

Medical Intelligence

Cardiovascular Manifestations of Tetanus

Kentaro Tsueda, M.D.,* Prince B. Oliver, M.D.,† Ralph W. Richter, M.D.‡

ALTHOUGH TETANUS has been rare in the United States, an increase in its incidence may be anticipated in view of recent trends in drug abuse. Tetanus is one of the few infectious diseases which still carries a high mortality rate. Some patients have died of respiratory complications¹⁻³ resulting from the muscle rigidity and reflex muscle spasm that characterizes the disease. Others have suffered sudden unexpected apnea with or without muscle spasm. The control of muscle activity, treatment of respiratory failure, and availability of resuscitative measures¹⁻⁴ would be expected to decrease the mortality rate of the disease. Encouraging communications⁵⁻⁷ followed Lassen's⁸ successful application of *d*-tubocurarine and mechanical ventilation in the management of severe tetanus. However, these have gradually been replaced by reports describing a disturbingly high mortality rate associated with this regime.⁹⁻¹³ The prevention of death from respiratory causes disclosed the cardiovascular manifestations of tetanus. This article presents current concepts of the pathogenesis and management of the cardiovascular manifestations of tetanus. These are discussed in three areas—medullary effects, toxic myocarditis, and sympathetic nervous hyperactivity.

Medullary Effects

Tetanus exotoxin spreads along nerves, but usually the manifestations of tetanus assume a descending form, which starts with stiffness of the masseter muscles, followed by progressive spasticity of the neck, trunk and extremities. These features can be reproduced experimentally by intravenous injection of the toxin, suggesting spread through the blood stream.^{14,15} Early involvement of the lower cranial nerves has been suggested to result from their relation to area postrema on the floor of the fourth ventricle, where the blood-brain barrier does not exist.¹⁶

In 1942, Baker¹⁷ drew attention to widespread central nervous system involvement, especially brainstem lesions, in fatal cases of tetanus. Early changes in the nerve cells, slight swelling, and partial perinuclear chromatolysis were found after the third day of the disease. Perivascular demyelination, which appeared after the fifth day of the disease, was followed by formation of perivascular glial nodules. The nucleus of the vagus, particularly, was irreparably damaged on occasion. Therefore, it was concluded that certain cases of tetanus may terminate fatally because of brainstem damage that causes cardiac and respiratory failure. In 1961, Montgomery¹⁸ found histopathologic brainstem lesions when the clinical cause of death was sudden apnea with or without muscle spasm or sudden cardiac arrest, often following widely fluctuating vital signs or progressive hypotension. He concluded that medullary damage was the cause of death in some cases of severe tetanus.

Hypertension, tachycardia,⁸⁻¹⁰ vasomotor instability^{8,9,12,18} and cardiac arrest have been

* Assistant Clinical Professor of Anesthesiology; Chief, Respiratory Care Unit and Anesthesia Pulmonary Laboratory. Present address: Department of Anesthesiology, Virginia Commonwealth University, Medical College of Virginia, Richmond, Virginia 23219.

† Clinical Fellow in Anesthesiology.

‡ Associate Clinical Professor of Neurology; Director of Neurology.

Received from the Departments of Anesthesiology and Neurology, Columbia University, College of Physicians and Surgeons, Harlem Hospital Center, New York, N.Y. Accepted for publication February 20, 1974.

observed in well-ventilated and paralyzed patients in the absence of pulmonary complications, infection, electrolyte imbalance, or fever,¹³ yet they are not observed in other patients treated in the same way. Tachycardia has been found even in association with hypothermia.^{11,19} Bradycardia appears to be less common. Kloetzel,²⁰ in a series of 84 patients treated conservatively, observed three instances of bradycardia that progressed to cardiac standstill. Vakil *et al.*²¹ had one patient in whom bradycardia progressed to cardiac standstill in a series of 200 successfully resuscitated by external cardiac massage. Other investigations^{22,23} have described bradycardia as a terminal event or as a concomitant of labile vital signs. All of these cardiovascular changes may be attributed to medullary damage.

