C. Tetani cultured from the wound of a patient with tetanus. Gram stain shows gram positive bacilli with terminal spore formation (Kindly provided by Mr J. Campbell, University of Oxford Wellcome Trust Clinical Research Unit, Centre for Tropical Diseases, Ho Chi Minh City, Vietnam.)

Tetanus

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Introduction

Tetanus is a rare disease in the UK (about 6 cases per year) but it is an important disease world-wide – approximately 500 000 neonates, and similar numbers of adults and children, die from tetanus every year (Dietz *et al.* 1996). Although much is now known about the pathophysiology of the disease, rather few advances have been made in treatment and the mortality remains high despite modern intensive care facilities. This article will present a general review of the literature concerning tetanus. It will focus on what evidence there is for optimal diagnosis and management, and highlight the key clinical issues that concern the physician when caring for a patient with tetanus

Aetiology

Tetanus is caused by a neurotoxin produced by the bacterium *Clostridium tetani* (*C. tetani*), which is an ubiquitous organism found in the soil, and human and animal faeces, throughout the world. The bacteria persist as resilient spores, capable of surviving most household disinfectants and boiling in water for several minutes. Only in conditions of low oxygen tensions do the spores germinate and the vegetative bacteria multiply to secrete their neurotoxin. The spores are rapidly removed from healthy well-oxygenated tissues by phagocytes.

Epidemiology

Neonatal tetanus usually arises from contami-

nation of the umbilical stump by traditional midwifery practices such as cutting the cord with grass, or with dirty scissors (Eregie & Ofovwe 1995). Ear piercing and circumcision can also cause infection. Malaria and HIV infection reduce transplacental transfer of protective antibodies, so many neonates may still be at risk despite maternal vaccination programmes (de Moraes-Pinto *et al.* 1996; Brair *et al.* 1994). In children and adults, tetanus is usually acquired through skin lacerations. Otitis media, poor dentition, and non-sterile surgical instruments can also serve as sources of infection. However, up to 25% of patients admitted to our hospital with tetanus have no obvious source. A particularly poor prognosis is associated with tetanus arising from intramuscular injections, especially of quinine. The low pH of quinine may facilitate tetanus toxin entry into nerves and result in more severe disease (Yen *et al.* 1994). Drug abusers also experience a particularly fulminant form of tetanus. This may again be due to the effect of quinine; its bitter taste resembles that of heroin and so it is often mixed with the narcotic (Cherubin & Sapira 1993).

Pathophysiology

Tetanus toxin is a potent neurotoxin. It is produced as a single chain, encoded by a 75-kB plasmid, which undergoes post-translational cleavage to form a heavy (100 kDa) and a light chain (50 kDa) linked by a disulphide bond. The

two chains must separate to allow the intracellular action of the toxin. The heavy chain mediates internalization and intraneuronal trafficking, while the light chain is responsible for inhibition of synaptic transmission (Welle & Dauzenroth 1989).

Tetanus toxin enters the nervous system after internalization by motor nerve endings in adjacent infected muscle, or after dissemination by the systemic circulation or lymphatics. In the case of localized tetanus, only nerves in the immediate vicinity of the wound are affected. The toxin binds preferentially to motor neurones. Once inside the neurone, the toxin is transported retrogradely up the axon to the central nervous system where it is able to cross the synaptic cleft to exert its action.

The light chain of tetanus toxin is a zinc-dependent endopeptidase, which cleaves synaptobrevin/VAMP (vesicle-associated membrane protein) in mammals at a single peptide bond (Gln76-Phe77). This molecule is necessary for the fusion of synaptic vesicles with the cell membrane, and so cleavage inhibits neurotransmitter release. As a result of synaptobrevin cleavage, tetanus toxin produces a large reduction in the amplitude of action potential evoked postsynaptic responses, and a large reduction in spontaneous quantal release (Humeau *et al.* 2000).

