REVIEW OF LITERATURE
SHORT EVOLUTIONARY HISTORY

The disease Tetanus prevails in every part of the world and is known by different names in different countries. It is known as "Dhanurvata" (India), "Heusa" (Nigeria), "Mal de Arco" (Mexico), "Disease of seventh day" (Algeria) and 'Po-shian fong' (China).

In ancient India Charak described Tetanus as 'wind disease'. Hippocrates in 460 BC described the poor prognosis of the disease. In 1884 Nicolaier isolated the clostridium tetani. Evidence regarding the central action of bacillus was produced by Morax (1902), Wright (1956) confirmed the passage of toxin though the nerve roots.

In the year 1890, Von-Behring and Kittasato produced the successful immunization against tetanus by repeated injections of small doses of toxin and neutralization of toxins by specific antisera. Roman and Zoeller (1933) introduced the antitoxin for human use. Baver suggested that the pregnant women can be immunized to protect the new born infants.

As one moves from polar areas toward the equator, the morbidity and mortality gradually increases with its peak in the tropical and subtropical countries. In India, the annual incidence rate of tetanus during the year 1973-1982 was about 6.7 per lacs population (Sokhney, 1983).
ORGANISM AND PATHOGENESIS

The clostridium tetani is a gram positive spore bearing obligate anaerobic bacillus. Spores are present usually at the terminal end of the bacillus which gives a drum stick appearance to the organism. It produces two distinct toxins - (i) tetanospasmin (Neurotoxin) and (ii) tetanolysin. Tetanospasmin is a selective neurotoxin with a molecular weight of about 67000.

PATHWAY OF TETANUS TOXIN IN C.N.S.

The toxin tetanospasmin is produced locally and is absorbed by the motor nerve endings. Then it is transported to central nervous system along the peripheral nerves. The neural pathway of the spread of toxin to the central nervous system has the following links.

Neural motor endings in muscle - muscle nerve- anterior roots - anterior horn cells of the spinal cord or motor neurones in the brain stem (Kryshanovsky).

The toxin enters the C.N.S. by two pathways -
1. Regional neural pathway.
2. General neural pathway.

The clinical features of the disease depends upon which pathway has been involved in the toxin transport to C.N.S.. If the toxin enters by the regional pathway, there arises a local and ascending tetanus in animals and partial tetanus in human. Such condition may also arise if the toxin spread is locked by anti-toxin.
The general neural pathway represents the sum of regional neural pathways, from all the muscles. When toxin enters the blood it enters all the muscles and then through the general neural pathway enters the C.N.S.. In such a condition the toxin first enters the motor nuclei and travels through the shortened neural pathways to the muscles of head and face giving the typical features like risus Sardonicus and trismus. The toxin enters the C.N.S. by longer neural pathways to produce opisthotonous and generalized rigidity. This is known as tetanus descending (Kryzhanovsky, 1974).

BINDING OF TOXIN BY BRAIN TISSUE

The receptors for the tetanus toxin in the brain substance is represented by gangliosides forming a complex with the cerebrosides (Heyningen, 1959) aided by the sialic acid in gangliosides (Mellanby et al, 1967). The toxin bound with protagon (the non-purified mixture of gangliosides with cerebrosides obtained from brain substance) retains the capacity of being neutralized by antitoxin without being split from protagon(Kryzhanovsky, et al, 1970).

Tetanus toxin possesses three active functional groups:

1. Antigenic : It ensures binding of toxin with antitoxin.

2. Neurotrophic (Gangliosidotrophic) : ensures binding with brain receptors.

**BINDING OF TOXIN BY NEURONAL MEMBRANE**

Synaptosomes have the greatest affinity for toxin binding (Mellanby et al, 1965). This is due to the fact that the membrane of synaptosome contain gangliosides (Dahirmenjian et al, 1969). Toxin neutralized by anti-toxin is also bound by synaptosomes (Kryzhanovsky et al, 1973).

