REVIEW OF LITRATURE
Tetanus is an acute toxemic problem caused by soluble exotoxins of bacterium 'Clostridium tetani'.

It prevails in every part of the world and takes a heavy toll of 50000 every year, all over the world (E. Bytchenko 1966).

**History**

Hippocrates, father of modern medicine in 460 B.C., described the poor prognosis of the disease.

Charak stated that this disease is caused by wind.

In (1884) Nicolaier isolated the *Clostridium tetani* for the first time and its relationship to tetanus was established by Kitasato (1889).

Wright (1936) confirmed the passage of toxin through the nerve root.

Antitoxin was introduced for human use by Ramon and Zoeller (1933).

Bouyer (1926) suggested that pregnant women can be immunized to protect the new born infants.

**Incidence**

The incidence of tetanus is more in tropical and subtropical countries.

In India, average annual incidence rate of tetanus during 1973 to 1982 was approximately 6.7 per lakh population.
**Tetanus Neonatorum** – It is one of the leading causes of neonatal death in different parts of the world. About 5 to 10 lakh deaths occur every year worldwide due to tetanus, of which approximately 50% are neonates (Bytchenko 1972, Cook, 1983).

In India Shah and Udani (1969) reported it to be second most common cause of death.

**Childhood tetanus**

Patients below the age of 12 years constitute 42.8% of total cases (Athavale 1974).

**Adult tetanus**

It is more common between 20 to 40 years of age and affects those persons who are exposed to trauma at this during work.

**Rural and Urban** – According to sample survey (1981) Unicef in India, mortality in rural areas varied from 16.4 to 71.7%, while in urban areas 0 to 64.7%.

Sharma P.D. et al in 1984 reported cases the fatality rate was around 97% in rural areas and 30% in urban areas.

**Sex** – The prevalence and mortality rate of tetanus is higher in males than females in all ages, including new borns (Modi 1965).

Males appear to be more sensitive to tetanus toxin than females (Kasharevic 1952).
Indira Bai et al (1975) found lower mortality rate in males (74.0%) than females (88.0%).

Post abortion and post partum tetanus

Incidence of puerperal tetanus ranges from 10-12.7% cases according to studies of Shrivastava and Chatterji (1961), Shah et al (1962), Bhatt (1962).

Various authors have reported mortality rate 49-100%.

Seasonal variation

Higher incidence during rainy season. (Gupta 1977). Vakil et al (1964) did not find any significant seasonal variation.

Social factors - Poor socio-economic conditions along with illiteracy, religious prejudices, orthodox customs, lack of medical facilities are important factors implicated in prevalence of tetanus in India. Home delivery by untrained ayas and relatives increase the incidence (Barton, 1973).

Incubation period - Incubation period is defined as 'Time period between entry of the organism in the host and appearance of first symptom.

The incubation period ranges from 2 to 50 days. In tetanus neonatorum the incubation period corresponds to the age of the baby, in most of the cases Athavale (1974), Jaffari et al (1966) and Beatty (1980), noted high mortality with short incubation period.
**Period of onset** - Period of onset is defined as the time interval between first symptom of the disease and the first reflex spasm i.e. convulsive spasms superimposed on the underlying tonic rigidity. Longer the period of onset lesser the mortality. The case fatality rate was 51% when the period of onset was less than 10 hours and 15% when the period of onset was more than 72 hours (Armitage and Clifford, 1978).

**Grading of severity of tetanus**

Patel and Joag (1959) classified severity of tetanus on the following five criteria.

No. 1 - Lock jaw (Inability to suck)

No. 2 - Spasms

No. 3 - Incubation period 7 days or less

No. 4 - Period of onset 48 hours or less

No. 5 - Axillary temperature of 99°F or rectal 100°F on admission or within 24 hours of admission.

Cases having 4 criteria are graded IV, 3 criteria grade III and so on.

**Organism and Pathogenesis**

Clostridium tetani is a 2-5 micron long and 0.3 to 0.8 micron wide, anaerobic, gram positive, motile spore bearing in nature. Spores are usually at terminal end of the bacilli and giving it a drum stick appearance.

Two types of exotoxins are released by the bacilli; tetano spasmin and tetanolyasin. Tetano spasmin
is powerful selective neurotoxin. It is a water soluble, easily diffusible protein with a molecular weight of about 67000. The site of action of tetanus spasm is motor end plates of skeletal muscles, spinal cord, brain and sympathetic nervous system. (Kerr 1968, Stoll 1979).

