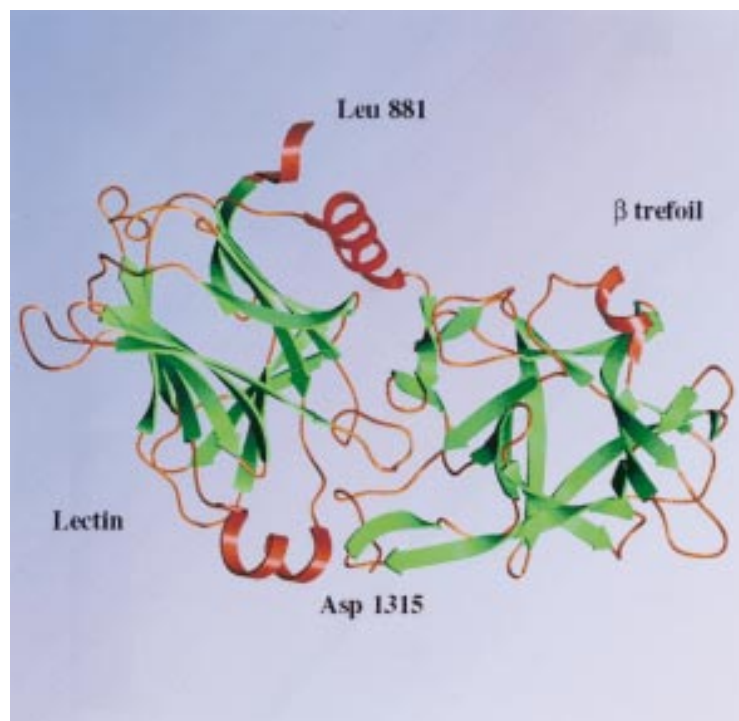


Figure 3 Three dimensional crystal structure of the Hc chain showing the two structural domains. Green and red ribbons correspond to  $\beta$  sheet and  $\alpha$  helical regions respectively.

domain will help to clarify the role of individual residues in binding and transport. In addition to a ganglioside receptor, a protein receptor for tetanus toxin has been hypothesised, but none has yet been identified.

#### Clinical features and management

Tetanus typically follows deep penetrating wounds where anaerobic bacterial growth is facilitated. The most common portals of infection are wounds on the lower limbs, postpartum or postabortion infections of the uterus, non-sterile intramuscular injections, and compound fractures. However, even minor trauma can lead to disease and in up to 30% of patients no portal of entry is apparent.<sup>23</sup> Tetanus has been reported after a myriad of injuries, including intravenous and intramuscular injections, acupuncture, earpiercing, and even from toothpicks. It can follow from chronic infections such as otitis media,<sup>24 25</sup> and has been reported via a decubitus ulcer.<sup>26</sup> Tetanus acquired after intramuscular injection with quinine is associated with a higher mortality than other modes of acquisition.<sup>27</sup>

The incubation period (the time from inoculation to the first symptom) can be as

short as 24 hours or as long as many months after inoculation with *C tetani*. This interval is a reflection of the distance the toxin must travel within the nervous system, and may be related to the quantity of toxin released. The period of onset is the time between the first symptom and the start of spasms. These periods are important prognostically, the shorter the incubation period or period of onset the more severe the disease. Trismus (lockjaw)—the inability to open the mouth fully owing to rigidity of the masseters—is often the first symptom. Tetanus can be localised at the site of injury causing local rigidity and pain. This form generally has a low mortality. However, when local tetanus occurs from head and facial injuries cephalic tetanus can develop, which is a local variant but has a higher mortality. Generalised tetanus is the most common form of the disease, and presents with pain, headache, stiffness, rigidity, opisthotonus, and spasms, which can lead to laryngeal obstruction. These may be induced by minor stimuli such as noise, touch, or by simple medical and nursing procedures such as intravenous and intramuscular injections, suction, or catheterisation. The spasms are excruciatingly painful and may be uncontrollable leading to respiratory arrest and death. Spasms are most prominent in the first 2 weeks, autonomic disturbance usually starts some days after spasms and reaches a peak during the second week of the disease. Rigidity may last beyond the duration of both spasms and autonomic disturbance. Severe rigidity and muscle spasm necessitates paralysis for prolonged periods in severe tetanus.