**EFFECT OF TETANUS TOXINS ON THE PRESYNAPTIC APPARATUS**

Tetanus toxin acts on the presynaptic apparatus of central synapses in the spinal cord (Curtis et al, 1968) as well as on the neuromuscular junction (Kryzhanovsky et al, 1971; 1972). It results in the disturbance of the release of central inhibitory transmitter glycine and GABA as well as excitatory transmitter acetylcholine in the neuromuscular junction. As a result of disturbance of transmitter release there occurs accumulation of a significant number of vesicles containing the transmitter in the axon terminal, in the poisoned neuromuscular synapses (Kryzhanovsky, 1973 and Pozdnyakov OM et al, 1971).

**FUNCTIONAL EFFECTS OF TETANUS TOXIN ON SYNAPTIC APPARATUS**

As a result of disturbance of transmitter release by the presynaptic apparatus a block of synaptic transmission takes place. The characteristic effect of tetanus toxin on C.N.S. is the disturbance of functioning of the

PATHOGENESIS OF MUSCLE RIGIDITY AND GENERALISED CONVULSIONS

Muscular rigidity is due to the disturbance of inhibitory process occurring in the system of motoneurons and associated interneurons. As a result, the capacity of the efferent output is increased, the polysynaptic reflexes are enhanced and the periphery receives a strengthened and permanent flow of afferent impulses which produces growing muscular tension, contraction and hypertone (Agheson et al, Devies et al, 1954; Kryzhanovsky, 1965; 1966).

Convulsions are the result of disturbances of inhibitory mechanisms in the system of spinal interneurons.

In the last fifteen years, treatment of patients with this disease by total paralysis and intermittent positive pressure ventilation (IPPV) has made it possible to overcome the lethal effects of the muscle spasm. Nevertheless, the mortality rate from tetanus has remained at a much higher level than in other conditions in which severely paralysed patients are treated with prolonged artificial ventilation. In seeking a reason for this continuing high mortality it becomes apparent that many of
the severely ill tetanus patients presented a characteristic clinical picture which has not been observed in other patients require similar treatment including those with milder attack of tetanus (Kerr et al, 1968). This clinical picture has been 'Brain stem intoxication' (Glossop and Low 1957; Moastogomery, 1961), 'Toxic myocarditis' (Alhady et al 1960) and 'Late toxemia' (Macrae, 1967). Since many of clinical features resembled those seen in 'flight or fight' reaction and in patients with pheochromocytoma, it was suggested that clinical syndrome in severe tetanus was due to fluctuating overactivity of sympathetic nervous system (Kerr, 1967 and 1968).

The signs include fluctuating tachycardia, hypertension, some times followed by hypotension, peripheral pallor and sweating and have been associated with increased catecholamine excretion and raised carbon dioxide output in paralysed patients with and without pyrexia due to overactivity of sympathetic nervous system (Kerr et al, 1968).

**BLOOD PRESSURE VARIATIONS**

A most striking features were those relating to the cardiovascular system. The records of many of the patients with severe tetanus showed hypertension which started a few days after IPPV commenced and disappeared by the time the patient left hospital with increase in the level of the blood pressure. There was an increase in its variability and successive half hourly reading of systemic
pressure often varied by more than 100 mm Hg. The pulse rate also tended to increase and to fluctuate with blood pressure so that the highest rates tended to accompany the high pressure. Most of the patients with severe or moderate tetanus sweated profusely at some stage of their illness. The metabolic observations included the finding that paralysed and artificially ventilated patients with severe tetanus had increased carbon dioxide output and also that they tended to excrete large amount of catecholamines.

