CHAPTER XXIII

TETANUS

The word tetanus is derived from the Greek word τετανός meaning "stretched" or "under tension." The disease was known to Hippocrates who saw its effects among wounded Greeks. In the "Regimen of Acute Diseases" he devotes several chapters to its treatment and in the "Aphorisms" he states: "Such persons as are seized with tetanus die within four days, or if they pass these they recover."

The description of tetanus by Aretaeus, the Cappadocian, is unsurpassed:

"Tetanus, in all its varieties, is a spasm of an exceedingly painful nature, very swift to prove fatal, but neither easy to be removed. They are affections of the muscles and tendons about the jaws; but the illness is communicated to the whole frame, for all parts are affected sympathetically with the primary organs. There are three forms of the convolution, namely, in a straight line, backwards, and forwards. Tetanus is in a direct line, when the person labouring under the distention is stretched out straight and inflexible. The contractions forwards and backwards have their appellation from the tension and the place; for that backwards we call Opisthotonos; and that variety we call Empysochoonon in which the patient is bent forwards by the anterior nerves. For the Greek word ῥανων is applied both to a nerve, and to signify tension.

The causes of these complaints are many; for some are apt to supervene on the wound of a membrane, or of muscles, or of punctured nerves, when, for the most part, the patients die; for, 'spasm of the tendons and spine, and of the muscles connected with the jaws and cheek; for they fasten the lower jaw to the upper, so that it could not easily be separated even with levers or a wedge. But if one, by forcibly separating the teeth, pour in some liquid, the patients do not drink it but squirt it out, or retain it in the mouth, or it regurgitates by the nostrils; for the isthmus faecium is strongly compressed, and the tonsils being hard and tense, do not coalesce so as to propel that which is swallowed. The face is ruddy, and of mixed colours, the eyes almost immovable, or are rolled about with difficulty; strong feeling of suffocation; respiration bad, distraction of the arms and legs; subsitus of the muscles; the countenance variously distorted; the cheeks and lips tremulous; the jaw quivering, and the teeth rattling, and in certain rare cases even the ears are thus affected.

BLACK DEATH TO WHITE PLAGUE

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BACILLARY INTOXICATIONS

"... Opisthotonos bends the patient backward, like a bow, so that the reflected head is lodged between the shoulder blades; the throat protrudes; the jaw sometimes gapes, but in some rare cases it is fixed in the upper one; respiration stertorous; the belly and chest prominent, and in these there is usually incontinence of urine; the abdomen stretched; and, resonant if tapped; the arms strongly bent back in a state of extension; the legs and thighs are bent together, for the legs are bent in the opposite direction to the hams.

"But if they are bent forwards, they are protuberant at the back, the loins being extruded in a line with the back, the whole of the spine being straight; the vertex prone, the head inclining towards the chest; the lower jaw fixed upon the breast bone; the hands clasped together, the lower extremities extended; pains intense; the voice altogether dolorous; they groan, making deep moaning. Should the mischief seize the chest and the respiratory organs, it readily frees the patient from life; a blessing this, to himself, as being a deliverance from pains, distorsion, and deformity; and a contingency less to be lamented by the spectators, were he a son or a father. But should the powers of life still stand out, the respiration, although bad, being still prolonged, the patient is not only bent up into an arch but rolled together like a ball, so that the head rests upon the knees, while the legs are bent forwards, so as to convey the impression of the articulation of the knee being dislocated backwards.

"An inhuman calamity! an unseemly sight! a spectacle painful even to the beholder! an incurable malady! owing to the distortion, not to be recognized by the dearest friends; and hence the prayer of the spectators, which formerly would have been reckoned not pious, now becomes good, that the patient may depart from life, as being a deliverance from the pains and unceasing evils attendant on it. But neither can the physician, though present and looking on, furnish any assistance, as regards life, relief from pain or from deformity. For if he should wish to straighten the limbs, he can only do so by cutting and breaking those of a living man. With them, then, who are overpowered by the disease, he can merely sympathize.

The mortality rate was from 85 to 100 per cent.