Some groups have attempted to devise scoring systems to assess prognosis; the Phillips score and the Dakar score (tables 1 and 2) are two examples.<sup>28 29</sup> Both these scoring systems are relatively straightforward schemes which take into account the incubation period and the period of onset as well as neurological and cardiac manifestations. The Phillips score also factors in the state of immune protection. The

Table 1 Prognostic scoring systems in tetanus: Dakar score

Prognostic factor	Dakar score	
	Score 1	Score 0
Incubation period	<7 days	$\geq 7$ days or unknown
Period of onset	<2 days	$\geq 2$ days
Entry site	Umbilicus, burn, uterine, open fracture, surgical wound, intramuscular injection	All others plus unknown
Spasms	Present	Absent
Fever	$>38.4^{\circ}\text{C}$	$<38.4^{\circ}\text{C}$
Tachycardia	Adult $>120$ beats/min Neonate $>150$ beats/min	Adult $<120$ beats/min Neonate $<150$ beats/min
Total score		

Table 2 Prognostic scoring systems in tetanus: Phillips score

Factor	Score
Incubation time:	
<48 hours	5
2–5 days	4
5–10 days	3
10–14 days	2
>14 days	1
Site of infection:	
Internal and umbilical	5
Head, neck, and body wall	4
Peripheral proximal	3
Peripheral distal	2
Unknown	1
State of protection:	
None	10
Possibly some or maternal immunisation in neonatal patients	8
Protected >10 years ago	4
Protected <10 years ago	2
Complete protection	0
Complicating factors:	
Injury or life threatening illness	10
Severe injury or illness not immediately life threatening	8
Injury or non-life threatening illness	4
Minor injury or illness	2
ASA Grade 1	0
Total score	

more clinical grading system developed by Udwardia is also useful.<sup>30</sup>

The diagnosis is a clinical one, relatively easy to make in areas where tetanus is seen often, but often delayed in the developed world where cases are seen infrequently.<sup>31</sup> The differential includes tetany, strychnine poisoning, drug induced dystonic reactions, rabies, and orofacial infection. In neonates the differential diagnosis would also include hypocalcaemia, hypoglycaemia, meningitis and meningoencephalitis, and seizures.

Penicillin remains the standard therapy for tetanus in most parts of the world, although antibiotics for *Clostridium tetani* probably play a relatively minor part in the specific treatment of the disease. The dose is 100 000–200 000 IU/kg/day intramuscularly or intravenously for 7 to 10 days. Johnson and Walker were the first to report that intravenous administration of penicillin could cause convulsions, and went on to show, in animal models, that penicillin caused myoclonic convulsions when applied directly to the cortex.<sup>32</sup> Penicillin became the standard model for induction of experimental focal epilepsy. The structure of penicillin, distant to the  $\beta$ -lactam ring is similar to  $\gamma$ -aminobutyric acid (GABA) the principal inhibitory neurotransmitter in the CNS. Penicillin therefore acts as a competitive antagonist to GABA. Penicillin does not readily cross the blood-brain barrier, but in high cumulative doses it can cause CNS hyperexcitability. In tetanus this side effect of penicillin could synergise with the action of the toxin in blocking transmitter release at GABA neurons.

Metronidazole is a safe alternative, and may now be considered as the first line therapy. After rectal administration metronidazole is rapidly bioavailable and causes fewer spasms than repeated intravenous or intramuscular injections. Ahmadsyah and Salim were the first to compare penicillin and metronidazole, and showed a reduction in mortality in the metronidazole group (7% compared with 24%).<sup>33</sup> In a much larger study Yen *et al* recruited over 1000 patients and showed that there was no significant difference in mortality between the penicillin and metronidazole group.<sup>34</sup> However, the 533 patients randomised to metronidazole required fewer muscle relaxants and sedatives compared with 572 patients randomised to penicillin. This may be explained by the action of penicillin at GABAergic synapses and may therefore apply to the third generation cephalosporins. The structure of these drugs is similar to that of penicillin and ceftazidime has been shown to induce absence seizures with spike and wave discharges.<sup>35</sup> If metronidazole is available and applicable this should be considered as the drug of choice in the treatment of tetanus. The dose is 400 mg rectally every 6 hours, or 500 mg every 6 hours intravenously for 7–10 days. Erythromycin, tetracycline, vancomycin, clindamycin, doxycycline, and chloramphenicol would be alternatives to penicillin and metronidazole if these were unavailable or unusable in individual patients.<sup>36 37</sup> There is little or no indication for the use of other antibiotics in the management