Tetanus toxin preferentially blocks inhibitory (GABA-ergic and glycinergic) synapses afferent to motor neurones in the spinal cord and brainstem. This causes the characteristic clinical picture of muscle rigidity and spasms. However, a flaccid paralysis can occur, sometimes seen in cases of cephalic tetanus. Botulinum toxins also cleave the proteins involved in the endocytotic apparatus. Indeed botulinum toxin B cleaves VAMP at the same peptide bond as tetanus toxin, but because botulinum toxins inhibit acetylcholine release at the neuromuscular junction the clinical picture is different.

Clinical Features

Following wound contamination, a period of days known as the incubation period elapses before symptoms arise. Initial symptoms are caused by an increase in muscle tone: back pain, trismus and muscle stiffness are almost universal symptoms, and over 80% of patients experience dysphagia (Farrar *et al.* 2000). Facial muscle involvement results in the characteristic appearance of 'risus sardonicus', while opisthotonus results from increased tone in the muscles of the

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Snake bite to hand resulting in severe tetanus. Vasoconstriction and necrosis produced by venom creates anaerobic conditions in which *C. tetani* can multiply. (Kindly provided by Mr J. Campbell, University of Oxford Wellcome Trust Clinical Research Unit, Centre for Tropical Diseases, Ho Chi Minh City, Vietnam.)

Laryngeal spasm involving the vocal cords can result in acute airway obstruction

back and trunk. Rigidity is usually greatest in the muscles adjacent to the contaminated wound.

In very mild forms of tetanus, stiffness and rigidity may be the only symptoms. However, in most patients the disease progresses and spasms occur. Spasms are phasic amplifications in muscle tone, varying in intensity and duration from brief twitches to prolonged contractions. They may occur spontaneously or as a result of stimuli such as loud noise, bright light or physical manipulation. Spasms can be strong enough to cause vertebral fractures or tendon avulsions. They are excruciatingly painful – perhaps in part due to disinhibition of pain pathways in the spinal cord.

Spasms involving the respiratory muscles may cause asphyxia, if frequent or prolonged. Laryngeal spasm involving the vocal cords can result in acute airway obstruction. This complication is particularly common in the elderly, who may experience few generalized spasms. Aspiration is a particular problem in tetanus – a consequence of the excessive bronchial secretions, hyper-salivation and dysphagia. Together, these factors explain why hypoxia is a common feature in those presenting with moderate to severe tetanus (Femi-Pearse 1974).

In localized tetanus, spasms and rigidity are restricted to the area of the body next to the wound. This form of tetanus is generally mild, except in cephalic tetanus when the cranial nerves are affected and the mortality is high, probably because of involvement of the brainstem and subsequent autonomic dysfunction (see below) (Jagoda *et al.* 1988). The VIIth cranial nerve is most commonly-affected in cephalic tetanus, usually apparent as an ipsilat-

eral lower motor neurone palsy. Lower cranial nerves may also be involved, and occasionally a concomitant IIIrd nerve palsy occurs. (Fig. 1)

Autonomic nervous system dysfunction occurs in severe forms of tetanus – labile hypertension, tachycardia, pyrexia, and profuse sweating. Fluctuations in blood pressure can be extreme, and are primarily due to changes in systemic vascular resistance, with little change in the cardiac index (De Michele & Taveira Da Silva 1983). Circulating catecholamines are raised, sometimes up to levels seen in pheochromocytoma (Kelty *et al.* 1968). In addition to their actions at adrenergic receptors, catecholamines may cause direct myocardial toxicity (Rose 1974). Bradyarrhythmias, refractory hypotension, and even cardiac arrest may occur.

Excessive production of bronchial secretions, gastric stasis, and diarrhoea are other common manifestations of autonomic system dysfunction. The syndrome is also associated with acute renal failure (characteristically non-oliguric) (Daher *et al.* 1997). Volume depletion and rhabdomyolysis may also contribute to renal failure.

Diagnosis

The diagnosis is based solely on the history and examination findings. There are no confirmatory tests, although culture of *C. tetani* from a wound may be supportive. A careful search for a nidus of infection must be made, although tetanus commonly occurs without an obvious wound.

Early on in the disease, rigidity is often most marked in the abdominal muscles, and the diagnosis can be mistaken for an acute abdomen. Strychnine, a competitive antagonist of glycine, produces a similar clinical syndrome to tetanus.