A temporary increase in B.P. in some patients with severe tetanus has also been recorded previously by other workers. Lassen et al. (1954), Kloetzel (1963) and Albett (1967) reobserved that hypertension was often precipitated by pulmonary collapse and hypercupremia but Glossop and Law (1967 and Kerr et al. (1968) showed that a raised B.P. was observed predominantly in the presence of normal or low arterial carbon dioxide level. The observed blood pressure changes did not seem to be related to muscular activity for they developed some days after the appearance of spasms and were still present after curarisation, when movement was almost totally abolished. In the moderate group of patients in whom the degree of control of spasms ranged from complete in those treated with curare to slight, in some treated with mephenisin, there was no obvious difference in the blood pressure pattern (J.K. Kerr, J.L. Cobrat, C. Drys-Robirts, A crampton Smith, J.M.K. Spadling, 1968).
A renal cause for hypertension in tetanus has never been postulated, because hypertension is associated with high and low values of blood urea, urinary flow and specific gravity (Kerr et al, 1968). Glossop (1967) discussed vasomotor instability postulated on functional disorganisation of vasomotor centre.

The hypertension seen in some patients with polyneuritis, porphyria and bulbar poliomyelitis is thought to have a neurological origin (Taylor and Dawson, 1961) and has some features in common with the changes in tetanus in that the blood pressure fluctuates widely and usually settles with recovery. But intense muscular spasms superimposed on a background of considerable muscular rigidity are characteristics of untreated tetanus and result from variable but continuous overactivity of somatic motor neurons. It may be that the sympathetic nervous system in patients with tetanus shows a similar continuous but variable overactivity.

The increased sympathetic activity as a cause for the hypertension in tetanus is suggested both by increased catecholamine secretion (Kerr et al, 1968) and by the increased blood levels which was reported by Keitty et al (1968). Kerr et al (1968) measured cardiac output. The cardiac indices ranging from 160% of predicted basal in a 73 years old women to 250% in a boy aged 9 years. The arteriovenous oxygen contents differences (1.7-3.8 vol. %)
was found. In severe tetanus patients' study indicate that cardiac output was disproportionately increased in relation to metabolic rate and this would be explained by excessive sympathetic drive to heart. Though the elevated cardiac output were often accompanied by high blood pressure systemic vascular resistance was not increased on many occasions when the measurement was made.

Important myocardial changes occurring in tetanus include protein and vacuole dystrophy, inhibition of the activity of oxidase, disturbances of microcirculation, intravascular thrombosis, perivascular haemorrhage and disturbances of lymphocirculation.

Biochemical changes include marked change in carbohydrate metabolism of the heart occurring after contact with adrenaline. Some of these are due to the direct action of adrenaline to alter the activities of the enzymes of glycogen metabolism but most are secondary to changes in concentration of the three adenine nucleosides (ATP, ADP, AMP) which are in turn secondary to ionotropic response. The early findings of a correlation between the activation of phosphorylase and the positive ionotropic response to adrenaline in isolated rat heart led to the suggestion that the activation of phosphorylase was in some way responsible for the increased force of contraction.

Following the period of fluctuating hypertension some of the severely affected patients developed hypotension accompanied by hyperpyrexia and profound peripheral
vasoconstriction with a glove and stocking distribution. The treatment in this late stage was very discouraging as many other have found (Alhady et al, 1960; Clifton, 1964 and Macrae, 1967).

The hypotension has been attributed to body fluid and electrolyte disturbances, to episode of hypoxia and over indulgent drug therapy (Adams et al, 1966, Albert, 1967). Septicemia may present as similar picture (Clifton, 1964; Adams et al, 1966, Clark & Taylor, 1966 and Macrae, 1967). The toxic myocarditis could be a cause of hypotension (Lassen et al, 1954; Alhady et al, 1960; Stirnemann, 1966; Macrae, 1967). Sympathetic overactivity has been suggested as the cause of hypotension (Clifton, 1964) and there have been poor results from treating it with sympathomimetic agents because of development of tachyphylaxis (Alhady et al, 1960; Clifton, 1964, Adams et al, 1966 and Macrae, 1967). It has been suggested that sustained nervous or humoral sympathetic stimulation may be noxious to the heart (Melville, 1966; Northfield, 1967). Sympathetic stimulation will also produce systemic vasoconstriction and this may cause local hypoxia with increased cell permeability, resulting in decreased circulating fluid volume (Freeman, 1933; Moverat et al, 1958).