of tetanus. There is a need for an up to date assessment of the antimicrobial sensitivity patterns of clinical isolates of *C tetani*.

Pyridoxine (vitamin B6) is a coenzyme with glutamate decarboxylase in the production of GABA from glutamic acid, and increases GABA concentrations in animal models. In an unblinded open trial 20 neonates with tetanus were treated with pyridoxine (100 mg/day) and compared with retrospective records. The mortality in the pyridoxine treated group was reduced.<sup>38</sup> The role of pyridoxine in the management of neonatal tetanus should be re-examined in a blind randomised trial.

The evidence for a role of steroids is not convincing. They have been reported to be of benefit in tetanus; however, as is often the case in studies on this disease the trials have not recruited enough patients to be convincing or have been inadequately controlled. In two studies betamethasone has been shown to reduce the mortality, but only a few patients were studied.<sup>39–41</sup> Steroids should not be recommended in the management of tetanus unless further blinded controlled studies are conducted in large enough numbers to show significant differences.

Respiratory failure is the commonest direct cause of death from tetanus in the developing world, particularly when artificial ventilation may not be available for every case. Where it is available attempts should be made to anticipate and detect patients at risk from hypoxia and airways obstruction, aspiration hypoventilation, pneumonia, and respiratory arrest. Early airways protection and ventilatory support is often needed. The effects of different modes of assisted ventilation in tetanus have not been evaluated. The modes used will often be limited by the complexity of the ventilators available in the intensive care unit. Those areas with many cases are likely to be those with rudimentary equipment. In the early stages of the disease when rigidity and spasm are prominent muscular paralysis and controlled mandatory ventilation are necessary. Poor compliance and oxygenation due to muscular rigidity or pulmonary complications may be overcome by a combination of pressure controlled ventilation and positive end expiratory pressure (PEEP). In the later stages of the disease modes of ventilation that allow spontaneous ventilation (synchronised intermittent mandatory, continuous positive airway pressure and biphasic positive airway pressure ventilation) are generally preferred and may optimise the respiratory pattern, reduce sedation requirements, minimise muscle wastage, and reduce the likelihood of acquired critical illness neuropathy or myopathy. However, there is little evidence base in tetanus for these advanced modes of support.

Percutaneous tracheostomy is now a routine technique on many intensive care units. It is particularly suitable for patients with tetanus. Patient transfer to and from an operating theatre (entailing unnecessary stimulation) is avoided. Other potential advantages over traditional open surgical techniques include reduced blood loss, reduced operative

morbidity and reduced long term sequelae.<sup>42-43</sup> The single step forceps dilatational method is rapid and can be used for emergency airway management and the serial dilation technique is useful for intubated patients requiring tracheostomy.<sup>44-46</sup>

Traditionally the long acting agent pancuronium has been used for muscular paralysis. Pancuronium is an inhibitor of catecholamine reuptake and as such could worsen autonomic instability in severely affected patients. There have been isolated reports of worsening hypertension and tachycardia associated with its use in tetanus.<sup>47</sup> Alternatives include the older agents *d*-tubocurarine and alcuronium which have been reported to reduce haemodynamic instability, but may also be a cause of hypotension through histamine release. Vecuronium has been proposed as it is “cardiovascularly clean” but is relatively short acting.<sup>48</sup> Longer acting agents are preferable as they lend themselves to administration by intermittent bolus rather than requiring infusion. Of the newer agents pipercuronium and rocuronium are long acting and “clean” but are expensive compared with older drugs. Individual drugs have not been compared in randomised trials. The directly acting muscle relaxant dantrolene has been reported in one case in which spasms were difficult to control. Paralysis was unnecessary after administration of dantrolene, spasms reduced, and patient condition improved.<sup>49</sup> The sedative agent propofol may also have useful muscle relaxant properties. Sedation with propofol allowed control of spasms and rigidity without additional relaxant. Examination of EMG and neuromuscular function during propofol boluses showed an 80% reduction in EMG activity without alteration of neuromuscular function. However, drug concentrations were closer to anaesthetic than sedative doses and mechanical ventilation would be required.<sup>50-51</sup>