Figure 1 Vietnamese man with cephalic tetanus involving cranial nerves following trauma to left temporal region showing left IIIrd and VIIth nerve palsies. (Dr C. L. Thwaites, University of Oxford Wellcome Trust Clinical Research Unit, Centre for Tropical Diseases, Ho Chi Minh City, Vietnam.)

Although strychnine does not usually cause persisting abdominal rigidity between spasms, the diagnosis can only be confirmed by measuring urinary and serum strychnine. Other differential diagnoses include orofacial infections, dystonic drug reactions and hysteria.

Localized cephalic tetanus affecting one or two cranial nerves can often be difficult to differentiate from other causes of nerve palsies or dysphagia. Early recognition is important because sudden laryngeal muscle spasm and respiratory arrest can occur. Usually mouth-opening is reduced and the patient complains of difficulty swallowing. In difficult cases, the 'spatula test' may aid diagnosis: by stimulating the pharynx with a spatula, masseter muscle spasm is provoked and the patient bites hard on the spatula.

Natural history

The incubation period (time from injury to first symptom) is about 7–10 days. The period of onset is the time from the first symptom to the first spasm and varies from 1 to 7 days. A short incubation period and period of onset are associated with more severe disease (Phillips 1967). During the first week, muscle rigidity increases, usually beginning in muscles adjacent to the wound, if there is one, then spreads to other muscle groups. Once spasms begin they usually reach a peak in the second week of the disease. Spasms that remain strong and frequent after this time may indicate the continued presence of a foreign body in the wound and re-exploration should be considered. Muscle stiffness persists after the spasms have ended, perhaps for 6–8 weeks in severe cases. Autonomic disturbance usually starts several days after the spasms and is maximal during the second and third weeks.

Once the spasms have disappeared most adults recover completely. Some patients experience contractures of the limbs, sleep disturbance, epileptic fits, and myoclonus although these sequelae are uncommon (Illis & Taylor 1971).

The prognosis is worse following neonatal tetanus, especially in infants who suffered prolonged periods of hypoxia. Long-term follow-up has proved problematic, but there may be an increased risk of cerebral palsy, learning disability and behavioural problems (Anlar *et al.* 1989; Teknetzi *et al.* 1983).

Severity Grading

Several severity grading systems have been sug-

gested but the system suggested by Ablett is the most widely used (Ablett 1967) (Table 1). Prognosis depends on disease severity and the facilities available for treatment. Prior to the provision of artificial ventilation, many patients with severe tetanus died from acute respiratory failure. However, the advent of mechanical ventilation and treatment in an intensive care unit has reduced mortality to around 10% (Trujillo *et al.* 1968). The prognosis of neonatal tetanus remains poor with mortality frequently greater than 60%.

Grade

- I Mild to moderate trismus; general spasticity but no spasms or respiratory embarrassment; little or no dysphagia.
- II Moderate trismus; well-marked rigidity with mild to moderate spasms; respiratory rate > 30 per minute; mild dysphagia.
- III Severe trismus; generalized spasticity; reflex prolonged spasms; respiratory rate > 40 per minute; severe dysphagia; heart rate > 120 per minute
- IV Grade III and disturbance involving the cardiovascular system. Severe hypertension and tachycardia alternating with relative hypotension and bradycardia, either of which may be persistent.

Table 1 Ablett classification of severity of tetanus

Treatment

Tetanus results from poor public health programmes, primary and emergency medical care. The running of good-quality clinical trials under such conditions is extremely difficult and is reflected by the paucity of good evidence for most therapies. In most of the countries where tetanus is common, treatment decisions are also influenced by other factors such as cost and availability of drugs and facilities, creating a discrepancy between therapies that should be given and therapies that are actually given. The recommendations below are based on a combination of the limited evidence available, common-sense, and personal experience with large numbers of patients. Treatments that are reported to be beneficial, although impracticable in settings such as ours, are also mentioned for completeness. The main strategies involved in the management of tetanus are outlined in Table 2.