CARDIAC RATE

High heart rate also may be due to sympathetic stimulation and has been often reported in patients during
the critical period of severe tetanus (Dean, 1917; Garcia-Palmieri and Ramirez, 1957b; Montogomery, 1961; Kloetzel, 1963; Stirmann, 1966; Albett, 1967). They have attributed to increased body temperature and toxic conditions of the heart. Kerr et al (1967) reported that tachycardia occurred in both the presence and absence of secondary infection and pyrexia. Clark and Taylor (1966) reported that tachycardia occurred associated with hypothermia in tetanus. In myocarditis, high heart rates are not associated with hypertension, although Clark and Taylor have often observed the combination in patients of tetanus.


The responsible factor for the increased heart rate is an increased myocardial excitability, which could be due to high level of circulating catecholamines (Maling et al, 1960; Lepeshkin et al, 1960). The changes in rate and rhythm of heart rate are therefore compatible with sympathetic over activity.

**SKIN CIRCULATION**

Changes in skin blood flow and appearance have often been noted in patients with severe tetanus (Forrester,
1954; Lassen et al, 1954; Mollar et al, 1958; Wilton et al, 1958; Adams et al, 1966; Stirnemann, 1966, Ablett, 1967; and Macrae, 1967). Peripheral circulatory failure has been cited as a cause of death in tetanus (Molphy, 1958). A possible explanation for the blotchy appearance which may develop if the intense vasoconstriction persists (Clark and Taylor, 1960) is that skin becomes hypoxic and vasoactive metabolic end products accumulate causing dilatation of capillaries and veins. Stirnemann (1966) communicated that these appearances some time revert to normal very rapidly suggesting that nervous rather than hormonal factor may therefore be responsible. Profuse sweating, which often occurs in the patients with tetanus is unrelated to muscle relaxants (Courtois-Sufrut and Giroux, 1918; Wilson and Care, 1955; Kloetzel, 1963; Adams et al, 1966; Ablett, 1967), and often to body temperature though it may occur in association with increase in blood pressure (Stirnemann, 1966; Kerr, 1967; Pearce, 1967). Profuse sweating in normothermic patients is well known in sympathetic overactivity of shock and in presence of excess catecholamine in pheochromocytoma. Both the skin changes and increased sweating of patients with tetanus suggested over activity of sympathetic nervous system.

**HYPERPYREXIA**

Raised body temperature often occurs in paralysed patients with severe tetanus without secondary infections
(Glossop and Low, 1957; Kloetzel, 1973; Stirnemann, 1966) and usually develops rapidly with peripheral vasoconstriction (Mollaret et al, 1958; Macrae, 1967).

Disturbances of temperature regulating centre have been postulated as a case of hyperpyrexia in tetanus (Baker, 1942; Glossop and Low, 1957; Montogomery, 1961; Pearie, 1967), but another explanation is that a high metabolic rate is combined with a reduction in centrifugal heart transport, both of these factors being direct result of sympathetic overactivity.

Assessment of sympathetic activity by estimating the urinary excretion of catecholamines is made difficult by the noradrenaline reached from nerve ending (Peart, 1966) and except in presence of pheochromocytomas clearcut increase in catecholamine excretion rate are rare. Normal value for catecholamine excretion vary with the method of estimation (Hume, 1960) and the Colorimetric technique used in laboratory has given values of upto 450 ug per 24 hours in normal ambulent patients.