Autonomic disturbance with sustained labile hypertension, tachycardia, vasoconstriction, and sweating is common in severe cases. Profound bradycardia and hypotension may occur and may be recurrent or preterminal events. Involvement of the sympathetic nervous system was recognised in 1968.<sup>52</sup> Sedation, which is useful for controlling spasms and rigidity, is also the first step in reducing autonomic instability. Benzodiazepines augment GABA agonism by inhibiting an endogenous inhibitor at the GABA<sub>A</sub> receptor. Adequate sedation is essential in tetanus but is a double edged sword. Benzodiazepines are the most commonly used sedative agents. Diazepam has a wide margin of safety, has a rapid onset of action, can be given orally, rectally, or intravenously, and is a sedative, an anticonvulsant, and a muscle relaxant. It is also cheap and available in most parts of the world. However, it has a long cumulative half life (72 hours) and has active metabolites, in particular oxazepam and demethyl diazepam. Invariably, in the doses required to achieve adequate control of spasms (often up to 3–8 mg/kg/day in adults) respiratory depression, coma, and medullary depression are common. Establishing the correct

therapeutic window is extremely difficult, particularly in patients requiring prolonged support. Midazolam is an alternative, but it is usually not available or not affordable in regions where tetanus is seen often.<sup>53-54</sup>

Phenothiazines, particularly chlorpromazine, are useful sedatives with  $\alpha$ -adrenergic and anticholinergic effects. Phenobarbital has been widely used since the 1960s.<sup>55</sup> Morphine is particularly effective as sedation and cardiovascular stability may be achieved without compromising cardiac performance. Important actions in reducing cardiovascular instability include replacing depleted endogenous opioids and histamine release.<sup>56-59</sup> With all these drugs enormous doses may be required.

Basal catecholamine concentrations rise but noradrenaline (norepinephrine) rises more markedly than adrenaline (epinephrine). Noradrenaline concentrations may rise 10-fold, spontaneously or in response to stimulation, leading to a “sympathetic storm”.<sup>60-61</sup> These rises are similar to those found in pheochromocytoma. Sympathetic neuronal overactivity is generally more prominent than adrenal medullary overactivity and hypertension is accompanied by a rise in systemic vascular resistance without large changes in cardiac index.<sup>62-63</sup> Histological changes in the hearts of patients dying from tetanus are strikingly similar to those of patients with pheochromocytoma and the likely cause in both is persistently raised concentrations of catecholamines.<sup>64</sup>

Early attempts to control autonomic disturbance included  $\beta$  and  $\alpha$ -adrenoceptor blockers and combined block either with propranolol and betanidine or labetalol.<sup>65-66</sup> Mortality was not markedly reduced by this treatment and concerns about  $\beta$  blockade and sudden death have been raised.<sup>67</sup> Sudden falls in catecholamine concentrations after “sympathetic storms”, catecholamine induced cardiac damage, negative inotropism,  $\beta$ -blocker induced vasoconstriction, and unopposed parasympathetic activity are all plausible mechanisms. Esmolol, an ultrashort acting  $\beta$ -blocker, may have advantages over other  $\beta$ -blockers and its successful use has been reported.<sup>69</sup> However, it is expensive (\$450/day) and catecholamine concentrations remain increased.<sup>68</sup>