Tetanus patients should be nursed in a quiet, calm environment, and all unnecessary stimulation should be avoided. This is a difficult ideal to achieve because they are often critically ill and need a lot of nursing. Particular attention should be paid to fluid balance as tetanus

Eradicate causative bacterium	Debride wound	
	Antibiotics	Metronidazole (500 mg pr or 500 mg iv, 6- hourly for 7–10 days)
Neutralize any unbound antitoxin	Equine or human antitoxin	Human tetanus immune globulin (100–300 IU/kg i.m)
Supportive therapy during acute phase	Control muscle spasms	Diazepam (iv bolus) Midazolam (iv infusion/bolus) Vecuronium
	Sedation	Diazepam (iv bolus) Midazolam (iv infusion/bolus) Morphine (im/iv) Chlorpromazine
	Maintain airway/ventilation	Tracheostomy Intermittent positive pressure ventilation
	Maintain haemodynamic stability	Adequate volume replacement Sedation (as above) Inotropes
	Nutrition	
	Physiotherapy	
Rehabilitation		
Immunization	Full primary course of tetanus toxoid	

Table 2 Management of Tetanus

patients have high insensible losses and have often been unable to drink for several days due to dysphagia.

Antibiotic therapy

As *C. tetani* is an anaerobic bacterium, any wound should be thoroughly cleaned and debrided of necrotic tissue. Penicillin has traditionally been used to eradicate any remaining bacteria, but two trials have questioned this approach. An open randomized controlled trial (RCT) of 175 patients compared intramuscular penicillin with oral metronidazole. A significant reduction in mortality was reported in the metronidazole group (7% compared to 24%) (Ahmadisyah & Salim 1985). In a larger open RCT of 1059 patients with tetanus, Yen *et al.* failed to show a significant difference in mortality (49.9% penicillin vs. 50.1% metronidazole) (Yen *et al.* 1997), although patients treated with metronidazole required less sedatives and muscle relaxants. The structure of penicillin and γ -aminobutyric acid (GABA) are similar and penicillin may act as a competitive GABA antagonist. As GAB-ergic transmission is impaired in tetanus, penicillin may exacerbate neuronal disinhibition. In view of these theoretical concerns, and the evidence such as it is, the antibiotic of choice is metronidazole (500 mg rectally, or 500 mg intravenously,

6-hourly for 7–10 days). If penicillin is used, a dose of 100 000–200 000 IU/kg/day is recommended.

Antitoxin

Although tetanus antitoxin was first used in 1893, its subsequent role in the management of tetanus is still controversial and its administration is by no means routine. However, in view of the high mortality of the disease, our unit’s policy is to administer antitoxin to all patients.

Two preparations are available: human and equine. Only one double-blind randomised controlled trial has compared the two (McCracken *et al.* 1971) and found no significant difference in the mortality in 130 neonates. The risk of anaphylactic and other adverse reactions is

less with human immune globulin, and therefore this preparation should be the treatment of choice (100–300 IU/kg intramuscularly). If this is unavailable or too expensive, as is the case in countries where most tetanus occurs, equine antitoxin (500–1000 U/kg intramuscularly) is an alternative.

Almost 100 years ago, it was suggested that the administration of antitoxin by the intrathecal route limited the progression of tetanus and reduced mortality compared to other routes. In 1967, Ildirim reported the successful treatment of seven patients with intrathecal antitoxin and reawakened interest in this route of administration, provoking many studies with conflicting results. In an attempt to clarify the situation, a meta-analysis has been published (Abrutyn & Berlin 1991). Studies were divided by the type of preparation used (equine or human) and age of patients (neonatal or non-neonatal). No significant mortality differences were found in neonates, irrespective of preparation type or concomitant use of steroids. In adults, a modest benefit was seen only in those treated with equine antitoxin, not human immune globulin. As there remain concerns about using preparations by a route other than the approved one, and about the potential neurotoxicity of preparations containing thimerosal, the intrathecal route is not recommended.