In 1957, Glossop and Low⁹ pointed out that the characteristic clinical manifestations of tetanus involving the spinal cord were frequently associated with comparatively little change in the histologic appearance of the anterior horn cells. They suggested that the effect of toxin on the brainstem might be far more widespread than the microscopic observed anatomic lesions would suggest. The widely fluctuating blood pressure observed in bulbar poliomyelitis, porphyria, and polyneuritis with brainstem involvement is also neurologic in origin.²⁴ Pyrexia,^{2,17,18,20} a common occurrence in tetanus, is also observed in well-ventilated and paralyzed patients in the absence of muscle spasm and infection,¹³ and has been generally attributed to disturbance of the temperature-regulating center.^{9,11,17,18} Other clinical observations, *e.g.*, sudden and repeated apnea, gasping respiration, twitching of the tongue, dysphagia, intense diaphoresis, profuse salivation, and terminal hypothermia and muscle flaccidity, have been regarded as evidence supporting the brainstem effects of tetanus toxin.^{11,12,22}

Toxic Myocarditis

Since Lassen's demonstration⁹ of histologic evidence of toxic myocarditis, prolonged

hypotension has generally been recognized to be refractory to treatment. The common explanations given for this hypotension are electrolyte imbalance, overdoses of sedatives or *d*-tubocurarine, and episodes of hypoxia. However, hypotension is unlikely to result from proper sedation and curarization and proper intermittent positive-pressure breathing.^{9,11,12} Sepsis is usually ruled out as a cause of hypotension, as organisms are not recovered from blood cultures, and the response to antibacterial treatment is poor.^{11-13,19}

In 1960, Alhady *et al.*,¹⁰ in a series of ten patients with severe tetanus treated by *d*-tubocurarine and mechanical respiration, found histologic evidence of toxic myocarditis in one patient. Progressive hypotension and tachycardia associated with ST-T segment and T wave changes did not respond to vasopressors, digoxin, or fluid infusion, and thus toxic myocarditis was suggested as the cause of the preterminal hypotension. In a series of 200 patients treated conservatively, Vakil *et al.*²¹ found that progressive hypotension and tachycardia, often associated with pulmonary edema as the major problem, comprised a third of the cardiovascular complications. The hypotension did not respond to vasopressors, digoxin, or fluid administration. Demonstrating histologic evidence of toxic myocarditis in seven cases, they felt it possible that the toxin could have a deleterious effect on the myocardium. In 1969, Richter *et al.*²⁵ reported lesions in the cardiac conduction system in three fatal cases of tetanus, and attempted to explain the often-observed sudden cardiac standstill on this basis. In 1970, Drost *et al.*²⁶ reported the findings in a series of 16 fatal cases of tetanus and demonstrated an impressive correlation between toxic myocardial involvement and various clinical cardiovascular manifestations. Lundgaard-Hansen *et al.*²⁸ found significant increases in creatinine phosphokinase and alpha-hydroxybutyrate dehydrogenase, both of which participate in metabolic events in the heart. These authors suggested that since the changes were independent of oxygen tension, they were specifically caused by tetanus toxin.

The Syndrome of Sympathetic Nervous Hyperactivity

The concept of a toxic myocardial action of tetanus toxin has not gone without challenge.^{11,12} In 1964, reporting on four cases of refractory hypotension in which histologic evidence of toxic myocarditis was minimal, Clifton¹¹ felt that the syndrome of progressive hypotension, tachycardia, profuse diaphoresis and pulmonary edema was further evidence of brainstem involvement and suggested that continuous and intense sympathetic activity was occurring. Subsequent investigations demonstrated increased urinary catecholamine excretion.^{13,27} Prolonged sympathetic nervous stimulation^{28,29} or continuous catecholamine infusion^{30,31} can cause myocardial and vascular damage. Their clinical and histopathologic manifestations resemble those found in tetanus.^{13,32} Jeretin,³³ treating patients with propranolol, was able to reverse ST-T segment and T wave changes.

In 1968, Kerr *et al.*¹² described the syndrome of sympathetic nervous hyperactivity: sustained but labile hypertension, tachycardia, arrhythmias, high oxygen consumption, peripheral vascular constriction, intense diaphoresis, pyrexia, and increased urinary catecholamine excretion. They pointed out that this syndrome was an integral part of some cases of severe tetanus but was not observed in many other patients. Various arrhythmias occur, most commonly supraventricular tachycardias, and atrial and ventricular premature beats. Their common denominator is increased myocardial excitability, which could be due to sympathetic nervous stimulation or high levels of catecholamines. Pyrexia may be explained by a high metabolic rate and reduction of centrifugal heat transport, both of these factors being the result of sympathetic overactivity. Preterminal hypotension could be the result of prolonged sympathetic stimulation. The gastrointestinal complications, *e.g.*, paralytic ileus, may also be manifestations of the sympathetic effect. Kerr *et al.* considered this syndrome an important factor in the mortality of tetanus, especially in elderly patients.

