1946

Tetanus

Byron Bay Oberst
University of Nebraska Medical Center

T E T A N U S

By

BYRON B. OBERST

Senior Thesis

Presented

to

THE COLLEGE OF MEDICINE, UNIVERSITY OF NEBRASKA

OMAHA, NEBRASKA

1946

TABLE OF CONTENTS

page

1. Introduction 1

2. Brief Summary of the Subject 2

    1. Definition. 2

    2. Etiology. 2

    3. Symptoms. 2

    4. Clinical Course 3

    5. Laboratory Findings 3

    6. Termination 3

    7. Diagnosis 4

    8. Differential Diagnosis 5

    9. Complications and Sequels 6

    10. Pathology 6

    11. Prognosis 6

3. Bacteriology of Clostridium Tetani 7

    1. Morphology. 7

    2. Physiology. 7

    3. Types 8

    4. Toxin 8

    5. General Information 9

4. Physiology 12

    1. Old Theories. 12

    2. New Theories. 13

    3. Summary of New Developments 19

page

5. Immunity 21

1. Antitoxin 21

2. Toxoid. 28

6. Therapy. 47

1. General Information 47

2. Use of Sedation 48

3. Use of Curare 49

4. Use of Antitoxin. 55

5. Care of the Local Lesion. 57

6. Use of Newer Drugs. 58

1. Sulfa Compounds 58

2. Penicillin. 59

3. Streptomycin. 59b

4. Clavacin. 59b

5. Tyrothricin 59b

6. Actinomycin A 60

7. Pyocyanase. 60

8. Zephiran Chloride 60

9. Phenyl Mercuric Acetate 60

7. Recommended Form of Treatment 61

7. Analysis of Case Histories of University of Nebraska Hospital 61

8. Conclusions. 63

9. Bibliography 65

LIST OF TABLES

page

1. Table Number I 8

Duration of Spore Resistance to Various Antiseptic Measures

Table Number II. 22

Duration of Large Doses of Antitoxin 100,000 Units + in Eight Injected Children

Table Number III 23

Duration of Moderate Doses of Antitoxin 10,000 Units in Fourteen of Twenty-one Injected Children

Table Number IV. 24

Tetanus in World War I

5. Table Number V 29

Tetanus in Industrial Accidents

Table Number VI. 34

Number of Children with Antitoxin Titres Below 0.10 U/cc. When Tested 9-15 Months After Completion of Immunization

Table Number VII 36

The Average Levels of Antitoxin Titres One Year After the Booster Dose for the Four Groups of Children

8. Table Number VII 36

The Percentage of the Various Groups of Children in Which the Antitoxin Titre Dropped to Inadequate Levels

Table Number IX. 38

Speed of Increase in Antitoxin Following Reinjection with Either Alum Precipitated or Fluid Toxoid

10. Table Number X 41

Reactions to Tetanus Toxoid in People with a History of Allergy and without a History of Allergy

11. Table Number XI. 43

Percentage of Reactions Occurring with the Injection of Combined Alum Precipitated Diphtheria and Tetanus Toxoids Varying with the Duration after Basic Immunization

12. Table Number XII 56

Dosage Schedule for Atropine Sulfate and Epinephrine 1:1000 for Various Age Groups

13. Tables Referring to University of Nebraska Hospital Cases 61

INTRODUCTION

Tetanus is a threat to the life of every individual, and some people have a much greater exposure to the dangers of being infected with this disease than other people do.

The inspiration for the study of this subject came from watching a 42 year old woman, who was the mother of four small children, die from this disease.

The subject chosen is an extensive one, and much work has been done in this field during the past fifteen years which changes somewhat the concept and treatment of the disease.

In order to keep this paper from becoming unwieldy, much of the textbook material - such as history and clinical picture - is purposely either omitted or reduced to essential features. This step is necessary in order to place more emphasis on the etiology, pathological physiology, current methods of prophylaxis, treatment - including a recommended form of treatment, and an analysis of The University of Nebraska Hospital cases with a discussion of the errors in the treatment of each case.

This paper is written both for the author's own benefit and for an analysis of current advancement in the subject.

BRIEF SUMMARY OF THE SUBJECT

Definition: Tetanus is a specific disease entity caused by an infection with the bacillus Clostridium tetani and characterized clinically by a toxemia in which the central nervous system is involved, producing spasms of the muscles. (R. Spaeth - 1944)

Etiology: Tetanus is caused by the tetanus bacillus whose natural mode of infection is through wounds - especially those wounds contaminated with foreign material. (J. Brennemann - 1944) The bacilli remain localized at the site of entry, and these produce a toxin which causes the clinical picture.

Symptoms: There is usually an incubation period from one to twenty-one days, though it may extend as long as 120 days, before the onset of the symptoms.

1. Prodromal symptoms are as follows:

    1. Intermittent or persistent muscular spasm of various groups of muscles.
    2. Generalized basal muscular rigidity.
    3. Exaggerated reflex excitability characterized by acute repeated toxic spasms.
    4. Dysphagia.
    5. Stiffness of neck and back with severe backache.
    6. Stiffness of gait.
    7. Colicky cramp-like abdominal pains.
    8. Increased irritability and restlessness.

2. Clinical Symptoms are as follows:

    1. Trismus within 48 hours after first symptom.

    2. Risus sardonicus.

    3. Generalized rigidity - maybe opisthotonos.

    4. Tonic and asphyxial muscular spasms including respiratory and laryngeal muscles.

    5. Rigid abdomen.

3. Clinical course is as follows:

    1. Decreased urination, incontinence, and constipation due to spasm of sphincter muscle.

    2. Clear sensorium.

    3. Little increase in temperature.

    4. Slight increase in heart rate.

    5. Danger signs -

        1. Rigid abdomen and chest.

        2. Cessation of breathing.

        3. Markedly increased heart rate, indicative of exhaustion.

4. Laboratory findings are of very little value.

    1. WBC - 12,000-14,000 80-90% segmented.

    2. Cerebral spinal fluid - normal - increased pressure during muscle spasm.

    3. Occasional smears or cultures of wound show Clostridium tetani organisms.

5. Termination.

    1. Acute death.

        1. Asphyxial convulsion.

2. Delayed death from exhaustion.

3. Death from pneumonia or sepsis.

2. If no death occurs -

1. A gradual decrease in intensity and frequency of superimposed convulsions.

2. A gradual decrease in generalized rigidity.

6. Diagnosis (R. Dandurand & R. Dussault - 1943)

1. History of a septic wound or of a surgical wound with secondary infection.

2. Presence of painful muscular contractions with paroxysmal spasms - beginning usually in the muscles of mastication (causing the trismus and sardonic grin) later extending to the back and neck muscles (causing opisthotonos).

3. Slight polynucleosis.

4. Temperature 100-101° F.

5. Perfect lucidity.

6. Normal cerebrospinal fluid.

7. Electromyograms in diagnosis of obscure cases of tetanus (A.S. Watkins - 1942).

Localized and atypical tetanus present difficulty in making a diagnosis. Electromyograms of summated action currents of skeletal muscle are possible with the aid of an electrocardiograph (L. Gunther and J. E. Walker - 1943). This is done by the insertion of needle electrodes directly into the muscle mass. Abnormal electromyographs are diagnostic of tetanus.

The electromyographic studies in cases of atypical and localized tetanus are comparable in diagnostic significance

to the electrocardiographic tracings in cases of atypical and silent cardiac infarctions.

7. Differential diagnosis (L. C. Cole - 1942).

1. Local affections of the mouth - usually painful. Trismus is not painful.

1. Impacted wisdom tooth.

2. Tonsillitis.

3. Peritonsillar abscess.

4. Glands about the angle of the jaw.

2. Local tetanus.

1. Neuritis.

2. Arthritis.

3. Cephalic tetanus with cranial nerve palsy.

1. Bell's palsy.

2. Polio-encephalitis.

3. Meningitis.

4. Generalized meningitis or encephalitis.
(Note: for the last two conditions, do a lumbar puncture.)

4. Primary abdominal rigidity.

1. Acute appendicitis.

2. Perforated ulcer - usually has more pain.

5. Reflex spasms distinguished from convulsions.

1. Hysteria.

2. Epilepsy.

3. Strychnine poisoning.
(Note: A detailed history is usually sufficient)

7. Complications and sequels (R. Spaeth - 1944)

   1. Pneumonia.

   2. Compression fractures of the vertebrae.

   3. Respiratory obstruction.

   4. Constipation.

   5. Urinary retention - not due to muscular spasm. Cystomyograms indicate a paralysis of the bladder is due to an interference with the lower motor neuron mechanism. (P. F. Eastman and R. M. Nesbit - 1942) This interference is due to the tetanus toxin rather than to the antitoxin.

   6. Cranial nerve paralysis.

   7. Decubitus ulcers.

8. Pathology (R. Spaeth - 1944)

   The morbid anatomy has no real features to distinguish it from other infectious diseases in general. The postmortem findings represent secondary effects to the condition of the body per se.

9. Prognosis.

   Prognosis is very poor if the incubation period is less than ten days, and it becomes increasingly better in a ratio directly proportional with the length of the incubation period provided that complications are kept at a minimum.

BACTERIOLOGY OF CLOSTRIDIUM TETANI

1. Morphology: (Jordan and Burrows - 1942)

A slender, motile (20-30 peritrichous flagella), gram positive, sporulating rod with rounded ends. The rod possesses a characteristic drum-stick appearance when the spore is present. Isolated colonies in deep dextrose agar have a wooly appearance. Surface colonies are flat, rhizoid, or feathery, and usually are over 1 mm. in diameter. Colonies on blood agar cause hemolysis.

2. Physiology:

The organism develops in plain or dextrose broth and in brain, meat, agar, and gelatin from which air has been expelled by heating and excluded by some form of seal. Growth is greatly influenced by the presence of associated organisms. Dextrose and other carbohydrates are not fermented by this organism.

Sporulation is not inhibited by carbohydrates. Spore formation begins in about two days at 37°C - eight to ten days at room temperature. The spores are highly resistant. See Table Number I on the following page.

Table Number I

Duration of Spore Resistance to Various Antiseptic Measures

Type of Antiseptic Measure	Duration of Resistance
5% Carbolic Acid	10 hours
0.001% Bichloride of Mercury	3 hours
160°C Dry Heat	1 hour
120°C Live Steam	30 minutes

The tetanus bacillus can be destroyed by ordinary antiseptic measures.

3. Types:

There are ten known types of this organism. Types I, II, and III are the most common in this country. (Jordan and Burrows - 1942) The toxin produced is immunological identical; so the subdivision into the agglutinations types has no apparent practical significance.

4. Toxin:

The toxin produced is of a dual nature:

1. Tetanospasm - which affects the nervous system.
2. Tetanolysin - a hemolysin, which has no apparent significance in the sympton complex.

The toxin is filterable and can be separated from the bacteria. This substance is apparently protein in nature as it

is destroyed by proteolytic enzymes. The toxin retains its potency for a long time in a dry state and is an excellent antigen as it gives rise to a high titre.

This toxin is one of the most potent poisons known. If taken by mouth, this poison is harmless unless some lesion like an ulcer is present. (M. Fernan-Numez - 1938)

There are qualitative difference between the toxins produced by the different strains of Clostridium tetani in that various amounts of the antitoxin are required to neutralize the various toxins. (U. Friedemann and A. Hollander - 1943)

5. General Information:

The bacilli and the spores have a wide distribution in the feces of all domestic animals. There is a question whether or not the organisms multiply outside of the animal body, i.e., the intestinal tract. These organisms are more prevalent in certain areas. (J. Brennemann - 1944)

In a series of studies done on the distribution of the tetanus bacillus during the World War I, the cultures of 193 soil samples taken from European battle zones show positive cultures in 27% of the cases. (J. Boyd and J. Maclennan - 1942) In 57 out of 79 samples from the cultivated fields of England, the samples show positive culture; but no organisms are present in the samples taken from the "Wilds of Scotland".

The organism is present less frequently in the arid

desert soils of the Middle East. In 91 soil samples taken from Cyrenaica and the Egyptian Desert during World War II, only 8 samples yielded toxigenic cultures of Clostridium tetani.

The natural mode of entry into the body is through wounds - especially those wounds contaminated with foreign material. The order of frequency of infection by wounds is first by puncture wounds; next by abrasions; and lastly, by lacerations. The organism is probably introduced into the body in the spore form.

According to some experimental work done, there are many non-toxic producing strains of tetanus bacilli which exist. These strains exist in the soil, in dung, or even in a case of tetanus. (P. Fildes - 1927) These strains are a variation from the ideal tetanus bacillus. There is no apparent return of toxicity in any of these non-toxic strains.

There is, also, a great variation in the virulence of the toxic-producing strains.

There is recorded some experimental work which shows that humans carrying tetanus bacilli in the intestines frequently have blood serums which contain appreciable amounts of tetanus antitoxin. (M. Fernan-Nunez - 1938)

In the sera of 30 individuals in whose stools no tetanus bacilli-like organisms were found, with two exceptions, no antitoxin could be demonstrated. (C. Tentroeck and J. Bauer - 1923)

A small amount of the serum (.1 cc.) containing the tetanus antitoxin neutralized 10+ M.L.D. of toxin. It may be that acquired immunity is due to the bacilli's being present in the gastro-intestinal tract; for it is known that the tetanus bacilli will grown in this habitat.

Many of the individuals who have no tetanus bacilli in the intestinal tract and whose serum is free of tetanus antitoxin show agglutinations to the tetanus bacilli. Probably these people have been carriers in the past; and the agglutinens have persisted longer than the antitoxin. Under the circumstances it seems likely that such individuals are potentially immune to tetanus; but there is no demonstrable immunity due to the environmental exposure. (J. Brennemann - 1944)

The fate of the tetanus bacillus in the tissues depends on many factors.

1. Phagocytosis does not prevent germination of spores.
2. Positive oxygenation prevents spore germination.
3. Spore germination is aided by -
    1. Trauma.
    2. Foreign bodies.
    3. Tissue necrosis.

(Note) These foregoing factors cause a hindrance to the blood supply which in turn gives poor aeration to the tissues and permits increased germination of spores (P. Fildes - 1

4. Secondary infections, especially other anaerobes. Manytimes, the local response of the tetanus bacillus is insignificant, and visible changes are hard to see. Suppuration and gangrene are due to secondary organisms.

PHYSIOLOGY

The tetanus bacilli multiply at the site of innoculation but these organisms remain localized and are never found in the blood stream. (J. Brennemann - 1944) These organisms liberate a toxin which is very virulent. (Note) See discussion of toxin under Bacteriology.