Jaysing et al (1970) in their experimental study have reported that in small doses, tetanus toxin produces ionotrophic and chronotropic responses in the hearts of the rabbit and frog. However, high doses produces myocardial depression.
TREATMENT OF SYMPATHETIC OVERACTIVITY

Kerr, Corbut, Prys-Roberts, Crompton, Smith and Spadling (1969) noticed a syndrome compatible with over activity of the sympathetic nervous system in severe tetanus treated by tracheostomy, curarisation, sedation and intermittent positive pressure ventilation (IPPV). Many of the complications encountered in severe tetanus and some of the mortality of the disease may be attributed to this syndrome. In these conditions the suppression of adrenergic mechanism by specific therapy has substantially improved the morbidity and mortality.

The drugs were chosen on the assumption that the disturbances over the result of sympathetic over activity. These are described in the order in which they were used both historically in the treatment of tetanus.

A. CHLORPROMAZINE

The chlorpromazine has been widely advocated for use in tetanus (Laurence et al, 1958; Ablett, 1967). Its complex pharmacological actions include partial blockage of alpha receptors and action on the brain stem reticular formation (Jarvide, 1965).

Chlorpromazine also has a limited anti-adrenergic activity. It results in a moderate reduction of B.P. and C.V.P. but no reduction in average heart rate.

B. GENERAL ANAESTHETIC DRUGS

1. Nitrous oxide
2. Halothane
3. Trilene
1. **Nitrous Oxide**

Within minutes of administering of nitrous oxide and oxygen by IPPV, the patients become unconscious and blood pressure and heart rate falls. Withdrawal of nitrous oxide results in a rapid return of initial levels and within 10 minutes instability of both heart rate and blood pressure returned.

2. **Halothane**

Halothane (0.2–4%) in humified air administered from a calibrated E.M.O. "Draw over" vaporiser results in fall of blood pressure and heart rate to state of normalcy within few minutes. When Halothane was temporarily withdrawn during the second day of administration the muscle spasm reappeared within 5 minutes, blood pressure and heart rate began to rise and fluctuate. The patient's skin which until then had been pink and warm became pale over extremities and trunk appeared blotchy. Halothane had been shown to have hepatotoxin effect (Backer, 1968) and leads blood dyscrasia.

3. **Trilene**

Patients anaesthetised by Trichloroethlene vaporised in humified air form and E.M.O. calibrated vaporiser concentration 0.5% initially then 0.35% for 1 hour resulted in marked decrease in blood pressure, heart rate and fall in rectal temperature.

The Trichloroethlene which gave adequate control of the blood pressure was less effective in controlling
the heart rate. It increases myocardial irritability especially in the presence of, exogenous symphatomimetic drugs and longer dysrhythmias. The prolonged administration of nitrous oxide is contraindicated on the grounds of possible bone marrow depression and leukopenia (Lassen et al, 1956; Parbrook, 1968).

**BETA ADRENERGIC BLOCKERS**

The use of specific blockade of adrenergic effector mechanism to suppress the cardiovascular effects of sympathetic over activity is analogous with the use of neuromuscular blockade in the treatment of somatic manifestations of tetanus. Beta adrenergic blockade is indicated when tachycardia occurs in severe tetanus together with continuous or intermittent dysrhythmias.

It is obvious that tetanus toxin like adrenaline and isoprenaline has some beta stimulant action which resembles the action of adrenaline and isoprenaline on the frog's heart (Jay Singh et al, 1970).

Propanoalol the prototype of beta adrenergic blockers is the most commonly used drug. Dexamethasone also is capable of blocking the beta stimulant action of tetanus toxin. These experimental observation underline the possible utility of beta blockers and dexamethasone in the management of tetanus cases having sympathetic over activity.

By the analogy with the neuromuscular blockage used to suppress the somatic manifestation of tetanus, it
seemed logical to control the cardiovascular disturbances by blocking adrenergic effector mechanism. Blockade of beta adrenergic receptors (Ahlquist, 1948) was used in patients, some of whom showed labile tachycardia with dysarrhythmia of both articular and ventricular origin. In a study when propanolol (3 mg) was administered intravenously over a period of fifteen minutes using 0.2 mg increments there was a reduction of the heart rate from 180 to 120/min. Subsequent intragastric administration of propanolol (10 mg 8 hourly) further reduced this rate to between 95 and 100/min.