Other reported treatments for the autonomic disturbance in tetanus include atropine, clonidine, and spinal bupivacaine. Unfortunately most reports are either case reports or small series and there are few trials that are designed to compare treatments or examine outcome measures adequately. There have been reports of successful management of autonomic disturbance with intravenous atropine.<sup>69</sup> Doses of up to 100 mg/h were used in four patients. The authors argued that tetanus is a disease of acetylcholine excess and used these high doses to achieve muscarinic and nicotinic blockade providing autonomic blockade, neuromuscular blockade, and central sedation. Blockade of the parasympathetic nervous system was reported to markedly reduce secretions and sweating. Oral or parenteral clonidine has been used with variable success. In one report of 27 patients treated over 12 years, the group randomised to

receive clonidine had a significantly lower mortality.<sup>70-71</sup> Epidural or spinal bupivacaine have also been reported to improve haemodynamic instability.<sup>72-74</sup> Unfortunately, most reports are either case reports or small series and there are few adequate trials that have compared treatments or examined important outcome data.

Intrathecal baclofen (a GABA<sub>B</sub> agonist) has been reported in some small series with varying success.<sup>75</sup> Doses have ranged from 500 to 2000 mg/day and have been given as boluses or infusion. Larger doses and boluses are associated with more side effects.<sup>76</sup> In all reports a significant number of patients developed coma and respiratory depression necessitating ventilation. In some cases adverse effects were reversible with the GABA<sub>A</sub> antagonist flumazenil, but this is not reliable. The technique is invasive, costly, and facilities for ventilation must be available immediately. Tetanus patients are at risk of sepsis and may require anticoagulation which makes repeated or continuous spinal techniques a significant risk.

Magnesium sulphate has been used both in ventilated patients to reduce autonomic disturbance and in non-ventilated patients to control spasms.<sup>56-77-78</sup> Magnesium is a presynaptic neuromuscular blocker, blocks catecholamine release from nerves and adrenal medulla, reduces receptor responsiveness to released catecholamines, and is an anticonvulsant and a vasodilator. It antagonises calcium in the myocardium and at the neuromuscular junction and inhibits parathyroid hormone release so lowering serum calcium. In overdose it causes paralysis and probably sedation or anaesthesia, although this is controversial.<sup>79-81</sup> In the paper by James and Manson, patients with very severe tetanus were studied and magnesium was found to be inadequate alone as a sedative relaxant but an effective adjunct in controlling autonomic disturbance.<sup>56</sup> Serum concentrations were difficult to predict and regular monitoring of serum magnesium and calcium concentrations were required. Muscular weakness was readily apparent and ventilation was required in all cases. Attagyle and Rodrigo studied patients at an earlier stage of the illness yet all cases were probably severe.<sup>78</sup> They used similar doses of magnesium to try to avoid sedatives and positive pressure ventilation and reported successful control of spasms and control of rigidity. Magnesium concentrations were predictable and readily kept within the therapeutic range by using the clinical signs of the presence of a patella tendon reflex. In both studies the absence of hypotension and bradycardia was by contrast with results with  $\beta$  blockade. Both groups agreed that tidal volume and cough may be impaired and secretions increased: tracheostomy is mandatory and ventilatory support must be readily available.<sup>56-80</sup> More work is necessary to define the role of magnesium both with regard to the physiological effect it exerts on neuromuscular function in the presence of tetanus and secondly to establish what role if any it has in the routine management of severe tetanus.

In patients with a deep wound thorough debridement and toilet are critical to reduce the anaerobic conditions that bacteria thrive in.

The common complications in tetanus, such as nosocomial infection, bed sores, tracheal stenosis, and gastrointestinal haemorrhage, are often attributable to prolonged periods of immobility, critical illness, and intensive care. Tracheal stenosis can be a problem in children, although it is probably underreported in adults. Secondary infections are a frequent complication, most commonly associated with the lower respiratory tract, urinary catheterisation, and wound sepsis. Attempts must be made to prevent secondary infection and much is achieved by attention to detail in basic care. Maintaining adequate spacing between beds and general standards of cleanliness such as regular hand washing by staff and visitors are simple effective measures.<sup>82</sup> Tracheostomy site cleaning, strict sterile technique during tracheal suction, and basic care of peripheral or central venous access sites and the urinary catheter are all fundamental to good treatment. Respiratory complications from aspiration and hypoventilation are common and may be reduced by early tracheostomy, avoiding nasogastric tubes where possible, and nursing patients in a 15°-30° sitting up position. Gram negative organisms, particularly *Klebsiella* and *Pseudomonas* are common, and staphylococcal infections are also often encountered.