There are theories concerning the distribution of this toxin. The older theory is that this exotoxin diffuses through the organism by means of the blood stream and by means of ascending either along or through the peripheral nerve trunks as far as the nerve centers. (Dandurand and Dussault - 1943) This toxin, then, becomes fixed in the nerve cells causing an increased irritability of the neuromuscular system. The nerve cells, especially the motor nerve cells, are hypersensitive to the action of the toxin; and so the tetanus becomes fatal when a certain amount of the toxin has been absorbed and fixed.

During the past ten years, a great deal of work has been done on the physiological processes of tetanus which alters somewhat the older concept of treatment and prophylaxis of this disease. The following material is a brief summary of

this new information.

The toxin is a water soluble substance of high molecular weight. When the incubation period for the onset of the clinical picture caused by this toxin is less than 5 to 6 days; then, the mortality is about 90%. If the incubation period is 10 days or more; then, the mortality is about 50%.

There is no route of the toxin to the central nervous system by the nerve fibrils or neural lymphatics. The only route is arterial. (J. Abel - 1934) This highly toxic blood can penetrate every region of the body during the incubation period without manifesting any evidence of poisonous nature. Equal volumes of blood and lymph contain the same amount of toxin.

A close association exists between the hemoglobin of the blood and the tetanospasm of the toxin during the acute stages of the disease as shown by experiments with guinea pigs. (G. Shwartzman - 1940) Under experimental conditions, the tetanospasm concentration of the blood is approximately directly proportional to the hemoglobin concentration.

The amount of toxin bound by the tissues is relatively greater when it is introduced into the body in small amount over a period of time. (J. Abel - 1934).

There is a rapid transfer of the excess toxin to the blood-lymph system. According to experimental evidence,

any amount of toxin above the lethal dose, whether introduced into the body by subcutaneous or intramuscular injections, is so transferred. (J. Abel, E. Evans, and B. Hampil - 1936) The excess toxin continues to accumulate here. Small amounts of the toxin can get into the very narrow tissue spaces by means of the lymph system.

The toxin is never found in muscles; it does persist for a short time in the spleen, liver, and for a longer period of time in the blood, lymph, lymph glands, and the peripheral part of mixed nerves. (J. Abel - 1934) Occasionally, the toxin is found in the urine.

The toxin may exert some secondary actions. (J. Abel, B. Hampil - 1936) In some cases, the liver might rupture. Metabolic alterations might occur so that there is a decreased weight accompanied by a shock-like weakness and sometimes emaciation even with a good food supply. Should the toxin reach a certain concentration in the cells of the non-reacting organs capable of absorbing the poison, then, a derangement of function might occur in these organs.

The cause of the muscular rigidity as seen in local and general tetanus is not an action of the toxin on special centers but in its action on voluntary muscles. (J. Abel, B. Hampil, A. Jonas, and W. Chalian - 1938)

The toxin exhibits a two-fold action; one, a central effect, and the other, a peripheral effect. (A. M. Harvey - 1939) (J. Abel, W. M. Firor, and W. Chalian - 1938)

The central effect, which is characterized by reflex motor convulsions, is due to the poisoning of the motor nerve cells of the spinal cord, medulla, and pons. The peripheral effect, recognized by the unremitting rigidity of voluntary muscles, results from the fixation of the toxin upon the motor-end plates. This last observation is supported experimentally by the knowledge that tetanus toxin is unable to produce rigidity in denervated muscles; and, also, that muscles which have become rigid as the result of the toxin relax at once providing the nerve section is carried out soon enough. Furthermore, the intraneural injection of a nerve with antitoxin - taking caution against leakage into the surrounding tissues - is unable to prevent the development of a local tetanus in the leg produced by multiple intramuscular injections of toxin. At the same time, the same type of tetanus is produced in the opposite unprotected leg.

The determing factor in the peripheral effect of the toxin is the integrity of the motor-end plates and not the connection with the spinal cord. (A. M. Harvey - 1939) Impulses from the cord contribute to the local tetanus earlier in its development.

In general, in tetanus involving muscles remote from the site of the production of the toxin, the persistent contraction of the muscles - like those of the jaw - involves an effect of the toxin on the motor endings of the muscles.

The rigidity of the muscles is not due wholly to a state of contracture; for the muscle fibers are involved in continuous, asynchronous, propagated contractions with different and fluctuating rhythms. After a period of tetanic stimulation, the muscles in local tetanus show a great enhancement of irregula activity; this being due to a decreased threshold of excitation at the motor-end plates during a period of tetanus.

The transmission of the stimulation is mediated by an impulse of a small charge of acetylcholine from the nerve endings. This substance acts as a direct stimulation of the muscle fibers at the motor-end plates.

By means of a three-fold action, tetanus toxin produces a method for the persistent irregular activity of the muscle fibers.

Tetanus Toxin Causes
- Increased liberation of acetylcholine
- Increased synthesis of acetylcholine
- Decreased concentration of cholinesterase which destroys acetylcholine.

This persistent irregular activity of the muscle fibers is the central feature of local tetanus.

By further experimentation, it has been determined that there must be a period of incubation between the inocculatio and the onset of symptoms and signs in both the peripheral and central tetanus. (J. Abel, B. Hampil, A. Jones, W. Chalian - 1938 It is also noted that there is a complete absence of an upward

passage of the toxin in the spinal cord - which finding helps to refute the older theory.

In approaching the last phase of this discussion of the physiological aspect of tetanus - the cause of death - the experimental evidence suggests that the time of death is predetermined by the fact that an absolute amount of toxin has been fixed by the various organs of the body within the first few hours after the requisite threshold concentration of toxin has been reached or surpassed in the tissue spaces. (J. Abel, E. Evans, and B. Hampil - 1936)

There is no blood-brain barrier for the toxin that prevents the poison from gaining access to the susceptible neurons of the neural axis. Instead, the responsive parts of the central nervous system begin to absorb and irretrievably fix the toxin from the moment it reaches the nervous system via the blood streams. The central nervous system acts exactly as do the other organs of the blood which have an affinity for the tetanus toxin.

The toxin is fixed in a non-recoverable and non-assayable form in a relatively short time by all organs of the body that have an affinity for the poison including the motor neurons of the central nervous system and the end-plates of the voluntary muscles. (J. Abel, B. Hampil, A. Jones, and W. Chalian - 1938)

Direct penetration of the nerve cells and their

stimulation by the tetanus toxin is not essential for the production of generalized tetanus. (P. N. Kartashov - 1939) The process of tetanus develops from the time of contact of the toxin with the peripheral receptors. Further progress of the disease, its generalization, and even its residuals occur without participation of the specific agent causing the condition tetanus toxin.

From the moment after the activity of the irritant, certain nerve mechanisms acquire a dominant importance in determining the course of the succeeding reactions after the new irritant has affected the nerve nests.

It is not impossible for the onset of tetanus to occur under the influence of a non-specific irritant at some later date after the infection when no traces of the tetanus toxin are present in the body

The metabolic changes consequent to the constant muscular spasms are not the principle factor in causing death. (W. M. Firor, A. Lamont, and B. H. Schumaker - 1940) In the absence of muscle spasm, life is prolonged to some extent; but death ensues fairly promptly. The prolongation is probably due to the impaired circulation of the spinal cord and not due to the abolishion of the convulsive movements. Experimentally, there are no blood changes in dying dogs which could account for the death.

The lethal agent does not pass up the spinal cord

in the cerebrospinal fluid or within the substance of the cord itself.

Toxin in the cerebrospinal fluid has the same lethality and action as when it is injected into the blood stream. (W. M. Firor, H. B. Schumaker, and A. Lamont - 1940)

The toxin is not multiplied and retained in the lumbar cord; therefore, the lethal agent must reach some vital center by way of the blood-lymphatic system. (W. M. Firor, H. B. Schumaker, and A. Lamont - 1940)

If the toxin was multiplied and absorbed by the blood stream in amounts sufficient to cause death, there would be present such signs of general tetanus as already described. These signs do not appear in experimental animals dying from the injection of the toxin into the spinal cord.

Death still occurs even though the blood and lymph contain large amounts of antitetanic serum through the entire course of the experiments. Obviously, if the toxin was multiplied and absorbed by the blood stream, it would be neutralized by the antitoxin.

On the basis of the foregoing information, the following theory has been advocated.

1. The toxin in the spinal cord is altered into a new lethal agent that is absorbed by the blood stream and is carried to some vital center where it has its lethal effect.

2. This new toxin is not neutralized by the tetanus

antitoxin.

Accordingly, the administration of antitoxin is ineffective once the lethal dose has been fixed and the symptoms of central nervous system tetanus are present; but since in humans there is no way of telling whether a lethal dose has been fixed, the antitoxin should be given and continued to be used in local or general tetanus in the hopes that a lethal dose has not yet been fixed by the body tissues.

It is suggested that the respiratory center is the vital center on which the new lethal agent acts and that this new agent's action may be enhanced by respiratory depressants. For example - in experiments with animals that have the symptoms of tetanus present, the injection of the usually safe dose of nembutal will kill the animal in a short time.

In animals in which the toxin is given intravenously, and convulsions result, the administration of enough avertin or nembutal to stop these convulsions will shorten the animal's life.

The injection of toxin into the medulla oblongata of dogs causes death to occur two times as fast, and much smaller doses of the toxin are needed; therefore, care should be exercised in the use of respiratory depressants for the treatment of tetanus.

IMMUNITY

An attack of clinical tetanus does not stimulate the production of any antitoxin. (J. V. Cooke and F. G. Jones - 1943) Because of this situation, there is no natural immunity to the disease as such - though some investigators claim that certain people have circulating antitoxin titres produced possibly by having the tetanus organisms inhabit the gastro-intestinal tract. (See the discussion of the bacteriology of the disease.)

In cases of tetanus, the amount of tetanus toxin absorbed is so small that it is insufficient to produce a primary stimulation or sensitization to produce an active immunity to the disease.

As indicated in the introductory remarks concerning the disease in general and in the discussion of the bacteriology of this disease, there is a definite need for prophylactic measures against tetanus.

At the present time, there are two methods for producing this needed prophylaxis.

1. By the use of antitoxin which produces a temporary type of immunity on a passive basis.

2. By the use of toxoid which produces a more permanent type of immunity on an active basis.

Tetanus antitoxin has been in use for a considerable

number of years. The accepted indication for the use of antitoxin is, merely, any injury in which there is the slightest danger that the tetanus bacilli might be carried into the wound.

As a general rule, if 1,500-5,000 units of tetanus antitoxin are injected subcutaneously within a few hours of injury, tetanus will fail to develop. (J. K. Calvin - 1941) In severe injuries of the crushing type or compound fractures, or after a considerable lapse of time from the injury, doses from 5,000 to 10,000 units are indicated. In these latter types of injuries, a combination of gas bacillus antitoxin with the tetanus antitoxin is a good and safe policy to follow.

From the work done on the use of toxoid, it has been established that a titre of 0.10 units of antitoxin per cubic centimeter of blood gives ample protection against the tetanus toxin. (L. Unger - 1942)

The following tables show the duration of the passive immunity as rendered by the injection of antitoxin. (J. V. Cooke and F. G. Jones - 1943)

Table Number II

Duration of Large Doses of Antitoxin - 100,000 Units + in Eight Injected Children

Titre Level	Duration after Injection
Initial	Fell quickly
1.0 units	3-4 weeks
0.1 units	6-10 weeks
0.01 units	8-11 weeks

Table Number III

Duration of Moderate Doses of Antitoxin - 10,000 Units in Fourteen of Twenty-One Injected Children

Titre Level	Duration after Injection
0.1 units	4-6 weeks
0.01 units	6-10 weeks

The use of 1,500-4,500 units of antitoxin rarely gives an adequate protection of 0.1 units in the blood titre. There is a rapid fall after seven days to zero at three to four weeks. (L. A. Yeazell and W. C. Deamer - 1943) The average incubation period is seven to fourteen days.

The fact that the prophylactic use of tetanus antitoxin is warranted in non-immunized individuals is borne out by observations made during World War II. The following instructions were issued in England for the treatment of air raid casualties. (J. Boyd and J. Maclennan - 1942)

1. Surgery to remove any foreign body or necrotic tissue.
2. Three thousand units tetanus antitoxin prophylactically to slight wounds.
3. Six thousand to nine thousand units tetanus antitoxin prophylactically to severe wounds.

During a two-year period in one London sector, there were seven deaths due to tetanus, six of these individuals had received prophylactic doses of antitoxin.

Table Number IV

Tetanus in World War I
(L. A. Yeazell and W. C. Deamer - 1943)

Military Force	Incidence of Tetanus per 100 wounded men	Percentage of Mortality
British Expeditionary Force 1915-1919	1.5	50.0
Germans - all fronts 1914	3.8	75.0
United States 1917-1918	0.2	11.1

There are recorded in the literature many routes of administration of antitetanic serum. (S. Ciancarelli - 1940)

1. Intracerebral)
2. Intracarotid) Not of much proven value.

3. Intravenous)
4. Intramuscular) Widely used.
5. Subcutaneous) Large amounts are tolerated.

6. Intraspinal) Good results obtained by some men.
7. Intracisternal) Use condemned by others.

In experiments on dogs, it is shown that the intracisternal injection of antitoxin yielded better results on dogs suffering from moderately severe tetanus than did the intravenous injection of the antitoxin. (W. M. Firor - 1940) In animals with severe tetanus, the results obtained by the use of the various routes of injection showed very little variance. The intracisternal injections showed better results than did the lumbar injections. The results may be due to the production of a non-specific inflammation.

This method of direct injection into the cerebrospinal

canal has been advocated by other workers as well (R. Spaeth 1941).

There are objections to this route of administrati: in that it produces an increased intensity of the neuromuscul irritability in tetanus. (R. Spaeth - 1941)

As for the accessibility of the antitoxin to the central nervous system, there is no blood-brain barrier for the antitoxin; and neither is there any barrier for the tetar toxin. (J. Abel, E. Evans, and B. Hampil - 1936) The cerebra capillaries of both the rabbit and the guinea pig are equally permeable to antibodies. (U. Friedmann, B. Zuger, A. Hollande 1939). These capillaries are impermeable to substances carry a negative charge but are permeable to substances carrying a positive charge; therefore, the permeability of the capillari depends on the amphoteric nature of the antibody.