Subsequent labile hypertension without changes in heart rate was interpreted as evidence of excessive activity at alpha adrenergic receptors. It was felt that the combination of relatively long acting alpha and beta blockage would leave the cardiovascular system effectively denervated and refractory to stimulation.

**PROPANOLOL**

The drug propanolol is a non selective adrenergic blocking agent. Experimentally is proved that in isolated frog and rabbit heart tetanus toxin acts as beta stimulant (ionotropic and chromotropic in action). The propanolol is sympathetic blocking drug. So by its beta blocking action as well as by its direct
action as the CNS decreases the synaptic out flow

(Buhler et al, 1979).

Propanolol gets widely distributed through out the body especially producing higher concentration in central nervous system and crosses the blood brain barrier and has sedative and anticonvulsant effect in the laboratory animals. This action is unrelated to beta blockade (Satostean, 1983).

**CHEMISTRY OF PROPAZOLOL**

This organic drug has the following structure:

![Chemical Structure](image)

The noradrenaline receptors are special chemical sites on heart muscle which first recognise and combine with noradrenaline and then trigger the changes in cellular enzyme which make the heart beat faster and more strongly. The propanolol has been found to be a drug which is recognised and bound by the heart's noradrenaline receptors but which not only fails itself to trigger the usual changes in enzyme activity but also, by occupying the receptor, prevents noradrenaline from doing so.
<table>
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<tr>
<th>Treatment</th>
<th>Total Concentration (mg/ml)</th>
<th>Oral Clearance (ml/min/kg)</th>
<th>Half Life (hours)</th>
<th>Total Oral Excretion (%)</th>
<th>Bound Plasma (%)</th>
<th>Total Excretion (%)</th>
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<tr>
<td>Hepatitis</td>
<td>Hep</td>
<td>12.4 ± 3.6</td>
<td>3.9 ± 0.6</td>
<td>3.9 ± 0.6</td>
<td>9.3 ± 1.2</td>
<td>70.5 ± 4.3</td>
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<td>Chronic</td>
<td>Cml, HPH</td>
<td>0.74 ± 0.03</td>
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<tr>
<td>Crohn = Crohn's disease</td>
<td>Hep = Hepatitis</td>
<td>Cml = Cytomegalovirus</td>
<td>HPH = Hyperthyroidism</td>
<td>Hep = Hepatitis</td>
<td>0% decrease in exercise induced</td>
<td>74.5 ± 4.3</td>
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<td>Age = Age</td>
<td>Age = Age</td>
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<td>20 mg/ml</td>
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Pharmacokinetics
Diffusion of Propanolol

The ionising group of base propanolol has a pK a of 9.4. The propanolol will enter the lipid phase at least 20 times more readily than metaprolol. The greater lipid solubility of propanolol is also evident clinically since it enters the CNS much more readily than metaprolol and has a greater likelihood of causing central side effects.

The drug propanolol when used for rapid control the I/V route is preferred. Small incremental doses effectively suppressed cardiac dysrrhythmias. Adult patients received propanolol 1 mg I/V in TID doses in severe tetanus and the moderately severe patient 1 mg I/V in BID doses.

OTHER BETA ADRENERGIC RECEPTOR BLOCKER

1. Atenolol

This is cardioselective blocking drug (Beta₁) having a plasma T½ of about 9 hours. This is suitable for once in a day administration. This drug can be further investigated for adrenergic blockers in severe tetanus.

2. Labetalol

It has both beta and alpha adrenoreceptor blocking actions in the potency proportion is 3:1:1. Due to this action it can be further investigated for treatment of adrenergic blockers in severe tetanus.