**Pathway of tetanus toxin to C.N.S.**

The neural pathway of toxin spread consists of following links (Kryzhansky 1972). Neural motor ending in muscles - Muscle nerve - anterior root - anterior horn of the grey matter of spinal cord or motor nuclei in brain stem.

There exists two pathways for the toxin entrance into C.N.S.

(1) Regional neural pathway

(2) General neural pathway

Entrance of toxin only by regional neural pathway causes partial tetanus in human and a local and ascendens tetanus in animals.

The general neural pathway represents the sum of regional neural pathway from all muscles. The clinical picture of disease greatly depends on the neural pathways involved, in the process of toxin transport into C.N.S.

When toxin enters in the blood, it enters in all the muscles and then through general neuronal pathway it enters in C.N.S. Under these conditions toxin enters first into the motor nuclei and travels through the shortest
neural pathways to the muscles of head and face, giving typical signs of the disease, trismus and risus sardonicus. Toxin enters the C.N.S. by longer neural pathways resulting in ophisthotonus and generalized rigidity. This is called as tetanus descendens. (Kryzhanovsky 1966).

**Binding of toxins by brain tissue**

The physicochemical receptors of tetanus toxins in brain substances are represented by 'gangliosides' forming a complex with the cerebrosides (Heyningen, 1959). Sialic acid of the gangliosides plays an important role in the binding (Mellamphy et al, 1967). Toxin previously neutralized by antitoxin can also be fixed on protagon (The non purified mixture of gangliosides, with cerebrosides obtained from brain substances).

Also the toxin bound with protagon retains the capacity of neutralization by antitoxin without being split off from protagon. The data and the fact that protagon binds the inactive toxoid have permitted the conclusion to be drawn that tetanus toxin possesses at least three functional groups. (Bondartsehuk N.G. et al, 1973).

(1) Antigenic - ensuring binding of toxin with antitoxin.

(2) Neurotropic - ensuring binding with brain receptors or gangliosidotropic.

(3) Toxophoric - ensuring the pathogenic effect.
like protein of synaptic vesicles and also established the changes in the protein synthesis, along with it, a rise of new antigen substance in the nerve ending (synaptosomes) isolated from spinal cord in tetanus intoxication.

Pathogenesis of Muscle rigidity and generalized convulsions

Disturbance of inhibitory processes, is the basic mechanism for muscle rigidity and generalized convulsions in tetanus.

Muscle rigidity - In the system of the efferent output of spinal cord, that is, in the system of motor neurones and the associated neurones, there is disturbance of inhibitory processes. The through out capacity of efferent output is increased, the polysynaptic reflexes are enhanced (Kryzhanovsky 1974) and the periphery receives a strengthened and practically a permanent flow of efferent impulsion (Laurance et al, 1966 which produces a growing muscular tension, contraction and hypertonia. This phenomena is based on the increase in the activity of the alpha - motoneurones. Recently study has indicated, participation of the gama system in the muscle contraction in tetanus (Takano et al, 1973).

Convulsions - Disturbance of inhibitory mechanism in the spinal interneurones, cause the pathogenic movement of generalized convulsions. (Kryzhanovsky, 1967). The stimulation of the limb, injected with toxin produce a generalized convulsions.
binding to toxin by neuronal membrane

Synaptosomes show the greatest affinity for toxin for binding. This may be due to the fact that membrane of synaptosomes contain gangliosides. Toxin, previously neutralized by antitoxin, is also bound by synaptosomes.

Effect of tetanus toxin 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 that of the neuromuscular junction (Kryzhanovsky, 1971). Its effect consists of the disturbance of the transmitter release, at the neuromuscular junction, excitatory transmitters (acetylcholine) and at the central inhibitory transmitters (glycine and GABA).

Tetanus toxin has an universal effect on the presynaptic apparatus of various synapses and not depending on nature of synapse. In tetanus intoxication the affected neural tissue shows a disturbance of the activity of transport A.T.P. age. It is also possible that in such interaction, the toxophoric group of toxin is also activated, and it might split off from the toxin molecule and penetrate the neuronal membrane (Kryzhanovsky, 1974).