The exchange of antibodies between blood and tissues is extremely rapid. Antitoxin injected into a pregna woman passes through the placenta and can be detected in the cord blood of the newborn. (M. Fernam-Nunez - 1938)

In view of what has been presented previously as re the physiology of tetanus, the reports in the literature of last few years contain some experiments that might alter the role played by the antitoxin serum.

The time of death is fixed by that fraction of the toxin which has been fixed by the specifically reacting orga

of the body in the first few hours during which exposure to the requisite threshold concentration of the poison occurred. (J. Abel, B. Hampil, A. Jonas, and W. Chalian - 1938) This toxin begins to be fixed in an irreversible manner from the moment it begins to reach, via the blood stream, the motor neurons of the central nervous system and the end-plates of the voluntary muscles. The antitoxin neutralizes only that toxin which has not been irreversibly fixed by the motor neurons and the end-plates.

Further experiments show that the antitoxin is powerless to reduce or abolish the existing symptoms of tetanus in humans whose tissues have fixed one or more lethal doses of the toxin before the serum was used. (J. Abel and W. Chalian - 1938)

This antitoxin fails if its injection is delayed until the incubation period merges with the onset of symptoms.

In the cases of humans, however, the knowledge of whether a full lethal dose of toxin or one that allows recovery has been fixed is unknown; therefore, every type of a prior local tetanus in which an intense vasodilatation occurs with edema of the skin, muscles, bursae, and joint tissues. As the serum sickness is primarily a disorder of blood vessels, the nutrition of the tissues - especially of the nervous system - is impaired. This reaction causes a temporary interference in the activity of the nerve cells and fibers. Occasionally

this interference is permanent and cell death with parenchymal necrosis follows. Edema of the perineural sheaths gives the neural syndromes - either radicular or spinal.

The following reports emphasize the complications of serum sickness - especially those of the nervous system.

1. Thirty-four of forty-nine cases of nerve involvement followed use of tetanus antitoxin. (H. M. Taylor - 1942)

   1. Paralysis of the brachial plexus - most common.

   2. Optic nerve paralysis - next most common.

   3. Cranial nerve VIII involvement resulting in permanent paralysis - fairly common.

2. Case of paralysis of recurrent laryngeal nerve - temporary. (K. Schauwecker - 1933)

3. Five cases of brachial plexus involvement with permanent residuals. (H. Sprockhoff and I. Ansorge - 1938)

4. Report on 18 cases found in German literature plus a case of 5-6 cervical nerve involvement.(G. Weber - 1939)

5. Report on a case of anaphylactic shock which resulted in hemoconcentration. (H. Blotner - 1942)

6. Report on a death which followed a prophylactic injection. (A. Gommelgaard)

   The autopsy showed the following findings.

   1. Capillary hyperemia of the organs and edema.

   2. Perivascular hemorrhages in the brain-especially in the medulla oblongata.

3. Small hemorrhages in the kidneys.

4. Ecchymosis in the myocardium.

There was no manifestation of shock until 15 minutes before death occurred. There was no history of previous anaphylactic reactions and no history of previous injections of serum. The perivascular hemorrhages in the brain were consid the cause of death.

7. Report of University of Nebraska Hospital Cases Four out of six cases treated with multiple doses of antiseru resulted in some form of serum reaction. (2 cases of urticari 1 case of serum sickness, and 1 case of permanent motor and sensory paralysis from level of xyphoid process down.) Note: See case reports at end of paper.

In an effort to prevent antitoxin reaction, the oral use of 20 units of histaminase every four hours until th patient was symptom free for both generalized and localized serum reactions failed to show any effect on either the durat or the intensity of the symptoms. (S. A. Eger and J. E. Stone 1944)

As is seen from the foregoing discussion, the use of tetanus antitoxin is a serious matter; and it warrants car and discretion.

In order to produce a more lasting immunity and to lessen the dangers of serum reactions, a method of active immunization has been developed during the past decade.

There are certain advantages connected with this type of immunization. (R. A. Cooke, S. Hampton, W. B. Sherman, and A. Stull - 1940)

1. The serum antitoxin titre is raised to a level higher than that level obtained with a prophylactic dose of antitoxin.

2. The titre obtained by active immunization is more lasting.

3. The titre is rapidly elevated by an injection of tetanus toxoid in an emergency.

4. This method of prophylaxis avoids the real dangers of reactions or sensitizations incident to serum administration.

This type of immunization is very useful where the threat of tetanus is ever present due to accidents.

Table Number V

Tetanus in Industrial Accidents
(P. Campiche - 1943)

Vital Statistics from the United States Census Bureau	
Year	Number of Deaths from Tetanus
1933	1253
1934	1226
1935	1057
1936	1088
1937	930
1938	637

There are many professions and states in life that have a particular exposure to tetanus. (M. Fernan-Nunez - 1938)

1. Pregnant women
2. Children
3. Athletes
4. Soldiers
5. Sailors
6. Physicians
7. Bacteriologists
8. Farmers and dairymen
9. Poultry men
10. Cattlemen
11. Cement workers
12. Truck drivers
13. Policemen
14. Industrial workers

Active immunization is a safe, practical, and desirable procedure and should be employed routinely in children, farmers, and all others whose vocations or avocations make them liable for tetanus infection. (J. H. Lyons - 1944)

Basic immunity is the goal desired in active immunization. This basic immunity is a measure of the ability of the tissue to react with the production of antitoxin. (J. J. Miller and J. B. Humber - 1943)

The tetanus toxoid is prepared from tetanus toxin produced in broth. The M.L.D. doses of tetanus toxin do not parallel the antigenicity of the tetanal toxoids prepared therefrom. (W. L. Koerber - 1943) The combining power values (L^+ or L_f of tetanal toxins cannot always be used for evaluation of the antigenicity of the corresponding toxoids; however, for certain toxins compared under definite conditions, a parallelism exists. The most reliable test for determing the antigenicity of the

tetanus toxoid is by means of an antigenicity test or guinea pigs or mice.

The toxin, now being used as a standard for the production of the toxoid is produced in a hog stomach - autolysate plus veal infusion broth so that the toxin contains 100,000 M.L.D. per milleliter. (D. T. Fraser, D. L. MacLean, H. C. Plummer, and F. O. Wishart - 1943)

There are various types of toxoids manufactured. The alum precipitated toxoid appears to be superior to fluid toxoid. (J. J. Miller and J. B. Humber - 1943) In turn, aluminum hydroxide seems superior to alum in the preparation of tetanus toxoid. (J. J. Miller, J. B. Humber, and J. O. Dowrie - 1944) More stable levels are produced with very little tendency to decrease.

There is some dispute as to what is the best method of producing active immunization. The following regime is used by the United States Army. (Major A. P. Long - 1943)

1. The original toxin is produced in Witte or Berna peptone broth and contains 10,000 M.L.D. per milleliter.

2. A plain fluid toxoid is used.

3. One (1) milleliter of fluid toxoid is given every three weeks for three (3) injections.

4. One (1) milleliter of toxoid is given one year after the completion of the basic immunization.

5. One (1) milleliter of toxoid is given at the time

of departure for the combat zone unless the previous "booster dose" was given within the past six months.

6. One (1) milleliter of toxoid is given at the time of injury.

Antitoxin production begins on about the fifth day, and the peak is reached on the tenth to fourteenth days. (J. Boyd and J. Maclennan - 1942) There are certain conditions which influence the process of active immunization.

1. There is found occasionally a subject who does not react to the innoculation with toxoid.

2. For a week, the circulating antitoxin may be small in quantity.

3. Antitoxin production may be less active in a badly wounded and shocked subject.

In guinea pigs immunized with two doses of alum precipitated toxoid and infected with tetanus spores, there is no increase in the antitoxin titre evident for eight to ten days. (B. Zuger, C. Greenwald, and H. Gerber - 1942) If, however, at the time of infection with the spores an additional dose of toxoid is given, the antitoxin titre increases rapidly within five days.

There is some discussion at the present time as to whether two or three injections of toxoid are necessary to produce an adequate basic immunization.

In a plan proposed to eliminate the low levels of

antitoxin titre obtained one year after basic immunization, it is suggested that instead of the intervals between the primary injections of one cubic centimeter of toxoid being six weeks apart this interval should be two to three months apart. There is a large increase in the antitoxin titre following a third dose of toxoid which is given seven to nine months later. (D. M. Marvell and H. J. Parish - 1940).

Two injections of one-half cubic centimeter of alum precipitated toxoid injected subcutaneously at intervals of two to three months will protect almost all individuals. (L. Unger - 1942) After the two injections, the amount of tetanus antitoxin increases to over 0.10 units per cubic centimeter. This titre gives ample protection.

If this titre is not reinforced by a "booster dose" of toxoid, it will steadily decrease from its peak. A stimulating dose of toxoid at the time of injury will rapidly restore the titre to a safe level.

Another investigator shows that after the administration of a third dose of tetanus toxoid there is an increase in the concentration of the antitoxin in the blood. (D. C. Evans - 1943) For at least eighteen months, a higher concentration of antitoxin remains than that antitoxin titre resulting from two doses of toxoid.

Some investigators on a series of children contrasting the two types of basic immunizing procedures show remarkable

results. (J. J. Miller and J. B. Humber - 1943) One series of children received two injections of one cubic centimeter of toxoid at eight-week intervals. The other series of children received two injections like the first group plus another injection at sixteen weeks.

Table Number VI

Number of Children with Antitoxin Titres Below 0.10 U/cc When Tested 9-15 Months After Completion of Immunization

Three Injections	Two Injections
4 in series of 42 9.2%	15 in series of 54 27.7%

(Note: The difference in the percentages is 18.2% $\pm$ 7.2%)

The foregoing information is important as it shows that complete protection is rendered for a given period of time even though reinjection is unintentionally omitted after trauma has occurred - in an instance like this one, the circulating antitoxin is of prime importance.

Tetanus toxoid should be administered at the time of trauma as most all people who are immunized respond rapidly to the "booster injection" within the incubation period of the diseas which may be only five days.

The work of other investigators has clarified the situation still further. One pediatrician, Peshkin, has been conducting series of immunizations for the past several years. According to his work, the critical blood titre level is 0.01

American units of antitoxin per cubic centimeter of blood. (M. M. Peshkin - 1943)

The children in his series had adequate basic immunity after receiving two initial doses of combined diphtheria - tetanus toxoid. When the "booster dose" is given two years after basic immunization, an adequate protection by blood titre develops within one month which is higher and lasts longer than when the "booster shot" is given from three to fifteen months after basic immunization. The antitoxin titre is adequate on the seventh day after giving the third injection; and in most instances, the titre is at its maximum level.

In another series of children, similar studies are undertaken; only, this time the third dose of toxoid is given three years after basic immunization. (M. M. Peshkin - 1944) A similar response results. At the end of one year after the injection, one hundred percent of the series still had an adequate immunity.

Studies on another group of twenty-five children who received the "booster dose" four years after basic immunization show that seven days after the injection the blood levels of 0.2 units are present. (M. M. Peshkin - 1945) One year later seventeen children, who were available out of the group of twenty-five, still have an adequate blood titre. This observation is very important as there is no cutaneous test to determine the status of immunity, and blood titrations are an

impractical laboratory procedure.

The following tables are the composite results from the foregoing series of immunizations.

Table Number VII

The Average Levels of Antitoxin Titres One Year After the Booster Dose for the Four Groups of Children

Group	Level of Antitoxin Titre
4 years	0.24 units
3 years	0.373 units
2 years	0.298 units
3 months to 15	0.083

Table Number VIII

The Percentage of the Various Groups of Children in Which the Antitoxin Titre Dropped to Inadequate Levels

Group	Level of Antitoxin Titre
4 years	0%
3 years	0%
2 years	3%
3 months to 15 months	7%

The conclusions reached are that the "booster dose" of alum precipitated toxoid should be given only two or more years after the completion of basic immunization with two doses

of combined toxoids.

A plan suggested to eliminate the low levels of tetanus antitoxin titre found one year after primary immunization involves a shortening of the interval between the primary series and the first "booster dose" of toxoid. (D. T. Fraser, D. L. MacLean, H. C. Plummer, and F. O. Wishort - 1943) This change causes a more rapid increase in the antitoxin titre. This "booster dose" should not be given in less than three nor more than six months after basic immunization; then a second booster dose is given fifteen to eighteen months after completion of the primary series.

The speed with which the antitoxin is produced in a basically immunized person is of prime importance in case of trauma. In these instances, either fluid or alum precipitated toxoid is recommended. (J. J. Miller and J. B. Humber - 1943)

The response to the "booster dose" of toxoid depends on the following factors:

1. The type of basic immunization.

2. The interval after the last injection - an uncontrollable variable in the case of trauma.

3. The type of toxoid used as a stimulus.

4. The dosage used.

5. The individual's immunity mechanism - a greatly variable factor.

Table Number IX

Speed of Increase in Antitoxin Following Reinjection with Either Alum Precipitated or Fluid Toxoid

		Number of Days After Injections							Total No. of Children
		1	2	3	4	5	6	7	
Reinjected with fluid toxoid	Increase				7	8	1	3	20
	No Increase				1				
Reinjected with alum precipitated toxoid	Increase				3	10	1	10	35
	No Increase			2	1	5	6		

(Note: In all cases, the last injection was given 12-15 months previous to this injection.)

The conclusion reached is that in case of trauma the injection of a "booster dose" of fluid toxoid gives a more rapid rise in the antitoxin titre.

In one author's experience, no one has failed to develop an immunity after three doses of one-half cubic centimeter of toxoid. (R. Spaeth - 1942) The immunity appears about two weeks after the second or third dose of toxoid.

Another investigator recommends three subcutaneous injections of one cubic centimeter of toxoid at three to four week intervals. (J. H. Lyons - 1944) This method confers an immunity for twelve to eighteen months. He recommends that a "booster dose" of one cubic centimeter of toxoid be given a year from the completion of the primary series and once a year thereafter and at the time of injury.

A note of warning is necessary as regards the effect

of passive immunization on active immunization procedures. Any considerable quantity of injected antitoxin prevents the development of primary sensitization or the primary response of the body cells by doses of toxoid injected during the first week of procedures so that later a single dose of toxoid is ineffective in stimulating the active production of antibodies. (J. V. Cooke and F. G. Jones - 1943) Only when the passive antitoxin titres have reached a relatively low level is active immunization effective. This condition is due to the inhibition by the heterologous antitoxin of the antigenic action of the toxoid. A delay of two to four weeks in the active immunizing procedures is necessary following an antitoxin injection.

These observations refute the value of the simultaneous serovaccination procedures.