Muscle relaxants and sedation

As inhibitors of an endogenous inhibitor at the GABA_A receptor, benzodiazepines oppose the effects of tetanus toxin on the GABA-ergic neurones and are extensively used in the treatment of tetanus. In 1966, Hendrickse reported one of the few randomised trials comparing diazepam (up to 4.4 mg/kg/day), chlorpromazine (up to 8.8 mg/kg/day), and phenobarbitone (4.4–6.6 mg/kg/day) with chlorpromazine and phenobarbitone alone in 104 neonates and 45 older children (Hendrickse & Sherman 1966). Mortality in the neonates was identical in the two groups. In children, however, mortality was almost halved in those treated with diazepam, but the results failed to reach statistical significance.

Sedation with benzodiazepines is currently the mainstay of treatment for tetanus. Diazepam is the most commonly used drug, although its long half-life and those of its metabolites may cause prolonged effects. Doses up to 100 mg/h (intravenously) have been reported and up to 200 mg a day is common. Diazepam is usually given as intravenous boluses and changed to oral administration during the recovery phase. An alternative drug, with a shorter half-life, is intravenous midazolam.

Chlorpromazine has been reported to be a useful adjunct. It has complex pharmacological effects, including central alpha antagonistic action. However, Prys-Roberts found it insufficient in severe tetanus (Prys-Roberts *et al.* 1969). Propofol has also been used for sedation, as well as providing muscle relaxation. Unfortunately its use in most of the world is limited by the cost.

Other muscle relaxants

If spasms persist despite sedation, mechanical ventilation is required in order to allow either even heavier sedation, or the use of neuromuscular blocking agents. Historically, tubocurarine has been recommended for paralysis in tetanus, as its ganglion-blocking properties have led to improvement in cardiovascular stability, but it has now been replaced by more modern agents (such as vecuronium) that are free from cardiovascular adverse effects. Pancuronium should be avoided as it exacerbates tachycardia and hypertension in severe tetanus (Buchanan *et al.* 1979).

Tracheostomy is the preferred means of securing the airway. In patients with frequent generalized spasms, or localized pharyngeal

spasm (which may indicate impending laryngeal muscle spasm), early tracheostomy is recommended. As well as allowing mechanical ventilation, the copious salivary and bronchial secretions may be cleared more easily through a tracheostomy.

Other drugs, such as the GABA_B agonist baclofen and the directly acting muscle relaxant dantrolene, have been tried. (Demaziere *et al.* 1991) (Tidyman *et al.* 1985). However, their use is not widespread, and as baclofen must be administered intrathecally, its use is restricted to centres with sufficient facilities to perform this safely.

Control of autonomic dysfunction

The cardiovascular instability in severe tetanus is usually apparent as hypertension and tachycardia. Rapid fluctuations in blood pressure and heart rate occur and inotropes may be required to maintain an adequate blood pressure. No studies have been performed to guide the choice of inotrope. In view of the high systemic vascular resistance, some authors advocate the use of agents with vasodilatory properties, but equal success has been reported using noradrenaline (King & Cave 1991). Rapid swings in blood pressure make treatment of hypertension difficult. In severe autonomic disturbance it is unusual for a single drug alone to control cardiovascular instability and a combination of drugs is required to achieve a satisfactory response.

Propranolol, with or without concomitant alpha blockade, was the first beta-blocker used in the treatment of tachycardia. Its relatively long half-life and reports of unresponsive hypotension have limited its use. The combined alpha and beta-blocker, labetalol, has been used orally and intravenously with success in some patients. However, the largest series reported (15 patients; Wesley *et al.* 1983), concluded that blood pressure fluctuation was reduced in only a few patients: some patients' blood pressure actually increased, three patients died from sudden cardiac arrest and a further three died following periods of profound and unresponsive hypotension. Experience with beta blockers in our unit is similarly disappointing and they are no longer used. A possible exception may be esmolol, an intravenous beta-blocker with a short half-life. However, despite its brief duration of action, King still reported that a noradrenaline infusion was required to compensate for periods of hypotension (King 1991).

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Morphine induces peripheral venous and arteriolar dilatation by reducing sympathetically mediated alpha-adrenergic tone, probably by decreasing sympathetic discharge centrally. Morphine has the advantages of being cheap and easily available, and may be given intravenously or intramuscularly. It may also be reversed by naloxone, should hypotension ensue. Doses of up to 140 mg/day have been reported as successful in reducing blood pressure and systemic vascular resistance (Rie & Wilson 1978).