Effect of tetanus toxin on synaptic apparatus

Kryzhanovsky (1974) showed that tetanus toxin in vitro can effect the contractile ability of actinomysin
This phenomena is due to - groups of spinal interneurons with disturbed inhibitory processes following the action of toxin and become generators of pathologically potenti- ated excitation (dispatch station) which arises at trigger stimulation (afferent flow from tetanus limb) and spreads over the whole C.N.S. producing generalized convulsions.

This tetanus ascends phenomena is character- ized by "universal dispatch station."

In generalized blood borne tetanus paroxysmal generalized convulsions arise, on the back ground of general muscle rigidity.

*Functional changes in vegetative (Autonomic) Nervous system* -

Tachycardia, changes in the arterial pressure, increased basal metabolism, intense perspiration, hyper thermia, indicate the involvement of the autonomic nervous system into the pathological process of tetanus toxemia (Paer et al, 1973). According to Karr et al (1972) a sympathetic hyperactivity suggesting an immediate affection of the sympathetic nervous system by tetanus intoxication.

*Changes in Endocrine system*

Pathological process of tetanus intoxication involve the system of hypothalamus - hypophysis. According to Mikhailev (1968) a disturbance of water and electrolyte balance in tetanus occur. The amount of catecholamines in
hypothesis is increased. There arises a peculiar lack of glucocorticoids and noradrenaline in tissues (Zorkin et al 1972).

Changes in important visceral organs

Pulmonary complications - In tetanus in intoxication, death due to pulmonary complications is most common. Ultrastructural and microcirculatory changes in lungs are serious concomitants of tetanus intoxication. They can arise in the preconvulsive and even in the incubation period (Kryshnovsky et al, 1970). This leads to extensive congestion and may cause pneumonia secondarily.

Myocardial changes

According to Kryshnovsky (1972), in tetanus a complex myocardial changes take place consisting protein and vacuole dystrophy, inhibition of the activity of oxidative restorative ferments, of (succinyl dehydrogenase), disturbance of microcirculation, intravascular thrombosis, perivascular haemorrhage and disturbance of lymphocirculation.

In acute tetanus intoxication, greater changes are localised in nature and are predominantly around blood vessels, but may assume most diffuse character with passages of time.

Mode of infection in tetanus

Tetanus disease occurs due to inoculation of the wound by tetanus spores which are present in the soil, specially highly enriched soil, for its use as manure in agricultural fields, usually containing faeces of animals.
Certain accessory factors trauma, haemorrhages, tissue necrosis, chemicals, calcium salts, and injection by other microbes, help germination of spores. In postoperative tetanus the spores may be derived from infected catgut. (Savolainen, 1950). Imperfectly sterilized instruments or dressings, contaminated dust of the operation theatre, may have tetanus bacilli.

It also follows, burn wounds, otitis media, dental infection, abortion, pregnancy. Neonatal tetanus usually follows umbilical sepsis. Spores may survive in the body for months to years and produce the disease after some minor trauma which alters the local condition. (Tullock, 1919).

Clinical manifestations - There are three clinical forms of tetanus.

(1) Localized tetanus - Causes pain and spasm of muscles in proximity to the site of injury. Sometimes localized tetanus may convert into generalized tetanus.

(2) Generalized tetanus - It is the phase of tonic rigidity and reflex convulsions. Tisusma is the first indication of tonic rigidity and usually the first symptoms. Stiffness in jaw, involvement of facial muscles lead to risus sardonicus. Tonic contraction of the abdominal and spinal muscles are responsible for posture of opisthotonus. In severe cases generalized convulsions start later on.

(3) Cephalic tetanus - This is usually due to injury of the face in which cranial nerves are involved and may progress to generalized tetanus.
Differential diagnosis -

Diagnosis of tetanus is mainly based on clinical signs. It has to be differentiated from epilepsy, meningitis, strychnine poisoning, neonatal hypoglycemic convulsions. Certain drugs may cause dystonic reaction (phenothiazine and metoclopramide) and produce a syndrome named pseudotetanus.

In meningitis there is high fever along with positive leg raising test and cerebrospinal fluid (C.S.F.) is diagnostic.

In epilepsy there is loss of consciousness, which do not occur in tetanus. Neonatal tetany and hypoglycemic convulsions, can be confirmed by investigating the serum level of calcium and glucose.

Prevention - Tetanus is preventive disease and whole population of the country should be actively immunized, regardless of age.

Active immunization

Two preparations are available

(1) Plain tetanus toxoids (2) Adsorbed vaccine. Due to higher antitoxin titres and longer lasting immunity adsorbed vaccine is commonly advocated.