The use of tetanus toxoid has another great advantage over tetanus antitoxin - it avoids the real dangers of reaction or sensitization incident to serum administration. (R. A. Cooke, S. Hampton, W. B. Sherman, and A. Stull - 1940)

Local reactions are few - about one percent of the cases. (L. Unger -1942) Systemic reactions are rare. The skin test is usually of some help. The reactions seen are usually urticaria or shock. No fatalities are recorded as yet.

The presence of allergy is no contraindication to the use of tetanus toxoid.

There are several routes for the administration of

the toxoid. The intracutaneous route has the advantage of producing less local reaction than the subcutaneous route while producing antitoxin levels higher than that produced by the use of antiserum. These levels, also, last longer. (T. B. Friedmann, J. A. Bigler, and M. A. Werner - 1942)

The intradermal injections seem to give more local reactions than do the intramuscular injections. (L. A. Yeazell and W. C. Deamer - 1943)

Severe reactions occur in about 1/10,000-50,000 cases. (J. H. Lyons - 1944) The patient should be kept under observation for a half an hour after being given toxoid. A syringe of adrenalin should be handy.

There is no difference in the antitoxin producing ability of the allergic child as compared with that ability of the non-allergic child of the same age and sex. (T. B. Friedman, J. A. Bigler, and M. A. Werner - 1942) The variation found among allergic children is comparable to that found among non-allergic children.

There is no danger in administering tetanus toxoid to allergic children. The stimulating dose of the toxoid gives a rapid and high response of antitoxin. Sensitization is not present among 109 allergic children nor in a similar group of non-allergic children.

Active immunization against tetanus or diphtheria in allergic children has no apparent effect on the allergic

manifestation, and concurrent allergic therapy has no effect on the antitoxin levels produced.

The skin test is advocated by some men as a method of avoiding reactions. In a group of adolescents, thirty-eight percent of the group with positive skin tests have asthma or hay fever; and about fourteen percent of the asthmatics have strongly positive skin tests. The local and systemic reactions are no more frequent among those individuals with a positive skin test than those without a positive test. (J. R. Gallagher, C. D. Gallagher, and G. G. Kaufman - 1942) Those people with strongly positive skin tests had received divided doses of toxoid. Thirty-six percent of those individuals with strongly positive skin tests gave no history of allergy. A number of those subjects with a negative history and a negative skin test gave unfavorable reactions. Neither the skin reactivity nor the history of allergy is a strong reliable indicator of possible local or systemic reaction.

Table Number X

Reactions to Tetanus Toxoid in People with a History of Allergy and without a History of Allergy

	TOTAL NO. CASES	Sore Arms		Malaise		Infirmary Admissions		Abcess	Urticaria
		No.of Cases	%	No.of Cases	%	No.of Cases	%	No.of Cases	No.of Cases
History of Allergy	75	16	21.3	3	4.0	2	2.7	0	0
No History of Allergy	434	75	17.0	16	3.7	10	2.3	2	1
TOTALS	509	91		19		12		2	1

(Note: In Table Number X, page 41, 3.7% of the group had a strongly positive skin test to the diluted tetanus toxoid.)

The work of another investigator shows that one case of urticaria was encountered in a group of thirty-one children who were immunized and then given a "booster shot" of combined diphtheria and tetanus antitoxin two years after basic immunization. (M. M. Peshkin - 1943)

In this same group of children twenty-two percent of the thirty-one gave a temperature for two days. Only three percent of a group of children who received a "booster shot" of combined toxoids three to fifteen months after basic immunization gave a temperature. Work by this same investigator on children who received a "booster shot" of combined toxoid reveals that no febrile or allergic reactions occurred after the injection - only three children had a moderate and one child a severe headache. (M. M. Peshkin - 1945)

The composite work of this investigator reveals that febrile and allergic reactions occurred only with the injection of combined alum precipitated diphtheria and tetanus toxoids; therefore, alum precipitated toxoid should be used alone for the "booster dose" when basic immunization has been produced with combined diphtheria and tetanus toxoids. This procedure will keep febrile, marked local, and systemic reactions at a minimum level.

Table Number XI

Percentage of Reactions Occurring with the Injection of Combined Alum Precipitated Diphtheria and Tetanus Toxoids varying with the Duration after Basic Immunization

Duration after Immunization	Percentage of Reactions
3-15 months	3%
2 years	22%
3 years	33%

In 186 allergic children who had received from two to five doses of combined toxoids, there were sixty-one children who received a third dose of uncombined tetanus toxoid. For a total of 534 injections, the incidence of reactions was 0.37 percent. Scratch tests done on all of the children of both single and combined toxoids did not produce positive reactions in any of the children observed. These skin tests were done both prior to the third dose and from one to six months following it. The conclusions reached were that a "booster shot" of alum precipitated tetanus toxoid be given only two or more years after completion of basic immunization with two doses of combined toxoids.

Another investigator recommends a similar plan for immunization but recommends three doses of toxoid be given initial (L. A. Yeazell and W. C. Deamer - 1943) With this latter method of immunization, a note is put on the certificate of immunization which reads as follows:

"To the Parent: Your child has received recorded immunization. If he has received injections against whooping cough or tetanus (lockjaw), he should receive a boosting injection against each of these infections not over two (2) years later.

If at any time because of injury it is necessary to raise his immunity, show this card to the doctor caring for the injury."

"To the Physician: If the above record shows that this patient has received basic immunization against tetanus (two (2) injections or more), we suggest, if possible, in case of injury calling for protection against tetanus, he receive an injection of tetanus toxoid (plain or alum precipitated) instead of tetanus antitoxin. It should be given promptly within twenty-four hours of the injury."

There are some records reporting sensitizations with the old Witte toxoids. (R. A. Cooke, S. Hampton, W. B. Sherman, and A. Stull - 1940) These anaphylectoid reactions resulted from toxoid prepared from toxin produced on Witte's peptone - veal infusion - glucose media. The potency of this toxin is 100,000 M.L.D. per milleliter. (E. M. Taylor - 1945) A new media (hog stomach autolysate and beef heart infusion) for the production of the toxin has given no anaphylactic reactions after extensive use for four years.

The results from the use of tetanus toxoid during the

World War II have been gratifying. The program of immunization began in the United States Army in June 1941. No cases of tetanus were reported from battle casualties. (Major A. P. Long - 1943) Since June 1941, only four cases of tetanus have developed in the whole army; and these cases were in non-immunized men. At the same time other types of anaerobic infections have developed in areas where the toxoid was used so tetanus per se was always a potential threat.

From the British records, similar results have occurred. During the campaign in Flanders and Dunkirk, about ninety percent of the British Expeditionary Forces were immunized. In 1800 non-immunized, wounded men, eight cases of tetanus developed. In 16,000 actively immunized men, no case of tetanus developed. Because of circumstances, no antitoxin was given in any case. (H. B. Schumaker and A. Lamont - 1942) (H. J. Bensted - 1940)

As was seen under Bacteriology, the distribution of the tetani bacilli is widespread. In swabs taken from wounds of 214 patients of the Middle Eastern Theatre, sixty-three patients had gas gangrene; but none of them had tetanus. (J. Boyd and J. Maclennan - 1942) About eighteen of these swabs had the Clostridium tetani organisms. Of swabs taken from the wounds of 494 wounded, two swabs had positive cultures; but there were no cases of tetanus present.

In the well immunized troops from the United Kingdom, Australia, New Zealand, and India, the incidence of tetanus per

thousand wounded was 0.13 percent. Four cases of tetanus developed - two cases in the Maoris and two cases in the Indians. One of the latter group was not immunized.

The South African Force was not so well immunized - either as early or as completely. The incidence of tetanus among these troops was 1.6 per thousand wounded.

During the first two years of the Middle East War, eighteen cases of tetanus developed; five cases developed in actively immunized men. Two of these cases recovered, and the other three cases died. In one of these latter cases, there was little or no response to immunization with two doses of toxoid. This situation reflects the need of a third dose. The other two fatalities had overwhelming infections from masses of necrotic tissue in the wound. This situation emphasizes the need of adequate surgery.

There is another case of a fatality due to tetanus in an actively immunized man; but after scrutinizing the record, it is seen that this person was not fully immunized with toxoid before he developed the tetanus. (R. J. McGill - 1943)

From the foregoing information, the value of the use of tetanus toxoid can be derived. A committee set up to study the problem came forth with the following recommendations: (Committee Report -1944)

1. There is administrative economy and efficiency in the use of multiple antigens.

2. The administration of plain or alum precipitated tetanus toxoid by itself in the pre-school group as a routine practice is not recommended.

3. The use of tetanus toxoid in combination with diphtheria toxoid is approved in this age group.

4. The administration of tetanus toxoid at any age is recommended, provided the environmental (social or occupational) conditions demand immunity.

5. The time for the administration of the "booster shot" is undetermined as yet.

THERAPY

Every case of tetanus is a grave emergency, and no time should be lost in instituting treatment regardless of how mild the case appears to be. (J. K. Calvin - 1941)

The actual therapy can be divided into four general divisions.

1. Nursing and symptomatic care.

2. Sedation.

3. Therapy with tetanus antitoxin.

4. Local treatment of the wound.

A standardized routine is a necessity for the favorable treatment of tetanus. The treatment should be handled, if possible, in a hospital by a trained team of experienced physician and nurses in the handling of this disease. (R. Spaeth - 1942)

The patient should never be left alone. A nurse should be in constant attendance. A quiet ward and a darkened room are essential features in this routine.

Sedation is the keystone of the therapy. Sedative therapy is to prevent or control convulsions and is indicated before attempting to carry out any other procedure. (J. K. Calvin - 1941) Sedation tends to prevent early death from suffocation, rapid aspiration pneumonia, or more rare - brain hemorrhage. (R. Spaeth - 1942) It is dangerous to omit sedation even in mild cases of tetanus.

The ideal antispasmodic should rapidly relax the patient enough to allay the convulsions and rigidity without complete loss of consciousness or collapse from the drug. (J. K. Calvin - 1941) If possible, the cough and pharyngeal reflexes should not be abolished.

Many drugs have been used to produce this sedation. Each drug has its champion defender. The more widely used drugs are contained in the following list.

1. Avertin
2. Sodium amytal and other barbiturates
3. Amylene hydrate
4. Chloral hydrate
5. Magnesium sulfate
6. Opiates
7. Sodium bromide

8. Inhalants

The inhalants are apt to produce fatalities more often. (V. S. Caviness - 1943)

All of the drugs listed above are respiratory depressants of one sort or another and exert some influence on the respiratory center in the medulla oblongata. According to the discussion of the pathological physiology of the disease, these drugs are apt to hasten the lethal action of the new proposed tetanus toxin. "W. M. Frior, H. B. Schumaker, and A. Lamont - 1940)

In view of this foregoing knowledge, the use of curare would seem to be the ideal drug to obtain good muscular relaxation. The site of action of the drug is peripheral rather than central. (S. C. Cullen and C. S. Quinn - 1943)

The action of this drug is to interrupt the synoptic transmission of the nerve impulse at the myoneural junction by depressing the nicotinic action of acetylcholine. This action gives paralysis without central depression.

The use of this drug by this depressant action would tend to disrupt the pathologic physiology of this disease as was discussed under the division of physiology. (A. M. Harvey - 1939)

Curare affects the skeletal muscles in the following order. (S. C. Cullen and C. S. Quinn - 1943)

1. Cranial nerves.

2. Muscles of trunk and extremities.

3. Muscles of respiration.

4. Diaphragm.

This drug makes possible the release of the asphyxiating toxic fixation of the chest without the complete paralysis of the respiratory muscles.

Curare may be capable of acting anywhere in the nervous or muscular systems where acetylcholine is the chemical mediator. (E. G. Gross and S. C. Cullen - 1945) Therapeutic amounts of curare cause relaxation of the smooth muscle of the small intestine in experimental animals. This effect is due, in part, to the direct effect on the effector cells of the muscle.

Curare can produce a hypotension, but this reaction is probably of peripheral origin caused by the relaxation of skeletal muscles and the resulting hypotonia causing a decreased venous return.

These foregoing observations suggest that large single doses of curare should be avoided.

The elimination of the drug occurs within two hours. Partial destruction of the drug takes place in the liver, and partial elimination of the drug occurs in the kidneys. (M. F. Mallinson - 1945) Kidney lesions do not contraindicate the use of this drug.

The use of curare in anesthesia shows there is an absence of toxicity either immediate or postoperative. (H. R.

Griffith - 1945) The drug has been given to anemic, frail, or shocked patients without harm. Doses up to 400 milligrams have been given without fatal results.

Curare is not effective by mouth and should be given either intravenously - the most widely used route - or intramuscularly.

In pediatrics at the present time, standardized curare is used as an adjunct to surgical anesthesia and in the treatment of spastic paralysis. (C. F. Church - 1945)

The various side reactions of curare - such as bronchial spasm and hypersecretions - are not troublesome.

The literature reports that forms of unstandardized curare were used as far back as 1934. The use of the drug has been retarded because of the lack of a standardized product. The list of the case reports using curare is as follows.

1. Tetanus treated with curare. (L. Cole - 1934) The dosage consisted of four doses of thirty-two milligrams of unstandardized curare given subcutaneously at six-hour intervals. The drug began acting within two hours and lasted about forty-eight hours. Good results were obtained, and the patient was allowed much comfort.

2. Case of tetanus treated with curarine. (J. S. Mitche 1935) The dosage consisted of .1 milligram initially and .1 milligram every four hours for the first day. The dosage was

gradually increased each day until eight doses of 0.5 milligrams were given in a twenty-four hour period. The total dosage for the period of twenty days was 48.1 milligrams of unstandardized curarine. Good results were obtained. No bad effecrs were seen. Repeated electrocardiograms showed no abnormalities even when taken immediately after the injection of the drug.

3. Case of intravenous curarine in the treatment of tetanus. (R. West - 1936) The dosage in this case consisted of an inflow of curarine of 0.25 milligrams per kilogram body weight per hour. This clinician recommended the use of this drug in advanced cases of tetanus.

He, also, states that when the incubation period of the disease is under seven days or the periof of development of generalized convulsions is less than three days, death is to be expected whatever the type of treatment adopted.

4. Curare in the treatment of tetanus. (S. E. Isacson and S. A. Swenson - 1941) These men used an aqueous solution of ten milligrams of the crude drug per cubic centimeter, and they started with four cubic centimeters of the solution injecte intravenously. When the effects began to wear off - a period of about an hour, three cubic centimeters of the solution was injected. In about an hour, two cubic centimeters of the solut were injected. They attempted to establish a maintenance dose of four cubic centimeters, according to the response of the patient.