Meticulous mouth care, chest physiotherapy, and regular tracheal suction are essential to prevent atelectasis, lobar collapse, and pneumonia particularly as salivation and bronchial secretions are greatly increased in severe tetanus. Adequate sedation is mandatory before such interventions in patients at risk of uncontrolled spasms or autonomic disturbance and the balance between physiotherapy and sedation may be difficult to achieve.

Energy demands in tetanus may be very high due to muscular contractions, excessive sweating, and sepsis. Weight loss is a universal finding and nutrition is of great importance. Enteral feeding should be established as early as possible. Enteral feeding has advantages over parenteral feeding as it maintains gastrointestinal integrity and reduces respiratory and generalised septic complications.<sup>83</sup> When facilities allow, percutaneous endoscopic gastrostomy may be established, so avoiding the stimulation and reflux associated with a nasogastric tube. In those patients unable to tolerate enteral feeding cytoprotection is best achieved with sucralfate or ranitidine.<sup>84-85</sup> Measures to avoid serious thromboembolic complications include compression stockings, subcutaneous heparin, and limb physiotherapy.

There is very little information on follow up of patients after tetanus, particularly for cognitive function. In one of the few studies to examine this question, Anlar *et al* found enuresis, mental retardation, and growth delay to be frequent sequelae after neonatal tetanus.<sup>86</sup> This is an area of clinical research in tetanus which deserves further attention.

The clinical features, admission severity scores, and outcomes from 500 consecutive

Table 3 Five hundred consecutive patients with tetanus: Centre for Tropical Diseases, Ho Chi Minh City

Demographic:			
500 Consecutive non-neonatal patients admitted between May 1997 and February 1999.			
343 Male		157 Female	
Age <15 years	18.8%		
Age >65 years	12.2%		
39 Neonates were admitted in the same time period			
Mortality in non-neonates	19%		
Mortality in neonates	45%		
Entry site:			
Lower limb	53.3%	Head	10.4%
Upper limb	10.8%	Injections	1.8%
Unknown:	22.2%		
Incubation period		Median (range)	9.5 days (1–60)
Time to first symptom		Median (range)	3 days (1–92)
Period of onset		Median (range)	48 hours (0–264)
Symptoms on admission:			
Lockjaw	96%	Spasms	41%
Back pain	94%	Sweating	10%
Muscle stiffness	94%	Difficulty breathing	10%
Dysphagia	83%	Fever	7%
Admission severity scores and mortality rates:			
Dakar score	Mortality	Phillips score	Mortality
≥3	35/59 (59%).	≥17	58/170 (34%).
<3	60/440 (14%).	<17	38/330 (11%).
RR 4.35 (3.17–5.97)		RR 2.96 (2.06–4.27)	
By combining the Dakar and Phillips scores in individual patients:			
Dakar ≥3 and Phillips ≥17 compared with Dakar <3 and Phillips <17			
RR 3.68 (2.49–5.45)			

RR = Relative risk.

patients admitted to the Tetanus Unit at the Centre for Tropical Diseases in Ho Chi Minh City are outlined in table 3.

### Vaccination

Passive immunisation with human or equine tetanus immunoglobulin shortens the course and may reduce the severity of tetanus. The human antiserum is isolated from a pool of plasma derived from healthy human tetanus immune donors, and has a half life of 24.5–31.5 days. The equine (or bovine) form, widely available throughout the developing world, has a higher incidence of anaphylactic reactions and a half life of only 2 days, but is much cheaper to produce. If available human antiserum should be administered but in most parts of the world equine antitoxin is the standard.