Schedule of immunization

The first dose of triple vaccine (DPT) should be administered with in 2 or 3 months of birth and second
and third doses should follow at 4 to 6 weeks interval. 4th dose after one year of third dose and booster at every 10 years interval. School children and adults should be immunized with 3 doses of tetanus, and diphtheria toxoids. Second dose should be given 4 to 6 weeks after the first and third 6 months to 1 year after the second and booster at 10 years interval (Smith et al., 1975).

In pregnancy recent schedule for immunization is at 7th and 8th months of pregnancy.

Bfman et al. (1981) have reported excellent protective response against tetanus, after 12 months by single dose tetanus toxoid, containing 3 times more potency (17.5 Lf) than normal tetanus toxoid (5 Lf).

Talwar (1985) developed a double acting vaccine against pregnancy and tetanus. The vaccine produces antibodies, acts against both human chronic gonadotrophin hormones as well as against tetanus toxins.

**Passive Immunization** - 250 I.U. of human tetanus immunoglobulins is recommended for prophylaxis which ensure the serum antibody levels of .01 unit/ml in all patients for 26 days or more.

Human immunoglobulin may be given together with tetanus toxoid (10 Lf dose) for active-passive immunisation.

Antitetanus serum (A.T.S.) can be used in doses of 1500 I.U., to 6000 I.U., intramuscularly after sensitivity test.
Management of case of tetanus

Investigation - Microscopic examination of pus or necrotic material shows bacilli with spores only in 30% of cases. Culture methods are of more importance. Granulocytosis is seen in one third of patients. Electrocardiogram usually shows sinus tachycardia.

In obscure cases of tetanus raised levels of serum aldolase and serum creatinine phosphotransferase may be diagnostic (Mullan et al, 1964).

General Management - An isolated calm, and quiet environment is required to cut off all external stimuli. All the patients require care of bowel, bladder and back. Suction of nose and oropharynx is done when ever required for keeping the airway patent.

Neutralization of the toxin

Equine anti-tetanic serum, was being used extensively for the prophylaxis and treatment of tetanus disease. Through Athavale Paken and Paul et al mention that it has definite role in treatment of tetanus disease. Bryant and Fairman (1940) and other are opinion that it has a controversial role in the treatment of the disease. There is always fear of severely allergic reaction by its use.

Laha and Vaishya (1965) found no significant difference in results when A.T.S. was administered by intramuscular, intravenous or combined route. Antiserum
does not neutralize tetanus toxin which is fixed in the C.N.S. and does little to ameliorate symptoms already present.

Intrathecal route for A.T.S. - According to Santers et al (1972), Ildirim (1974), Singh et al (1980), intrathecal A.T.S. has shown better results while Bhandari (1980), Neequaye (1983) have shown that it fails to improve the condition of tetanus patients.

Human tetanus immunoglobulin

Antitetanus human immunoglobulin is obtained by fractionation of (Hb Ag negative and AIDS antibody negative) plasma of human donors those who had been previous hyper immunized with tetanus toxoid. The globulin content is further purified by column chromatography techniques, including gel filtration ion exchange and affinity chromatography processes, ensuring optimal purity of above 99%, tested by immunoelectrophoresis.

Tetanus immunoglobulin is available as 250 I.U. (liquid) and 500 I.U. (freeze dried) vials.

Tetanus immunoglobulins (T.I.G.) is preferred over A.T.S. due to following (Vakil et al, 1979).

(i) T.I.G. is an immunoglobulin that is obtained from human serum, so it is virtually free from the risk of inducing hypersensitivity. On the other hand a person receiving A.T.S. may become sensitized to immediate and delayed
types of allergic reactions. Its incidence of local and general reactions is 5% to 50%.

(2) The half life of tetanus immunoglobulin (T.I.G.) is 20 to 40 days, whereas that of A.T.S. is 7 to 14 days.

(3) Protective level in A.T.S. is only for 4 weeks, while in T.I.G. protective level persists for 14 weeks.

(4) In T.I.G. there is no chance for anaphylaxis. Therefore sensitivity test is not required.

(5) Since T.I.G. is lyophilised and is devoid of any preservative, can be used intrathecally.

(6) T.I.G. does not interfere with patient's antibody production.

For therapeutic purpose 3000-6000 I.U. of (T.I.G.) tetanus immunoglobulin, is recommended intramuscularly (Behrman et al, 1983). 30-300 I.U. per kg of body weight has also been recommended by Scott et al (1978).