Good muscular relaxation was obtained and better breathing occurred due to the relaxation of the respiratory muscles. The patient seemed more comfortable during the course of the disease.

5. The use of curare in the treatment of tetanus. (S. C. Cullen and C. S. Quinn - 1943) The preparation used was intocostrin (extract of unauthenticated curare). The drug was supplied as an extract, standardized by biological assay to contain 0.02 grams per cubic centimeter of a standard drug. There was no apparent difference in duration of the effect produced by intravenous and intramuscular injections. The onset of action was more rapid with intravenous administration.

Usually 0.050 grams of curare kept the patient comfortable and free from acute spasm for about three hours. The amount of drug administered was determined by the response of the patient About 0.008 to 0.010 grams of curare per kilogram body weight was satisfactory.

Marked relief was experienced by the patient. The patient was able to cough, expectorate, drink, and move about in bed.

From the foregoing case history, the plan of dosage of curate is drawn. Use 0.010 grams of intocostrin per kilogram body weight by either intravenous or intramuscular injection as indicated by the response of the patient - especially by the tone of the rectus abdominus muscle.

The administration of the drug needs experience in handling it and should have the following items on a stand-by basis. (S. C. Cullen and C. S. Quinn - 1943)

1. Anesthetic face mask
2. Rebreathing bag
3. Oxygen supply
4. Physostigmine and prostigmine methylsulfate 1-2 cubic centimeters of 1:2000 solution (C. F. Church - 1945)
5. Experience in administration of artifical respiration.

This drug gives adequate control of the muscle spasm plus a patient who is awake, able to move, able to void and defecate, and able to respire freely.

The effects of prolonged curarization are not known as yet. In experiments done on dogs, the postmortem findings revealed the heart - especially the right side - was consistently dilated and the liver and kidneys congested. (M. A. Perlstein and A. Weinglass - 1944) Atropine appeared to hasten the cause of death which may have been due to ventricular fibrillation caused by removal of the vagal nerve inhibitions. Atropine, also, delayed decurarization by neostigmine.

More information concerning the clinical application of curare is now becoming available due to its standardization and to its use as an adjunct in surgical anesthesia. The drug seems to be full of promise for the treatment of tetanus.

The third phase in the treatment of tetanus is the

use of tetanus antitoxin. As reviewed under passive immunity, there are many routes for the administration of the antitoxin. The literature, also shows quite a variation in the amount of antitoxin to be used seemingly without any rationale behind the dosages advocated.

The old routine of using successive massive doses of antitoxin is slowly being discarded as impractical, expensive, and dangerous. The use of 40,000 to 60,000 units of antitoxin in a single massive dose intravenously is a much more logical procedure. (R. Spaeth - 1942) Antitoxin given in this manner will rapidly reach and neutralize any unfixed tetanus toxin. (J. K. Calvin - 1941) This antitoxin should be diluted in at least 500 cc. normal saline and given slowly to avoid reactions. The use of 5% dextrose or Hartman's solution is acceptable. The rate should not exceed sixty drops per minute. (R. Spaeth - 1941)

A quick review of the discussion of the passive immunization shows that the blood titre after the injection of 10,000 units of antitoxin is at the protective level of 0.10 units for four to six weeks. (J. V. Cooke and F. G. Jones - 1943)

A method devised to help reduce reactions after the administration of antiserum is as follows. (R. Spaeth - 1941)

1. A hypodermic of atropine sulfate with epinephrine 1:1000 given thirty minutes before the use of antitoxin.

2. The dosage should vary with the age group involved.

Table Number XII

Dosage Schedule for Atropine Sulfate and Epinephrine 1:1000 for Various Age Groups

DRUG	AGE GROUP			
	6 months	2 years	5 years	adult
Epinephrine 1:1000	3 minims or 0.18 cc.	4 minims or 0.25 cc.	5 minims or 0.31 cc	8 minims or 0.49 cc.
Atropine Sulfate	grains 1/500 or 0.12 mgm.	grains 1/250 or 0.24 mgm.	grains 1/200 or 0.3 mgm.	grains 1/100 or 0.6 mgm.

There are several definite indications for the use of tetanus antitoxin. (R. Spaeth - 1942)

1. Blank cartridge and powder injuries.

2. Penetrating wounds.

3. Dirty lacerations.

4. Self induced or improperly performed abortions.

5. Soil contaminated wounds.

Usually, the local signs of tetanus appear in the injured limb before any generalized symptoms appear. This happening is an important warning that generalized tetanus will almost certainly appear and that antitoxin should be given immediately without waiting for further signs. (L. Cole - 1945)

Some people reject the use of antitoxin entirely and do so on three basic reasons. (P. Campiche - 1943)

1. The value of antitoxin has not been proven.

2. Cases of tetanus are known to appear after the prophylactic use of antitoxin.

3. Serum reactions are dangerous to the patient.

The fourth division in the treatment of tetanus is the care of the local lesion. Some men contend that the case of the local lesion is not an emergency. (R. Spaeth - 1941) The wound should be treated as it would be treated if tetanus was not present.

The care of the lesion is, in another man's eyes, the first principle in the treatment of tetanus. (J. H. Lyons - 1944) This investigator believes the condition is a surgical situation that requires aseptic technique.

Nearly everyone agrees on certain basic principles.

1. Debridement of all devitalized tissue.

2. Removal of foreign bodies.

3. Drainage of pus.

4. Leaving the wound open.

5. Irrigations with a cleaning and oxidizing bath.

6. Amputation if necessary.

The use of oxidizing substances facilitate drainage but do not destroy the tetanus bacilli locally. (R. Spaeth - 1941) The failure of these substances may be due to the reducing value of the tissues. (J. H. Lyons - 1944) Cauterization is contra-indicated as this procedure devitalized tissue.

The less the discomfort the patient has and the less the disturbance endured, the better the situation is for the patient. (R. Spaeth - 1942)

It might be well to cradle the bed clothes to decrease the irritation to the patient. (L. C. Cole O 1940)

At times, not even the combination of wound excision and serum injection is able to prevent tetanus. This might be due to a particularly high virulence of the organism. (E. Koenig - 1940)

These fatalities may also be due to the unwillingness of the practioner to submit the patient to extensive surgical treatment for slight wounds. (R. Spaeth - 1942) Multiple local wounds are an indication for multiple incisions. In spite of the removal of foreign objects, some spores persist.

In some cases, the tetanus bacilli may gain entrance to the body through undetected trivial wounds.

The development of new drugs in the past few years cause: new hope and speculation in the treatment of tetanus. The evaluation of the usefulness of these drugs is not yet possible as the medical literature is still too sparse on the results of their use.

The use of the sulfa drugs has shown varying results.

1. A survey of thirty-five cases of tetanus shows favorable result with the use of sulfapyradine in connection with evipan-sodium as the antispasmodic. This line of treatment is cheaper than serum therapy and should prove to have a place in the treatment of severe tetanus. (S. M. Ghosal and L. M. Chaudhury - 1942)

2. In a severe case of tetanus, incubation period of forty-eight hours, the administration of 520,000 units of tetanus antitoxin, sedation with sodium amytal and avertin, and an adequate blood level of sulfanilamide did not result in clinical improvement. (C. B. Penrod and A. E. Knoll - 1941)

3. Sulfanilamide contaminated with tetanus spores and implanted in a guinea pig will not protect these animals from the development of tetanus. The sulfanilamide may act as a tissue debilitant; and, in the presence of Clostridium tetani, the drug may be conducive to the development of tetanus; therefore, the sulfa powders for use in deep wounds should be sterilized (H. Welch, G. G. Solcum, and R. P. Herwick - 1942)

Penicillin has shown some experimental evidence that indicates it is of value in tetanus. (W. E. Herrel, D. R. Nickols, and D. H. Heilman - 1944)

In a report on two cases of tetanus, it was deemed apparent that the addition of penicillin to a large dosage therapy of tetanus antitoxin was a life-saving measure. (R. Buxton and R. Kurman - 1944)

Another clinician reports a case of tetanus treated successfully with massive doses of tetanus antitoxin and penicillin. (J. M. Albergotti - 1945)

Another case of successful treatment reports the use of avertin and penicillin. This author notes that the penicillin has no action on the toxin of tetanus. (H. A. Toyne and P. E.

Voss - 1945)

The development of the antibiotus also bears watching as regards the treatment of tetanus.

In some work done on white mice, the evaluation of the action of penicillin, clavacin, and streptomycin on tetanus toxin shows some interesting results. (E. Neter and D. Will - 1944)

The tetanus toxin was mixed with 100 units of sodium penicillin and injected immediately or after eighteen hours at icebox temperatures into white mice. The tetanus toxin thus prepared was as toxic as tetanus toxin injected alone.

The use of ten milligrams of streptomycin incubated for two to forty-eight hours at 37°C. with tetanus toxin did not reduce the toxicity of the toxin. Clavacin, alone, in the amount of 1.5 milligrams proved to be lethal for mice.

A mixture of 2.5 milligrams of clavacin and tetanus toxin and incubated at 37°C. proved to be non-toxic when .2 milliliters of a 1:10 dilution was injected into mice. The control mice injected with diluted tetanus toxin died of tetanus; therefore, it seems that 0.2 milligrams of clavacin delayed death in mice due to tetanus.

Tyrothricin (Gramicidin and Tyrocidin) in amounts of 0.05 milligrams or less has no immediate effect on the toxicity of tetanus toxin. (E. Neter - 1942) If the toxin has been diluted with physiological saline solution and incubated at 37°C. for

24 hours, then, varying amounts of tyrothricin (from 0.05 milligrams to 0.000005 milligrams) partially or completely inhibits the toxicity of the diluted toxin.

Actinomycin A. has no effect on the toxicity of the tetanus toxin.

Pyocyanase, in amounts of one milligram, inhibits the toxic and lethal effects of tetanus toxin in the presence of broth.

Zephiran inhibits tetanus toxin in the presence of infusion broth or human serum.

Zephiran chloride in concentrations which are bacteriostatic or bacteriocidal in vitro and in vivo, i.e., 1:2000 - inhibits the effect of tetanus toxin. (E. Neter - 1942) The inactivation of this toxin takes place immediately. The presence of human serum definitely interfers with this inactivation. Human serum in 1:100 dilution added to a mixture of zephiran chloride and tetanus toxin prevents the inactivation of the toxin while a 1:1000 dilution of serum does not.

Phenyl mercuric acetate antiseptic in pellets contaminated with tetanus spores delayed the development of tetanus but does not prevent it. (H. Welch, G. Slocum, and J. J. Durrett - 1942). The implantation of pellets in deficiency diseases is a hazard if the pellets are not sterile. The incorporation of antiseptics to prevent tetanus into such pellets during the manufacture is a useless procedure and is dangerous.

The general phases of the treatment of tetanus have been reviewed and corrected according to current trends.

A recommended scheme for the treatment of tetanus will now be set forth as seems feasible to the author.

1. Nursing and hospital care as recommended in the general considerations.

2. Sedation - curare for the reasons discussed.
Dosage - 0.010 grams per kilogram as often as indicated.

3. Serum therapy - one (1) dose of 50,000 units of antitoxin I.V. Skin test before administration.

4. Local therapy - moderate debridement of gross contaminants, and the immediate use of penicillin to control the organism per se.

START

Case	History and Prodromal Symptoms
# 45119 Male Age 9 Race - white Admitted - 9/19/33	1. Ran sliver in right knee 9/9/33. 2. Jaw stiff and couldn't open mouth 9/11/33. 3. Taken to LMD who said patient was alright. No tetanus antitoxin. 4. Went to school 9/19/33 but teacher called LMD at noon. 5. Incubation period - two days
# 39619 Female Age 7 Race - white Admitted - 7/7/32	1. Splinter of branch of tree ran in foot 6/7/32. 2. Foot was swollen & painful for two week 3. Convulsion occurred 7/1/32. First symptom. Several since. 4. Leg became spastic causing difficulty in walking for 11 days. 5. Jaw not spastic except with convulsions 6. Incubation period - about 21 days.
# 57640 Male Age 7 Race - White Admitted - 7/15/35	1. Horse stepped on foot in barnyard injuring big toe of right foot 7/9/35 2. Mother applied iodine & bandage only. 3. Some swelling developed but no suppuration. 4. Restlessness developed in a.m. 6 days later 7/15/45. 5. Jaws hurt at noon & couldn't open mouth wide. 6. LMD saw and sent to UNH 7. Incubation period - 6 days.

BRIEF SUMMARIES OF CASES OF TETANUS TREATED
in
THE UNIVERSITY OF NEBRASKA HOSPITAL
OMAHA, NEBRASKA

Admission Symptoms & Physical Findings	Treatment
1. Talks without opening jaws. 2. Jaws stiff. 3. Neck muscles stand out prominantly 4. Abdominal rigidity - no tenderness 5. Old wound - medial side of right knee	1. Sedation 1.Sodium luminal 2.Magnesium sulfate 3.Codeine sulfate 2. Serum therapy Moderate doses of antitoxin I.V., I.M., & intra-spinously. Total,85,000 units.
1. Spastic right leg. 2. Stiff jaw. 3. Cannot or will not open jaw. 4. Difficulty in suppressing tongue. 5. Crusted lesion below right patella 6. Healed wound on plantar surface of right foot. 7. Right foot - plantar flexion with some inversion. 8. Spastic gait with right leg. 9. Negative neurological examinations.	1. Sedation None 2. Serum therapy Repeated moderate doses of tetanus antitoxin Total - 50,000 units
1. Soreness of jaws & inability to open them. 2. Restlessness. 3. Mouth open $\frac{1}{4}$ of way. 4. Jaw muscles in spasm. 5. Pain on palpation of face. 6. Swollen big right toe. 1. Necrotic tissue about the toe nail. 2. No apparent suppuration.	1. Sedation 1.Phenobarbital 2.Codeine sulfate 2. Serum therapy 1.Ten thousand units intra-spinously. 2.Forty thousand units-divided doses intra-muscularly. Total - 50,000 units

Clinical Course	Termination
1. Patient had convulsions. 2. Urticaria developed on ninth day. 3. Gradual improvement. 4. Temperature gradually dropped from 102°F to 99°F.	1. Improved. 2. Dismissed 10/4/33. Duration - 15 days.
1. Developed a rash 10 days after admittance. 2. Red blotchy areas on shoulders and buttox, later became generalized. 3. Urticaria present 13 days after admittance. 4. Temperature ran 101°F down to 99.8°F. 5. Patient never seemed restless in the hospital.	1. Improved. 2. Dismissed 7/21/32. Duration - 15 days.
1. Patient developed serum sickness on 2 occasions. 2. Patient improved. 3. While in hospital patient developed acute tonsillitis with pharyngeal cellulitis and cervical lymphadenopathy controlled by hot saline irrigations.	1. Improved. 2. Dismissed 7/24/35. Duration - 9 days. 3. Diagnosis of tetanus not positive.