In established cases patients should receive 500–1000 IU/kg equine antitoxin intravenously or intramuscularly. Anaphylactic reactions occur in 20% of cases, in 1% they are severe enough to warrant adrenaline, antihistamines, steroids, and intravenous fluids. If available 5000–8000 IU human antitetanus immunoglobulin should be given intramuscularly; this has a lower incidence of side effects. Antitetanus toxin was first used in 1893, and there was a dramatic fall in the incidence of disease among soldiers in the first world after its introduction. Although the antiserum will have an effect only on circulating and unbound toxin (demonstrated in serum samples of only 10% of cases at presentation and in 4% of CSF samples, it should be administered to all patients with tetanus.<sup>87</sup> Whether it should also be infiltrated locally at the portal of entry is unclear and should be examined prospectively. For prophylaxis 1500–3000 IU equine or 250–500 IU human antitetanus immunoglobulin should be given.

Passive immunisation should be administered as soon as possible after the injury, once

the toxin is bound and internalised it will clearly have no effect. The blood concentration of passive antitoxin to protect a human against tetanus is approximately 0.1 IU/ml. When 3000 IU are administered intramuscularly maximum concentrations are reached in 24–48 hours and adequate concentrations are maintained for 10–15 days. It is not easy to assess the optimal dose of antiserum to give for prophylaxis. Extrapolation from animal work would suggest that these doses are too low and that 50 000 IU would afford greater protection; however, at such doses the incidence of side effects is higher. The side effects can be either acute anaphylactic reactions or delayed serum sickness. The incidence of immediate reactions can be reduced by simultaneous (or 15 minutes before use) injection with an antihistamine (promethazine). The use of the Besredka rapid desensitisation method does not necessarily prevent anaphylactic reactions. The use of human tetanus immunoglobulin is very rarely associated with anaphylactic reactions, creates a longer duration of protective immunity, and lower doses can be used (500–1000 IU). It is the passive immunisation of choice; unfortunately it remains unaffordable in many parts of the world.

Complete human immunoglobulin now can be engineered in vitro and designed for specific antigens.<sup>88</sup> This raises the possibility of producing human antibodies specific for the tetanus toxin, free from the risks of infection, easy to store, and potentially available at a cost affordable in the developing world. Owing to its smaller size it is possible that the antigen binding domain of the immunoglobulin, the Fab fragment, may gain better access to the toxin, and so enhance neutralisation. Fab fragments can be produced from donors, but the engineered approach to antibody production would facilitate this.

Intrathecal therapy with antitetanus serum has been subjected to clinical trials. A meta-analysis has concluded that there is currently no evidence of a beneficial effect in neonates or adults using equine or human tetanus immune globulin, and that the safety of their use intrathecally remains unproved.<sup>89</sup>

In addition to passive immunisation, active vaccination needs to be administered to all patients, so called active-passive immunisation. This adds to the short term immunity (passive), and to long term humoral and cellular immunity (active). As the first is declining the second appears and thus avoids a window of non-protection. From experimental work in animals it is clear that the toxoid starts acting a few hours after injection and before a humoral response is detectable. Presumably the toxoid saturates the ganglioside receptors and prevents wild type toxin binding. The toxoid and the human (or equine) antitetanus immunoglobulin should be administered at different sites on the body to prevent interaction at the injection site. If both are to be administered together no more than 1000 IU human or 5000 IU equine antitetanus immunoglobulin should be administered, higher doses can neutralise the immunogenicity of the toxoid.

Tetanus toxoid for vaccination is produced by formaldehyde treatment of the toxin and its immunogenicity is improved by absorption with aluminium hydroxide. Alum absorbed tetanus toxoid is very effective at preventing tetanus with a failure rate of 4/100 million immunocompetent people. In the United Kingdom and United States it is administered to children between 2–6 months (three doses at 4 week intervals) with boosters at 15 months in the United States and at 4 years (United Kingdom and United States). A further dose is recommended in both the United States and United Kingdom within 5–10 years (table 2). Serum antitoxin concentrations above 0.01U/ml are considered protective, although there have been patients reported with protective serum antibody concentrations.<sup>90–92</sup> A protective antibody concentration is attained after the second dose, but a third dose ensures longer lasting immunity. To maintain adequate concentrations of protection additional booster doses should be administered every 10 years.