Mc Craken (1971) concluded that there is no significant difference in mortality by intramuscular T.I.G., over intramuscular A.T.S.


Agnihotri et al (1984) showed a reduction in the mortality
from 22.7% to 15.56% by intrathecal T.I.C. and it also reduced the average hospital stay.

Thus even intrathecal administration of T.I.C. may not influence the course of already established disease process in C.N.S.

In earlier cases it can neutralize unfixed toxin and prevent mortality.

Local wound management

Prompt and adequate care of wound is very important. Incision and drainage is done if pus is present, use of local antibiotics and proper debridement of wound is most essential. Cleaning of wound with Hydrogen peroxide may be needed in grossly infected wounds.

Cord is cleaned with spirit and gentian violet 1% is applied on the cord. In cases of otitis media, ear is cleaned and few drops of antibiotic solution is instilled.

Chemotherapy - Procaine penicillin is advocated by Bhatt et al (1979) Bhandari (1980) advised the use of crystalline penicillin. If patient is sensitive to penicillin, Kansamycin can be used in two divided doses of, 10 mg/kg body weight.

To control spasms and convulsions

A combination of muscle relaxants, is more effective than massive dose of any single drug (Jolly, 1973) Methacarbamol (Robinex) 2 to 20 mg/day by intravenous
infusion or orally in divided doses, significantly reduce 
the spasms and convulsions.

Diazepam was first used by Weinburg in 1964. 
Hendrick and Sherman in 1965 used diazepam with Chlorpromazine for the first time.

Use of steroids with sedatives was recommended 

**Tracheostomy** - In severe tetanus cases complete relaxation 
with tubocurarine or other muscle relaxants, combined with 
tracheostomy and intermittent positive pressure ventilation has revolutionized the treatment.

The indication of tracheostomy is either 
laryngospasm or copious secretions. The need for tracheосо 
tomy should be recognised early and whenever possible it 
should be performed electively rather than as an emergency 
(Weinstein 1975).

Agnihotri et al (1984) performed tracheostomy 
in 103 cases out of 302 with mortality rate of 15.36%. Shah 
et al (1984) did tracheostomy in 209 cases out of 629 cases 
and showed the mortality of 19.25%.

**Complications and Cause of death**

Bhatt (1962) found that the chief cause of 
death is aspiration pneumonia and exhaustion due to repeated 
spasms. Death may also be due to hyperpyrexia, laryngeal
spasms or oedema, spasm of respiratory muscles, hypoxia, atelectasis and electrolyte imbalance.

**Prognosis** - There are number of prognostic factors.

**Age** - There is a reciprocal proportion between the age and mortality (Kehrotra, 1975).

**Sex** - There is often high mortality in males (Modi, 1965) but high mortality in females has been shown by Blankson (1977). No sex difference in mortality has been noted by Vakil et al 1974.

**Incubation period** - Greater the incubation period lesser the mortality rate (Vakil, 1964, patel and Joag, 1965).

**Period of onset** - There is poor prognosis if period of onset is less (Patel and Joag 1969), Srivastava and Chatterji (1961).

**Duration and frequency of convulsions**

Severity of disease depends on the duration and frequency of convulsions (Bhandari, 1980).

**Fever** - Fever is a bad prognostic factor (Laha and Vaishnava, 1965, Bhandari 1973).

**Miscellaneous**

**Corticosteroids therapy** - Betamethasone may be important due to its antitoxic and antihistaminic action (Sanders 1972).

**Beta Blockers** - Sainani (1972) concluded that tetanus toxin has the same effect as adrenaline or isoprenaline on frog's heart and propranolol can successfully block this action.
Dexamethasone is also capable of blocking the beta stimulant action of tetanus toxin.

**Cholinesterase restoration therapy in tetanus**

Use of pralidoxime methanesulphonate 40 mg/kg/day together with vitamin B₁₂ 100 mg/kg per day intramuscularly for 10 days may be beneficial in severe tetanus (Leonardi et al, 1974).

**Pyridoxine therapy**

Pyridoxine hydrochloride 100 mg per day intramuscularly decreased the mortality rate up to 15% (Godet et al, 1982).

**Metronidazole therapy**

Metronidazole is a highly effective agent for both treating and preventing a wide variety of anaerobic bacteria diseases (Ibrahim, 1985).