FINISH

Laboratory Work	Autopsy Findings
1. Urine - essentially negative 2. Blood Hb.....90% RBC....5.5 WBC....23,050 Seg....87 Staph..2 Lymph..5 Mono...5 Baso...1 3. Spinal fluid 9/20/33 - cloudy 8,880 cells/cu.mm 97% polys 9/23/33 - clear 185 cells/cu.mm. 4. Nose & throat cultures negative for diphtheria bacillus.	None
1. Urine - essentially negative 2. Blood Hb.....80% RBC....5.1 WBC....7,500 3. Nose & throat cultures negative for diphtheria bacillus.	None
1. Urine - essentially negative 2. Blood Hb.....80% RBC....4.0 WBC....9,140 Segs...62 Staph..24 Lymph..10 Mono...4 3. Spinal fluid 3 cells/cu.mm. Protein 7	None

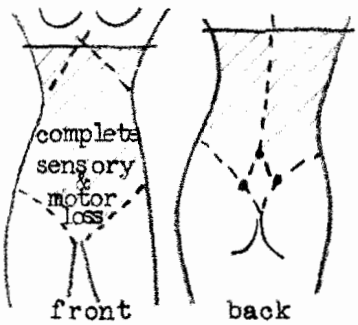
START

Case	History and Prodromal Symptoms
# 60122 Female Age 15 Race - white Admitted - 3/20/38	1. Fell on weed stubble and punctured lower inner aspect of right thigh 3/8/38. 2. Removed splinter but leg became sore and stiff. 3. LMD advised hot packs 3/10/38. 4. Developed signs of cold 3/16/38. 1. Soreness of throat on swallowing. 2. Inability to open mouth wide. 3. Stiffness and soreness of back. 5. Legs and neck became stiff 3/17/38. 6. Chewing became difficult. 7. Symptoms of 3/18/38 - 1. Neck drawn back. 2. Spells of arching of back. 3. Stiffness of body. 4. Choking and blueness of face - spells of 2 to 3 minutes. 5. Inability to eat solids. 8. Incubation period - 8 to 9 days.
# 75993 Male Age 9 Race - white Admitted - 8/13/42	1. Bruised lip on 8/7/42. 2. Jaw didn't work right 8/8/42. 3. Patient lethargic and had some facial spasm 8/9/42. 4. Right eye became swollen. 5. Had 3 convulsions - a stiff neck preceded the first one. 6. Incubation period - 1 to 2 days.
# 76150 Female Age 6 Race - white Admitted - 8/29/42	1. Ran sliver in foot which was partially removed immediately 8/17/42. 2. Backache and trismus developed 8/27/42. 3. Incubation period - 10 days.

BRIEF SUMMARIES OF CASES OF TETANUS TREATED
in
THE UNIVERSITY OF NEBRASKA HOSPITAL
OMAHA, NEBRASKA

Admission Symptoms & Physical Findings	Treatment
1. Moderate arching of back and retraction of neck. 2. Occasional twitching of side of mouth. 3. Sudden jerkings of trunk. 4. Bilateral nystagmus. 5. Inability to open jaws. 6. Rigidity and retraction of neck. 7. Abdominal rigidity. 8. Tenderness & pain on motion of spine. 9. Positive Kernig bilaterally. 10. Reddish-blue bleb 2 cm. in diameter with some induration on inner aspect of right thigh.	1. Nursing care. 1.Tried to use nasal tube for feeding-action caused too much spasm. 2.High Carbohydrate liquid diet. 3.I.V. fluids. 2. Sedation 1.Avertin. 2.Sodium amytol. 3. Serum therapy 1.Repeated massive doses of antitoxin, I.V. & I.M. 4. Total doses. 195,000 units I.V 175,000 units I.S 5. Local therapy 1.Debridement & removal of splinter 2.Hydrogen peroxide dressings.
1. Vague stomach aches. 2. Cramps in both popiteal fossae. 3. Neck partially stiff. 4. Abdominal spasm. 5. Semi-spasm of right face with some trismus.	1. Nursing care. 1.Diet by tube. 2.Fluids by clysis Glucose,Lactate ringers & cevatim 3.Carbon dioxide inhalation, 5 min t.i.d. 2. Sedation 1.Avertin 3. Serum therapy 100,000 units I.M
1. Trismus. 2. Neck rigidity. 3. Abdominal rigidity.	1. Nursing care. 1.Diet-liquid by tube. 2. Sedation. 1.Avertin 3. Serum therapy. 50,000 units I.M.

Treatment	Clinical Course
1. Nursing care. 1.Tried to use caused too much spasm. 2.High Carbohydrate liquid diet. 3.I.V. fluids. 2. Sedation 1.Avertin. 2.Sodium amytol. 3. Serum therapy 1.Repeated massive doses of antitoxin, I.V. & I.M. 4. Total doses. 195,000 units I.V. 175,000 units I.S. 5. Local therapy 1.Debridement & removal of splinter 2.Hydrogen peroxide dressings.	1. Improvement noticed by 3/26/38. 2. Last antitoxin was given on 3/25/38 but maculopapular rash developed 3/29/38. 3. Flaccid paralysis of lower extremities developed 3/31/38. Included loss of sensation from 10th dorsal segment on. 4. Distention developed. 5. Neurologist diagnosed transverse myelitis & treated with 200 cc. of 50% sucrose I.V. & spinal puncture. No improvement. 6. Temperature 101° to 104° at first, stayed high until 4/10/38, then gradually decreased to 98° F.
1. Nursing care. 1.Diet by tube. 2.Fluids by clysis Glucose, Lactate ringers & cevatim 3.Carbon dioxide inhalation, 5 min t.i.d. 2. Sedation 1.Avertin 3. Serum therapy 100,000 units I.M.	1. Gradual depression of hyperactivity. 2. Regular diet started 8/23/42.
1. Nursing care. 1.Diet-liquid by tube. 2. Sedation. 1.Avertin 3. Serum therapy. 50,000 units I.M.	1. Hospital course was satisfactory.

Termination
1. Tetanus recovered. 2. Dismissed 4/18/38. Duration - 29 days. 3. Residual changes - 1.Flaccid paralysis & sensory loss from level of xyphoid process. 2.Persistent slight urinary infection. 3.Inability to pass feces. Must be manually removed every day. 
1. Improved. 2. Dismissed 8/31/42. Duration - 18 days.
1. Improved. 2. Dismissed 9/18/42. Duration - 21 days.

FINISH

Laboratory Work	Autopsy Findings
1. Urine 3/31/38 4/12/38 Color str-clear cloudy Sp.G. 1.010 1.011 Ph. Alk. Alk. Alb. Trace Trace Sugar 0 0 Acetone 1+ 1+ Misc. WBC occas. 50/HPF 2. Blood 3/20 3/21 3/24 4/1 Hb - 95% - - RBC - 4.7 - - WBC 20,200 23,400 15,800 16,600 Seg - 79 - - Staph - 10 - - Lymph - 5 - - Mono - 6 - - 3. Spinal fluid 3/20 3/21 3/31 4/6 Cell Count 143 2100 41 8 Protein - - 60 16 Sugar - - 102Mg% 119Mg% Smear - - neg. neg. Culture - - neg. neg. Kline - negative Collod. gold - negative Wassermann .1- .2+ .4+ .1+	None
1. Urine - essentially negative. 2. Blood 8/13/42 Hb 13.5 RBC 4.15 WBC 13,250 Seg 68 Staph 10 Eosino 1 Lymph 17 Mono 4	None
1. Urine - essentially negative 2. Blood 8/29/42 Hb 14.7 RBC 4.8 WBC 17,680 No differential done.	None

START

Case	History and Prodromal Symptoms	Admission Symptoms & Physical Findi
# 39747 Female Age 3 Race - white Admitted - 7/17/32	1. Ran splinter in cheek 7/10/32. 2. LMD opened wound on outside. Attended 1-2x day. Treated with mercurochrome and iodine. 3. Wound broke on inside of cheek 7/15/32 4. Patient choked when swallowed water. Had eaten nothing since 7/10/32. 5. Abscess lanced at hospital 7/16/32. 6. No tetanus antitoxin given at all. 7. Jerked convulsively during sleep past three days. 8. Incubation period - 4 days.	1. Temperature 103°, heart rate 180. 2. Pupils sluggish. 3. Infected wound right cheek. 4. Jaw stiff at intervals. 5. Tongue swollen and bruised. 6. Right cheek and neck swollen. 7. Throat filled with purulent materi 8. Thorax - dullness on right with br breathing and rales. 9. Somewhat comatose. 10. Resting restlessly. 11. Breathing is difficult. 12. Some cyanotic. 13. Upper extremities stiffen convulsi ly at intervals.
# 45287 Female Age 10 Race - white Admitted - 10/10/33	1. Hands were partly pulled through pulley on farm 10/3/33. 2. LMD immediately sutured the tendons and treated minor lacerations. 3. Developed some stiffness of jaw 10/9/33. 4. Unable to open jaw 10/10/33. 5. No antitoxin given. 6. Incubation period - 6 days.	1. Stiffness and spasm of jaw. 2. Left hand had 1,2,3,& 4 fingers ba lacerated. 3. Right hand had several minor lacer ations.
# 45500 Male Age 50 Race - white Occupation - laborer Admitted - 11/6/33	1. Patient fell from wagon and lacerated scalp in parieto-occipital region to the bone 11/2/33. 2. Right shoulder was dislocated & bruised. 3. Bruises lower left chest and pain with respirations 4. Developed rigidity neck & jaw 11/6/33. 5. No antitoxin given. 6. Incubation period - 4 days.	1. Rigidity neck & jaw muscles with i ability to swallow. 2. Pain lower left chest with respira 3. Pain right shoulder. 4. Foul purulent drainage from scalp laceration. 5. Rigid jaws and neck. 6. Neck drawn back towards spine. 7. Spine not very rigid. 8. Extremities still flex.

BRIEF SUMMARIES OF CASES OF TETANUS TREATED
in
THE UNIVERSITY OF NEBRASKA HOSPITAL
OMAHA, NEBRASKA

Admission Symptoms & Physical Findings	Treatment	Clinical Course
1. Temperature 103°, heart rate 180. 2. Pupils sluggish. 3. Infected wound right cheek. 4. Jaw stiff at intervals. 5. Tongue swollen and bruised. 6. Right cheek and neck swollen. 7. Throat filled with purulent material. 8. Thorax - dullness on right with bronchial breathing and rales. 9. Somewhat comatose. 10. Resting restlessly. 11. Breathing is difficult. 12. Some cyanotic. 13. Upper extremities stiffen convulsively at intervals.	1. Nursing care. 1. Material aspirated from throat. 2. Sedation. 1. Sodium amytol.	1. Breathing became more & more difficult. 2. Pulse became rapid & irregular. 3. Temperature increased from 103_R to 106_R. 4. Patient died after being in hospital 2 hours.
1. Stiffness and spasm of jaw. 2. Left hand had 1,2,3,& 4 fingers badly lacerated. 3. Right hand had several minor lacerations.	1. Sedation. 1. Avertin 2. Serum therapy. 5,000 units I.M. 40,000 units I.V. in divided doses of 10,000 units. 3. Local therapy. Hydrogen peroxide dressings twice daily.	1. Spasticity increased. 2. Breathing became more difficult. 3. Temperature rose from 101_R to 108_R. 4. Heart rate increased from 144 to 160. 5. Patient died 10/12/33.
1. Rigidity neck & jaw muscles with inability to swallow. 2. Pain lower left chest with respirations. 3. Pain right shoulder. 4. Foul purulent drainage from scalp laceration. 5. Rigid jaws and neck. 6. Neck drawn back towards spine. 7. Spine not very rigid. 8. Extremities still flex.	1. Sedation. 1. Magnesium sulfate 25% solution I.M. 2. Sodium luminal. 2. Serum therapy. 15,000 units I.V. 15,000 units I.S. 3. Local therapy. 1. Scalp wounds cleaned with hydrogen peroxide irrigations. 2. Lacerations dressed with moist hydrogen peroxide dressings.	1. Patient developed respiratory difficulty 11/7/33. 2. Temperature increased from 100.6_R to 103.8_R 3. Patient died 11/7/33.

FINISH

Termination	Laboratory Work	Autopsy Findings
1. Death by respiratory failure. 2. Duration in U.N.H. - 2 hours.	1. Nose and throat cultures were negative for diphtheria bacillus	1. Gross 1. Chronic bronchitis. 2. Atelectasis of lungs. 2. Microscopic 1. Bronchopneumonia. 2. Fibroma of kidney. Brain not posted.
1. Death by respiratory failure. 2. Duration in U.N.H. - 2 days.	1. Nose and throat cultures negative for diphtheria bacillus.	No autopsy performed.
1. Death by respiratory failure. 2. Duration in U.N.H. - 1 day.	1. Nose and throat cultures negative for diphtheria bacillus.	1. Gross 1. Tetanus. 2. Pulmonary edema. 2. Microscopic 1. Bronchopneumonia. 2. Brain - no abnormal findings determined.

START

Case	History and Prodromal Symptoms	Admission Symptoms & Physical Findi
# 47088 Male Age 2 Race - white Admitted - 5/18/34	1. No history of injury. 2. Patient was cross and irritable 5/3/34. 3. Bowels and appetite were all right. 4. Began having choking spells and became cyanotic for short periods 5/17/34. 5. No twitchings or generalized convulsions. 6. Appetite and bowels poor - 5/16 to 5/18/34. 7. No rigidity of neck or jaw muscles - able to eat. 8. Incubation period - 2 weeks.	1. Choking and irritable. 2. Unable to open mouth. Masseters see spastic, but may be voluntary. 3. Questionable neck rigidity. 4. Multiple old healed abrasions on bo hands, feet, and legs. 5. No spasticity. 6. No neurological findings.
# 51558 Male Age 42 Race - white Occupation- gardner Admitted - 10/14/35	1. Puncture wound of palm of left hand on 10/4/35. No antitoxin. 2. Feeling of malaise and increased irritability 10/13/35. 3. Constriction and pain in throat muscles. 4. Inability to open mouth fully. 5. Flexion contraction of fingers of left hand, retraction of head, and board-like rigidity of abdomen 10/14/35. 6. Incubation period - 9 days.	1. Neck hyperextended. 2. Risus sardonicus. 3. Claw-like deformity of left hand. 4. Inability to open mouth. 5. Neck rigidity. 6. Abdominal rigidity. 7. Puncture wound thenar eminence of le hand. 8. Tonic state of convulsion.