The complications of tetanus

System	Complications
Cardiovascular	Hypertension, hypotension Tachycardia, bradycardia, asystole Myocardial infarction Toxic myocarditis
Respiratory	Airway obstruction (salivary and bronchial secretions, laryngeal spasm) Type I respiratory failure due to acute respiratory distress syndrome, aspiration pneumonia or nosocomial pneumonia Type II respiratory failure due to apnoea, sedation, generalized muscle spasms
Musculoskeletal	Tendon avulsions Vertebral crush fractures Rhabdomyolysis
Gastro-Intestinal	Gastrointestinal stasis Diarrhoea Bleeding
Other	Acute renal failure Venous thromboembolism Weight loss

Clonidine also reduces sympathetic tone centrally and, like chlorpromazine, produces sedation and decreases spontaneous motor activity. In two case reports, it has proved a useful adjunct in severe autonomic disturbance (Sutton *et al.* 1990; Peduto *et al.* 1993).

Epidural administration of bupivacaine may also be helpful in controlling labile blood pressure, in addition to reducing spasms below the site of the block (Bhagwanjee *et al.* 1999), but this is not a very practical measure in most countries.

Recent interest has focused on magnesium. Magnesium has both pre- and post-junctional neuromuscular blocking effects and reduces myofibrillar excitability. It is a vasodilator, and reduces catecholamine secretion in animal models (Douglas *et al.* 1967), reduces atrial and ventricular arrhythmias, and is cardioprotective during ischaemia (Woods *et al.* 1992). There is

also evidence that magnesium is neuroprotective during hypoxia (Marinov *et al.* 1996). The potential benefits in controlling spasms and cardiovascular instability has led to renewed interest in its use. James and Manson conducted an open study of 10 patients with persisting cardiovascular instability despite heavy sedation (James & Manson 1985), and reported satisfactory cardiovascular control in all patients, except one, who died of sepsis. Attygale treated eight patients and found spasms were reduced within 2–3 h of beginning magnesium and abolished within 24 h (Attygalle 1996). Although the results of these studies are promising, they are yet to be confirmed in a randomised controlled trial.

Other therapy

Pyridoxine (vitamin B6) is a coenzyme in the production of GABA from glutamic acid and increases the production of GABA in rats. Several open trials have investigated the impact of pyridoxine administration on mortality in neonatal tetanus. The largest study recruited 270 patients (Hajailay *et al.* 1983) and reported a significant reduction in mortality (53% compared to 76%). Other trials have been much smaller, and report less dramatic, but still favourable results (Godel 1982). However, the lack of a blinded trial in this area means there is still no good evidence to support the routine use of pyridoxine.

Finally, as tetanus does not confer immunity to subsequent infection, a full immunization course should be given.

Prevention

Tetanus is prevented by vaccination and good post-injury wound care. Routine vaccination was introduced into the UK in 1961. The first dose is given at 2 months of age, followed by the second and third doses at four-weekly intervals (Stationary Office 1998). The vaccine is adsorbed toxoid, in combination with diphtheria toxoid and pertussis vaccine. Booster doses of tetanus and diphtheria toxoids are given at 3–5 years of age and at 13–18 years old. In the USA, a similar schedule is recommended, but with an additional dose at 6–12 months of age and booster doses every 10 years (CDC 1991). In the UK, five doses (primary course plus two boosters) are believed to be adequate, and additional boosters should only be given if a tetanus-prone wound occurs.

Neonatal tetanus may be prevented by the immunization of women during pregnancy if

they have not previously been vaccinated. Special care should be taken to ensure those with HIV or living in malaria endemic areas receive a full course of vaccination as transplacental antibody transfer is reduced in these diseases.

Antitoxin (human tetanus immune globulin, HTIG 250 units) should be given to people sustaining tetanus-prone wounds with incomplete, or unknown immunization status, or who had a booster more than 10 years ago. A dose of HTIG may be given even to an adequately immunized person if the risk of developing tetanus is high. If HTIG is not available, equine antiserum (1500 units) is an alternative.

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