Subsequent observations by Corbett *et al.*³⁴ in six cases of severe tetanus were consistent

with a generalized increase in the background sympathetic nervous activity upon which phasic hyperactivity was superimposed. They observed marked increases in arterial blood pressure and heart rate associated with high cardiac output, and great spontaneous variability of blood pressure, heart rate and central venous pressure. It was suggested that the sympathetic system was stimulated specifically by tetanus toxin, because the cardiovascular abnormalities did not rise early, when psychological effects might have been expected to be at their height. Nervous hyperactivity appeared to predominate over adrenal medullary stimulation, since the principal catecholamine found was norepinephrine.³⁵ Baroreceptor denervation was ruled out by demonstrating reflex bradycardia associated with blood pressure increase produced by tracheal suctioning and muscle spasms.

In 1969, Prys-Roberts *et al.*³⁶ described four patients with severe tetanus in whom sympathetic nervous hyperactivity was successfully controlled by various general anesthetics or with the peripheral blocking agents, bethanidine and propranolol. All four patients survived. Dundee and Gray³⁷ reported a 73-year-old patient who was successfully treated with propranolol and bethanidine. The series of Jenkins and Luhn³⁸ is of interest in that neither fatal progressive hypotension nor cardiac standstill was a problem. Their method of sedation was continuous infusion of thiopental sodium. It was probable that smooth continuous depression of the central nervous system could have played a role in their results.

Results in Nine Patients

Our own results in nine patients, all heroin addicts, have been disappointing. Only two survived and were discharged from the hospital.³⁹ The mortality rate is comparable to those of others.^{9,10,40-42}

Hypertension and tachycardia were intermingled with episodes of lower blood pressure and pulse rate in seven cases. Hypertension and slow pulse rate were also observed. Fluctuation of vital signs was marked in three cases. The sudden onset of bradycardia associated with loss of peripheral pulse

and heart sounds or sudden cardiac standstill was frequently observed. Brief external cardiac massage was effective on most occasions. Marked diaphoresis, observed in all patients, tended to decrease following curarization. Hypotension lasting more than several hours was preterminal, and was observed in three patients.

Cardiac arrhythmias occurred in five patients. They consisted of supraventricular tachycardia, atrial and ventricular ectopic beats. Bradycardia, sinus or nodal, was often fatal. Ventricular fibrillation was not observed. Pulmonary edema was observed in two patients.

Sudden onset of bradycardia and loss of peripheral pulse or sudden cardiac standstill caused cerebral death of four patients. Progressive and refractory hypotension associated with pulmonary edema was the cause of death of one patient. A massive septic pulmonary embolus and subsequent *Candida* sepsis caused the death of one patient.

If the episodes observed in this series were to be explained solely on the basis of myocardial action of tetanus toxin, it would be difficult to understand the ease with which the patients were resuscitated and the fact that following resuscitation the previous state of hypertension and tachycardia was restored. Most of the patients had multiple episodes of cardiac arrest, and these occurred when vital signs were labile. In one patient, arrest was clearly related to the cessation of sedation and curarization.

In our patients, and in those of others, the mortality rate in severe tetanus has not improved significantly in spite of the control of muscle activity, respiratory care, and other supportive therapy. Since a hyperactive sympathetic nervous system appears to play an important role in mortality from the disease, pharmacologic control of the sympathetic nervous system by continuous central depression, with peripheral blocking agents, or by the combination of both, seems justified.

Whether the control of both muscle activity and sympathetic nervous activity will generally improve survival rates in patients with severe tetanus is yet to be seen. It seems appropriate to cite Lassen's remark⁸ that the

application of curare and respirator management in severe tetanus might disclose further manifestations of the disease by preventing death from respiratory causes. The same reasoning may apply to control of the autonomic nervous system.

The authors are grateful to many doctors and nurses in the respiratory care unit and general adult intensive care unit for the care of the patients, and to Miss Joan A. Foley, pulmonary coordinator, and her staff of the pulmonary laboratory, Department of Anesthesiology, for their assistance in the respiratory studies.

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