BRIEF SUMMARIES OF CASES OF TETANUS TREATED
in
THE UNIVERSITY OF NEBRASKA HOSPITAL
OMAHA, NEBRASKA

Admission Symptoms & Physical Findings	Treatment	Clinical Course
1. Choking and irritable. 2. Unable to open mouth. Masseters seem spastic, but may be voluntary. 3. Questionable neck rigidity. 4. Multiple old healed abrasions on both hands, feet, and legs. 5. No spasticity. 6. No neurological findings.	1. Sedation. 1.Avertin 2. Serum therapy. 5,000 units I.M. 3. Local therapy. 1.Splinter found under left big toe. Appears to have been there about 2 weeks. 2.Debridement done.	1. Child became more restless despite sedation. 2. Some convulsions occurred. 3. Temperature increased from 100° to 106°. 4. Heart rate increased until not able to count. 5. Became cyanotic and died 5/21/34.
1. Neck hyperextended. 2. Risus sardonicus. 3. Claw-like deformity of left hand. 4. Inability to open mouth. 5. Neck rigidity. 6. Abdominal rigidity. 7. Puncture wound thenar eminence of left hand. 8. Tonic state of convulsion.	1. Sedation 1.Codeine sulfate 2.Magnesium sulfate 25% solution I.M. 3.Calcium gluconate. 4.Avertin. 5.Chloral hydrate 2. Serum therapy. 5,000 units subcu. 15,000 units I.M. 25,000 units I.V. in 2 doses. 10,000 units I.S. 3. Local therapy. Debridement of hand.	1. Rigidity increased. 2. No opisthotonos. 3. Generalized convulsions. 4. Respirations became labored. 5. Temperature increased from 100.4_R to 104_R. 6. Died on 10/16/35.

FINISH

Termination	Laboratory Work	Autopsy Findings
1. Death by respiratory failure. 2. Duration in U.N.H. - 3 days.	1. Urine - essentially negative 2. Blood Hb.....83% RBC....4.8 WBC....16,500 Seg....81 Staph..10 Young..2 Lymph..6 Baso...1 3. Cultures 1.Nose & throat - negative for diphtheria bacillus. 2.Splinter 1.Gram positive bacilli. 2.Gram positive cocci. 3.Bacillus tetanus. 3.Toe nail Same findings as from splinter. 4. Spinal fluid Cell count - 1	Autopsy not permitted.
1. Death by respiratory failure. 2. Duration in U.N.H. - 2 days.	1. Urine Color....amber Sp.G.....1.016 pH.....acid Alb.....1+ Acetone..positive Micro RBC.....2/HPF WBC.....10-15HPF Casts...2/LPF 2. Blood Hb.....102% RBC.....4.9 WBC.....9,700 Seg.....16 Staph....41 Youngs...14 Plasma...1 Lymph....21 Mono.....7 3. Spinal fluid 1. Cell count - 21 2. Sugar - 89mg.% 3. Protein - 7 4. Serology - negative	1. Gross 1. Tetanus. 2. Bronchopneumonia. 2. Microscopic 1. Foreign body in tissue. 2. Brain not posted.

START

Case	History and Prodromal Symptoms
# 57072 Male Age 4 Race - white Admitted - 5/16/27	1. Ran pitchfork into dorsum of left hand 5/7/37. 2. No apparent treatment. 3. Symptoms developed 5/15/37. Arching of back, convulsive seizures, stiffness of muscles of arm, neck, back, jaw, and difficulty in swallowing. 4. LMD gave 10,000 units I.M. 5. Incubation period - 8 days.
# 65102 Male Age 41 Race - white Occupation- farmer Admitted - 10/19/39	1. Stepped on rusty nail which penetrated about ½ inch 10/10/39. 2. Treated at home. No antitoxin. 3. Healed well. 4. Jaws began to get stiff and it was hard to swallow 10/17/39. 5. Neck stiff and not able to eat 10/18/39 6. LMD diagnosed tetanus and gave 2 doses of 40,000 units of antitoxin I.V. 7. Incubation period - 7 days.
# 76204 Male Age 4 Race - white Admitted - 9/3/42	1. Crushed left little finger with a cream can 8/25/42. 2. Received immediate attention & 1500 units antitoxin. 3. Symptoms developed 9/3/42. 4. Incubation period - 7 days.

BRIEF SUMMARIES OF CASES OF TETANUS TREATED
in
THE UNIVERSITY OF NEBRASKA HOSPITAL
OMAHA, NEBRASKA

Admission Symptoms & Physical Findings	Treatment	Clinical Course
1. Opisthotonos. 2. Rigidity masseter muscles. 3. Dehydrated appearance. 4. Small excoriation on dorsum of left hand- noninfected site of puncture wound. 5. Laceration of right thumb which is pustular. 6. Numerous excoriations on face & body.	1. Sedation 1.Morphine 2.Phenobarbital 3.Avertin 2. Serum therapy 20,000 units I.M. 30,000 units I.V.	1. Patient had several severe convulsions. 2. Adrenalin and caffeine needed for heart & respirations. 3. Temperature increased from 100.8_R to 103_R and the heart rate from 120 to 152. 4. Patient died 5/17/37.
1. Convulsive twitchings of lower extremities. 2. Rigid neck & jaw muscles. 3. Opisthotonos.	1. Sedation 1.Chloralhydrate 2.Sodium amytol 3.Morphine 2. Serum therapy 1.Two doses 20,000 units I.V. 2.One dose 5,000 units I.V. 3. Local therapy 1.Continuous boric acid packs to foot 2.Hydrogen peroxide irrigations. 4. Nursing care 1.Darkened room 2.Bed sideboards 3.Water & orange juice diet by nasal tube. 4.Fluids I.V. 5.Spinal tap & removal 15cc. fluid.	1. Patient sweat profusely. 2. Gradually became more restless and convulsive. 3. Respirations became labored. 4. Temperature gradually climbed. 5. Patient died 10/23/39.
1. Convulsions. 2. Trismus. 3. Risus sardonicus. 4. Rigidity of neck & abdominal muscles. 5. Opisthotonos. 6. Tonic spasms. 7. Crushed left little finger.	1. Nursing care 1.Fluids I.V. 2.Liquid diet of 1200 C/day by tube 2. Sedation 1.Avertin 3. Serum therapy 1.Single dose - 50,000 units I.M.	1. Convulsions not prevented by averti though deep narcosis produced. 2. Respiratory difficulty developed - nasal oxygen given. 3. Heart rate 100 on entrance, increas to 160. Given digitalis 2cc. 2x. Believed ventricles were dilating. 4. Patient appeared dehydrated & in acidosis. Given Hartman's solution and glucose. 5. Breathing became irregular - Biot's type. 6. Patient died 9/4/42.

FINISH

Termination	Laboratory Work	Autopsy Findings
1. Death by respiratory failure.	No laboratory work done.	1. Gross 1. Tetanus. 2. Pulmonary edema. 3. Bilateral bronchopneumonia 4. Clouding, swelling liver. 5. Clouding, swelling kidneys. 6. Slight cerebral hemorrhage 2. Microscopic 1. Foreign body reaction in skin. 2. Bronchopneumonia. 3. Brain appeared normal.
1. Death by respiratory failure. 2. Duration in U.N.H. - 4 days.	1. Urine - essentially negative. 2. Blood Hb.....88% RBC....5.02 WBC....8,950 Seg....47 Staph..8 Eosin..2 Lymph..37 Mono...6	No autopsy performed.
1. Death by respiratory failure. 2. Duration in U.N.H. - 1 day.	No laboratory work done.	1. Gross 1. Marked brain edema. 2. Few small areas of pulmonary consolidation.

START

Case	History and Prodromal Symptoms
# 68424 Male Age 5 Race - white Admitted - 7/30/40	1. Puncture wound of buttox by a rusty nail 7/22/40. 2. Mother treated it with hot packs. 3. Developed stiff leg & limped. Was irritablw & couldn't sleep 7/29/40. 4. Neck became spastic. Couldn't swallow 7/30/40. 5. Couldn't sit up. 6. Abdomen was rigid. 7. Incubation period - 7 days.
# 82972 Female Age 42 Race - white Admitted - 10/10/44	1. Sustained a compound fracture of tibia & fibula (right) with barnyard soil contamination. 2. Feeling of illness & aching jaws 10/18/44 3. Trismus 10/19/44. 4. Apparently LMD did not administer antitoxin at time of accident. 5. LMD gave 60,000 units 10/19/44. 6. Incubation period - 6 days.

BRIEF SUMMARIES OF CASES OF TETANUS TREATED
in
THE UNIVERSITY OF NEBRASKA HOSPITAL
OMAHA, NEBRASKA

Admission Symptoms & Physical Findings	Treatment	Clinical Course
1. Neck and leg rigidity. 2. Opisthotonos. 3. Difficulty in swallowing. 4. Pain & spasm of back.	1. Nursing care. 1.Fluids I.V. 2.Oxygen & carbon dioxide inhalations. 2. Sedation. 1.Avertin 3. Serum therapy 90,000 units in divided doses I.M. & I.V. 4. Local therapy Debridement of wound.	1. Avertin controlled the muscle spasm well. 2. Twenty-five cc. adrenaline given hypodermically & intracardias for imperceptible pulse. 3. Patient developed bronchopneumonia 4. Patient died 8/2/40.
1. Trismus. 2. Opisthotonos. 3. Generalized muscle spasm including neck, abdomen, and back. 4. Risus sardonicus. 5. Dyspnea. 6. Tachycardia. 7. Compound fracture right tibia & fibula.	1. Nursing care. 1.Darkened room. 2.Special nurses. 3.Fluids I.V. 4.Transfusion - 500 cc. 5.Oxygen inhalations. 2. Sedation. 1.Avertin 3. Serum therapy. Multiple doses of antitoxin I.V. & I.M. Total - 90,000 units. 4. Local therapy. 1.Debridement. 2.Hydrogen peroxide irrigations. 5. Additional therapy 1.Sodium sulfadiazine. 2.Penicillin.	1. The sedation controlled the spasms with increasing difficulty. 2. I.V. medication failed due to extensive 4+ edema which developed. 3. Respirations becoming increasingly difficult requiring frequent oxygen inhalations, artificial respiration, & respiratory stimulants of caffeine, metrozol and coromine. 4. Patient died 10/28/44.

FINISH

Termination	Laboratory Work	Autopsy Findings
1. Death by respiratory failure. 2. Duration in U.N.H. - 4 days.	1. Blood Hb.....13 RBC....4.98 WBC....17,400 Seg....69 Staff..15 Young..2 Lymph..12 Mono...2 2. Spinal fluid 1. Anaerobic - No growth in 24 or 72 hours. 2. Cell count - 4 3. Protein - 2	1. Gross 1. Tetanus. 2. Bronchopneumonia. 3. Pulmonary edema. 4. Brain 1.Flattening of convolutions. 2.Engorged vessels. 3.Tense tura. 4.Coning of cerebellum. 2. Microscopic. 1. Bronchopneumonia. 2. Pulmonary edema. 3. Clouding swelling of liver and kidney.
1. Death by respiratory failure. 2. Duration in U.N.H. - 8 days.	1. Urine - essentially negative. 2. Blood Hb.....13.7 WBC....11,600 Seg....54 Staff..24 Lymph..9 Mono...13 10/21/44 Total serum protein - 6.59% Blood NAN - 36.2 mg % Serum NPN - 31.9 mg % Albumin - 3.71 mg % Globulin - 2.88 % Chloride - 495 mg % as NCL_a 10/24/44 Co_2 combining power - 62.6 vol. % Blood NPN - 26.7 mg %	1. Gross 1. Tetanus. 2. Compound fracture. 3. Endometriosis. 4. Simplet cyst of ovaries. 5. Atelectasis of both lower lobes. 6. Edema of brain. 7. Fatty degeneration of liver and kidneys. 8. Pulmonary edema. 9. Uremia. 2. Microscopic. 1. Fatty degeneration of liver and kidneys. 2. Pulmonary atelectasis. 3. Endometriosis. 4. Tetanus.

ANALYSIS OF CASE HISTORIES OF UNIVERSITY OF NEBRASKA HOSPITAL

There have been sixteen cases of tetanus treated in the University of Nebraska Hospital since 1932. Of these sixteen cases, six patients recovered - one on whom the diagnosis was not proven - and ten patients died. Percentage of mortality is 62.5%, and the percentage of recovery is 37.5%. Twelve of the cases have been in children.

Among the six patients who recovered, four of them experienced some type of serum reaction with one patient developing a permanent partial paralysis. The percentage of serum reactions is 66 2/3%.

Autopsies were performed in seven of the ten mortality cases. A variation in findings is found except that there might be some significance to the brain postmortem. The brain was posted in five of the seven autopsies. In two of these five cases the brain appeared normal; but in the other three cases, there was marked cerebral edema.

This cerebral edema might be the result of a serum reaction due to multiple injections of antitoxin. In the two normal cases, one case received only two injections of 15,000 units of antitoxin at essentially the same time - one intraspinal and the other intravenously; the other case received a prophylact dose of 10,000 units intramuscularly by the LMD and received simultaneously on entrance to the hospital 20,000 units intramuscularly and 30,000 units intravenously. No repeat doses

were given.

Study of the case histories reveals that in many instances there was faulty treatment of the primary lesion by either the family or the local doctor. These people failed to recognize the seriousness of the situation.

The major fault in the treatment of the condition in the University of Nebraska Hospital was the consistent use of multiple doses of antitoxin which was unnecessary and which exposed the patient to greater dangers of serum reactions.

It is also noticeable that sedation was by respiratory depressants and that death occurred by respiratory failure.

These case histories further indicated the need for a new type of treatment of tetanus - such as the one advocated - and for a generalized prophylactic immunization of the people exposed to the dangers of the disease.

CONCLUSIONS

Tetanus is an important and ever prevalent disease. The newer developments of this disease during the past fifteen years have been reviewed in this paper. The following points have been emphasized.