Reactions to the tetanus toxoid are estimated to be 1 in 50 000 injections, although most are not severe; local tenderness, oedema, flu-like illness, and low grade fever are the most often encountered. Severe reactions such as Guillian-Barré syndrome and acute relapsing polyneuropathy are rare.<sup>93–94</sup>

In recent years there have been reports from Australia and the United States of tetanus occurring in patients over the age of 50.<sup>95–96</sup> In a survey from the United States 59% of women and 27% of men from an urban geriatric care centre did not have adequate antitetanus titres.<sup>97</sup> For every child in the United States who dies of a vaccine preventable disease, about 400 adults die of such a disease.<sup>98</sup> There is a strong argument for the introduction of a vaccination strategy for the immunisation of all adults at the age of 50.

Neonatal tetanus can be prevented by immunisation of women during pregnancy. Two or three doses of absorbed toxin should be given with the last dose at least 1 month before delivery. Immunity is passively transferred to the fetus and protective antibodies will persist long enough to protect the baby. There is no evidence of congenital anomalies associated with tetanus toxin administered during pregnancy.<sup>99</sup>

The influence of HIV infection on the transplacental transfer of tetanus specific maternal IgG is of critical importance. Polyclonal hyperimmunoglobulinaemia is common in HIV and may limit the transfer of protective maternal antibodies, as may HIV infection itself. The antitetanus antibody concentrations were lower in babies born to 46 HIV infected women than in a control HIV negative group, although still above 0.01 IU/ml.<sup>100</sup> About 10% of babies born to mothers with a placenta heavily infected with *Plasmodium falciparum* fail to acquire protective concentrations of tetanus antibody despite adequate maternal concentrations.<sup>101</sup> The antibody response to tetanus vaccination is reduced in HIV infected adult people with a CD4<sup>+</sup> lymphocyte count  $\leq 300 \times 10^6/l$ .<sup>102</sup> People infected with HIV

who completed their vaccination course before acquisition of HIV should maintain adequate protection against tetanus.

Research on tetanus vaccines has concentrated on a single dose vaccine, using technology such as microencapsulation.<sup>103</sup> This would be of most use in those countries where a three dose regime results in management difficulties. Strategies involving expression of the immunodominant H<sub>c</sub> domain in attenuated strains of *Salmonella* followed by oral immunisation have been successful in animals, and may form the basis of future multivalent oral vaccines.<sup>104</sup>

## Conclusion

The World Health Organisation resolved to eliminate neonatal tetanus by 1995. Three years after the deadline the infection still kills over 400 000 babies a year. A safe effective vaccine has been available for most of this century. If any one disease epitomises the health-care disparity between the developed and developing world, and the difficulties in overcoming that inequality, then tetanus is that disease. It is entirely preventable world wide. The priorities must be in prevention; universal vaccination, and the development of simpler immunisation schedules with longer protection. However, for the foreseeable future hospitals in many parts of the developing world will continue to see many patients with tetanus. Further work on pragmatic solutions applicable in these countries is needed on how to reduce the high mortality. A better understanding of *C tetani*, the toxin, its effects on the central and autonomic nervous system, and cardiac and respiratory function is needed. There is a tendency to accept a high mortality from tetanus, Udwardia *et al* have shown in India that it is possible to substantially reduce the mortality even in the absence of fully-fledged intensive care units.<sup>107</sup>

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 NEUROLOGICAL STAMP
 

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## Antonio Grossich (1849–1926)



Grossich studied medicine in Vienna, graduating in 1875. He went to Fiume and became Chief of the Surgery Division at the City Hospital. Grossich was among the first to use sterilisation of the operative field and in 1908 introduced tincture of iodine for rapid sterilisation of the human skin.

Fiume, formerly a port of Hungary was claimed by Yugoslavia and Italy after the first world war. Yugoslavia recognised Italy's claim and the city was annexed in January 1924. Fiume was named Rijeka after the second world war. It is now a port city.

Grossich is known more as a patriot and humanitarian than a surgeon. He was honoured philatelically by Fiume in 1919 on a semi-postal stamp (Stanley Gibbons 122, Scott B16).

L F HAAS