1. A brief outline of the clinical aspect of the disease.

2. The bacterial aspect as regards the organism and its toxin.

3. The necessity of understanding the pathological physiology of the disease process.

4. A contrast between the types of prophylaxis available for this disease with a discussion of their limitations.

5. The care needed in the administration of antiserum.

6. The need for a universal active immunization against the disease.

7. A discussion and criticism of the various types of treatment available today.

8. A presentation of a plan for the treatment of the disease.

9. An analysis of the case histories of patients treated in the University of Nebraska Hospital.

BIBLIOGRAPHY

J. J. Abel — 1934 — Science 79:121
On Poisons and Disease and Some Experiments with the Toxin of the Tetanus Bacillus

J. Abel, E. Evans, B. Hampil — 1936 — Johns Hopkins Hosp. Bull. 59:307
Researches on Tetanus: Distribution and Fate of Tetanus Toxin in the Body

J. Abel, B. Hampil, A. Jonas, W. Chalian — 1938 — Johns Hopkins Hosp. Bull. 62:91
Researches on Tetanus: Production of Reflex Motor Tetanus by Intraspinal Injections of Tetanus Toxin

1938 — Johns Hopkins Hosp. Bull. 62:522
Researches on Tetanus: 1. Time Required for Fixation of Fatal Concentrations of Tetanus 2. Return Passage of Toxin via Lymphatic Capillaries to the Cardiovascular System

1938 — Johns Hospkins Hosp. Bull. 62:610
Researches on Tetanus: At What Point in the Course of Tetanus does Antitetanic Serum Fail to Save Life

J. Abel, W. Firor, W. Chalian — 1938 — Johns Hopkins Hosp. Bull. 63:373 (Dec.)
Researches on Tetanus: Further Evidence to Show that Tetanus Toxin is not Carried to the Central Neurons by way of the Axis Cylinders of Motor Nerves

J. M. Albergotti — 1945 — J. South Carolina M.A. 41:55 (Mar.)
Treatment of Tetanus with Tetanus Antitoxin and Penicillin

H. J. Bensted — 1940 — Lancet 2:788 (Dec.)
Immunization Against Bacterial Toxins

H. Blotner — 1942 — J. A. M. A. 118:219 (Jan.)
Anaphylactic Shock with Hemoconcentration Treated Intravenously with Sodium Chloride Solution

J. Boyd, J. Maclennan — 1942 — Lancet 2:757 (Dec.)
Tetanus in War Time

J. Boyd
J. Maclennan 1942 Lancet 2:745 (Dec.)
Tetanus in the Middle East: Effect of Active Immunization

J. Brenneman 1944 Practice of Pediatrics Vol. II, Chapt. 27:1 Edited by J. Brennemann
W. F. Prior Company, Hagerstown, Maryland

R. Buxton
R. Kurman 1945 J. A. M. A. 127:26 (Jan.)
Report of Two Cases of Tetanus Treated with Penicillin

J. K. Calvin 1941 New York State J. Med. 41:1636 (Aug.)
Tetanus - Its Prevention and Treatment

P. Campiche 1943 West. J. Surg., Obst., and Gynec. 51:359 (Sept.)
The Present Status of Tetanus Prophylaxis

V. S. Caviness 1943 North Carolina M. J. 4:6 (Jan.)
Tetanus and the Essentials of Its Successful Treatment

C. F. Church 1945 Am. J. Dis. of Child. 69:327 (May)
Pediatric Uses of Standardized Curare

S. Ciancarelli 1940 I. Polichlinico (sez. chir.) 47:99 (Mar.)
Clinical and Therapeutical Observations on 65 Cases of Tetanus

L. Cole 1934 Lancet 2:475 (Sept.)
Tetanus Treated with Curare

1940 Brit. M. J. 2:550 (Nov.)
War Medicine Series - Tetanus Therapy

1942 Brit. M. J. 2:550 (Nov.)
War Medicine Series - Tetanus

1945 Brit. M. J. 17:219 (Febr.)
Two Cases of Tetanus

Committee Report 1944 Am. J. of Pub. Health 34:452 (May)
Report of the Study Committee on Multiple Antigens

R. A. Cooke
S. Hampton
W. B. Sherman
A. Stull 1940 J. A. M. A. 114:1854 (May)
Allergy Introduced by Immunization with Tetanus Toxoid

J. V. Cooke F. G. Jones	1943	J. A. M. A. 121:1201 (April) The Duration of Passive Tetanus Immunity and its Effects on Active Immunization with Tetanus Toxoid
S. C. Cullen C. S. Quinn	1943	Surgery 14:256 (Aug.) Use of Curare in the Treatment of Tetanus
R. Dandurand R. Dussault	1943	J. de L'Hotel-Dieu de Montreal 12:289 (Sept.) Notes on the Treatment of Tetanus
P. F. Eastman R. M. Nesbit	1942	J. Urol. 48:219 (Aug.) Studies of Urinary Retention During Tetanus
S. A. Eger J. E. Stone	1944	Pennsylvania M. J. 47:371 (Jan.) The Use of Histaminase in Prophylactic Tetanus Antitoxin Reactions
D. C. Evans	1943	Lancet 2:216 (Sept.) Persistence of Antitoxin in Man Following Active Immunization
M. Fernan-Nunez	1938	Wisconsin M. J. 37:2 (Jan.) Tetanus Toxoid: Active Immunization against Tetanus
P. Fildes	1927	J. Brit. Exper. Pathology 8:387 (Oct.) Tetanus VI - The Conditions Under Which Tetanus Spores Germinate in Vivo
W. M. Firor	1940	Arch. Surg. 41:299 (Aug.) Intrathecal (Intracisternal) Administration of Antitoxin
W. M. Firor A. Lamont H.B. Schumacker	1940	Bull. Johns Hopkins Hosp. 67:25 (July) The Lethal Dose of Toxin in Experimental Tetanus
	1940	Ann. of Surg. 111:246 (Feb.) Studies on the Cause of Death in Tetanus
D. T. Fraser D. L. MacLean H. C. Plummer F. O. Wishart	1943	Am. J. Pub. Health 33:1107 (Sept.) Tetanus Toxoid and Its Use for Active Immunization

T. B. Friedman J. A. Bigler M. A. Werner	1942	J. Allergy 13:114 (Jan.) Immunologic Response of Allergic Children to Toxoid
T. B. Friedman A. Hollander	1943	J. Immunol. 47:292 (Oct.) Studies on Tetanal Toxin: The Antitoxin Requirements of Tetanal Toxin in the Direc and Indirect Intraventricular Tests
J. B. Friedman B. Zuger A. Hollander	1939	J. Immunol. 36:219 Quantitative Studies on the Neutralization of Pathogenic Agents in the Tissues by Ciroulating Antibodies The Permeability of Cerebral Capillaries to Antibodies
J. R. Gallagher C. D. Gallagher G. G. Kaufmann	1942	New England J. Med. 227:691 (Nov.) Tetanus Toxoid Immunization of Adolescents Skin Reactivity, Allergy, and Unfavorable Reactions
A. Gammelgaard	1941	Ugesk. f. laeger 103:1370 (Oct.) Death after a Prophylactic Injection of Antitetanic Serum
S. M. Ghosal L. M. Chaudhury	1942	Indian Med. Gaz. 77:533 (Sept) Sulfapyridine in the Treatment of Tetanus
H. R. Griffith	1945	Lancet 2:74 (July) Curare as an Aid to the Anesthetist
E. G. Gross S. C. Cullen	1945	Anesthesiology 6:231 (May) Action of Curare on the Smooth Muscle of the Small Intestine and on the Blood Pressure
L. Gunther J. E. Walker	1943	War Med. 4:57 (July) Localized Tetanus - Use of the Oscillograph Electrocardiograph for Recording of Normal and of Abnormal Action Currents of Skeletal Muscle
A. M. Harvey	1939	J. Physiol. 96:348 The Peripheral Action of Tetanus Toxin
W. E. Merrell D. R. Nickols D. H. Heilman	1944	J. A. M. A. 125-1003 (Aug.) Penicillin: Its Usefulness, Limitations, Diffusion, and Detection with an Analysis of 150 Cases

S. E. Isacson S. A. Swenson	1941	Nebraska M. J. 26:136 (April) Curare in Treatment of Tetanus - Case Report
D. Jordon J. Burrows	1942	Textbook of Bacteriology, Edition 13 page W. B. Saunders Company, Philadelphia and London
P. N. Kartashor	1939	Vaach. delo. 21:509 Effect of Tetanus Toxin Applied to Terminal Fibers of Trigeminal Nerve in Experimental Animals
E. Koenig	1940	Der Chirug. 12:136 (March) Fatal Tetanus in Spite of Wound Excision and Prophylactic Serum Injection
W. L. Koerber	1943	J. Immun. 46:391 (June) Evaluation of Antigenicity of Tetanus Toxoi
Maj. A. P. Long	1943	Am. J. Pub. Health 3:53 (Jan.) Tetanus Toxoid - Its use in the United States Army
J. H. Lyons	1944	Virginia M. Monthly 71:71 (Febr.) Prevention of Tetanus
M. F. Mallinson	1945	Lancet 2:75 (July) Curare in Anesthesia
D. M. Marvell H. J. Parish	1940	Brit. M. J. 2:891 (Dec.) Tetanus Prophylaxis and Circulating Anti-toxin in Men and Women
R. J. McGill	1943	Brit. M. J. 1:40 (Jan.) Probable Tetanus Despite Innoculation with Toxoid - Case Report
J. J. Miller	1943	J. Pediat. 23:516 (Dec.) Observations on Tetanus Immunization: The Dosage of Alum Precipitated Toxoid and the Use of Fluid Toxoid after Trauma
J. J. Miller J. B. Humber J. O. Dowrie	1944	J. Pediat. 24:281 (March) Immunization with Combined Diphtheria and Tetanus Toxoids (Aluminum Hydroxide Adsorbed) Containing Hemophiles Pertussis Vaccine

J. S. Mitchell 1935 Lancet 1:262 (Febr.)
Case of Tetanus Treated with Curarine

E. Neter 1942 Proc. Soc. Exper. Biol. and Med. 51:254 (Nov.) Effect of Zephiran upon Tetanus Toxins

E. Neter
D. Will 1942 Science 96:209 (Aug.)
Effects of Antimicrobial Substances of Bacterial Origin upon Bacterial Toxins

E. Neter
D. Will 1944 J. Bact. 48:261
Effects of Penicillin, Clavacin, and Streptomycin on Tetanus Toxin

C. B. Penrod
A. F. Knoll 1941 M. Rec. 153:229 (April)
Tetanus - Failure of Adequate Sulfanilamide antitoxin Therapy - Report of a Case

M. A. Perlstein
A. Weinglass 1944 Am. J. Dis. Child. 67:360 (May)
Fatal Effects of Prolonged Complete Curarization

M. M. Peshkin 1943 Am. J. Dis. Child. 65:873 (June)
Immunity to Tetanus Induced by a Third Dose of Toxoid Two Years after Basic Immunization

1944 Am. J. Dis. Child. 67:22 (Jan.)
Immunity to Tetanus Induced by a Third Dose of Toxoid Three Years after Basic Immunization

1945 Am. J. Dis. Child. 69:83
Immunity to Tetanus Induced by a Third Dose of Toxoid Four Years after Basic Immunization

H. Schaer 1934 Schweiz. Med. Wchnschr. 64:791 (Aug.)
Tetanus Prophylaxis and Serum Disease

K. Schauwecker 1933 Zentralbl. f. Chir. 60:1411 (June)
Serum Disease with Paralysis of Recurrent Laryngeal Nerve after Prophylactic Injection of Tetanus Antitoxin

H. B. Schumacker
A. Lamont 1942 Sur., Gynec., and Obst. 74:433 (Febr.)
Some Problems Concerning Active Immunization against Tetanus

G. Shwartzman	1940	Proc. Soc. Exper. Biol. and Med. 44:112 (May) Association of Tetanospasm (Toxin) with Hemoglobin in Acute Stages of Tetanus Intoxication in Guinea Pigs
R. Spaeth	1941	Arch. Int. Med. 68:1133 (Dec.) Therapy of Tetanus - Study of 276 Cases
	1942	Am. J. Nursing 42:733 (July) Tetanus
	1942	Am. J. Nursing 42:1157 (Oct.) Prophylaxis Against Tetanus
	1944	Practice of Medicine Vol. V page 25 Edited by Tice - 1923 W. F. Prior Company, Hagerstown, Maryland
H. Sprockhoff I. Ansorge	1938	Deutsche Ztschr. f. Nervenh. 147:163 Contributions to the Knowledge of Neurolog: Affections after the Treatment with Tetanu Serum
L. S. Stern	1944	Am. Rev. Soviet. Med. 1:540 (Aug.) Direct Injection of Antiserum into the Cerebrospinal Canal
E. M. Taylor	1945	J. Immunol. 50:385 (June) Production of Tetanus Toxin
H. M. Taylor	1942	Laryngoscope 52:923 (Dec.) Neurological Complications of Serum Sickne with Special Reference to the Ear
C. Tenbroeck J. Bauer	1923	J. Exper. Med. 37:479 Studies on the Relation of Tetanus Bacillu in the Digestive Tract to the Tetanus Antitoxin in the Blood
H. A. Toyne P. E. Voss	1945	M. J. Australia 1:382 Penicillin in Tetanus - Three case Reports
L. Unger	1942	Illinois M. J. 81:139 (Febr.) Tetanus Toxoid in the Prevention of Reactions in Allergic Individuals
A. L. Watkins	1942	J. A. M. A. 119:261 (May) Electromyograms in Diagnosis and Prognosis of Tetanus

G. Weber	1939	Deutsche Med. Wchnschr. 65:604 (April) Paralysis of the Plexus after Protective Injection of Tetanus Antitoxin
H. Welch G. G. Solcum R. P. Herwick	1942	J. A. M. A. 120:361 (Oct.) Tetanus from Sulfonamide Dusting Powders Development in Guinea Pigs Treated with Sulfanilamide Powder
	1942	J. A. M. A. 119:1396 Production of Tetanus in Guinea Pigs by Subcutaneous Implantation of Pellets Contaminated with Spores
R. West	1936	Lancet 1:12 (Jan.) Intravenous Curarine in Treatment of Tetanus
L. A. Yeazell W. C. Deamer	1943	Am. J. Dis. Child. 66:132 (Aug.) Response to Stimulating Injection of Tetanus Toxoid - Report of Study of Children Previously Immunized with Combined Diphtheria and Tetanus Toxoid
B. Zuger C. K. Greenwald H. Gerber	1942	J. Immunol. 44:309 Tetanus Immunization: Effectiveness of the Stimulating Dose of Toxoid under Conditions of Infection