This is the great misfortune of the physician." 1

Tetanus has not had a profound effect on the destiny of mankind. It has not killed kings, popes, cardinals or generals. Contrary to general belief it is not primarily a war disease, but one which claimed its greatest number of victims among women and children. Remember the remark of Aretaeus "and women also suffer from this disease after abortion."

It is a popular belief that among primitive people childbirth is a simple physiologic function attended with little danger. Tales are told of Indians on the march whose women drop out of line, give birth to a child and, a few hours later, catch up with the column, none the worse for the experience. The ancient Greeks, of course, could hardly be regarded as primitive, although the term Spartan

Tetanus is not primarily a war disease.


TETANUS

has come to mean one incur by hardship. The hygienic conditions of their lying-in rooms, however, were probably much like those of more modern times in the prebacteriologic era, that is to say, only slightly superior to those of primitive people. Until the doctrines of Oliver Wendell Holmes and Ignaz Philipp Semmelweis received general acceptance in the latter half of the nineteenth century, puerperal sepsis caused a frightful mortality in all countries. Puerperal infections were generally caused by the streptococcus, but the tetanus bacillus nevertheless contributed its share. Among the poor and dirty hovels in which women gave birth to children under the guidance of ignorant and dirty midwives, tetanus puerperarum was a frequent visitor. The raw surface left by detachment of the placenta, the presence of clots and of pieces of membrane, and lacerations of the cervix and perineum, offered ideal sites for growth of the tetanus bacillus introduced by the woman herself, or by meddling attendants. Childbirth therefore is not a simple physiologic function, but is attended with grave danger of all sorts of infection in the presence of insanitary conditions. It is more nearly a physiologic process at present under the conditions of modern obstetric practice than it ever was in the past.

The uterus is protected by its location to some degree from accidental access of filth, but not so the umbilical stump of the newborn baby, which is in a position subject to soiling and infection. One observer of conditions among the Negroes of Tennessee before the Civil War described them as follows:

"When called to see their children we find their clothes wet around their hips, and often up to their armpits, with urine. The child is thus presented to us, when, on examination, we find the umbilical dressing not only wet with urine, but soiled likewise with feces, freely giving off an offensive urinous and fecal odor combined at times with a gangrenous fetor, arising from the decomposition, not desiccation of the cord."

Conditions such as these resulted in a high mortality rate from tetanus neonatorum in the South, the West Indies, Senegambia, the Sudan, the Gold Coast, the Cape and other areas in which Negroes predominated. It was common in certain parts of India, China, and in Polynesia. Of the presence of tetanus neonatorum in British Guiana it was said:

Both occur among primitive peoples.

"It is so frequent and fatal in the colonies of Essequibo and Demerara, that, at an average estimate, it kills half of the whole number of infants which are born there."

Among the Indians of Uruguay, Colombia, Venezuela and Brazil, tetanus neonatorum was as common as among the Negroes of the Caribbean islands. No doubt tetanus was just as common among earlier peoples. The foregoing is a truer picture of lying-in conditions among primitive people than the one which
makes childbirth little more than a minor annoyance. For many centuries, apparently, some mothers and many babies died of tetanus.

It might be assumed that in modern Europe, with its superior culture and its numerous hospitals and charitable organizations, such conditions could not have existed. Of course, the humanitarianism which led to the establishment of lying-in hospitals and of religious and lay nursing organizations of relatively recent origin. Even in the eighteenth century the practice of obstetrics was almost entirely in the hands of women. For a man to attend a woman in labor was curiously regarded as indecent. The effect of such obstetric care may be easily imagined. In certain years 74 per cent of all children born in the city of London died at less than 2 years of age and accounted for about half of the total death rate. English obstetrics really began with William Smellie (1667–1763), who trained a great many men in better methods. From his time on, midwives played a rôle of diminishing importance.

Those who have studied the history of obstetrics know that confinement in a lying-in hospital was often more dangerous to both mother and baby than confinement in the home. Death, in the form of puerperal sepsis, stalked from ward to ward, carrying there all too often from the dissecting room on the hands of the surgeon. Dirt, in the form of ordinary soil, was carried in from the outside and in it there lurked the spores of the tetanus bacillus. In the Great Rotunda Hospital of Dublin, of 17,609 children born from 1757 to 1782, 2,944, or 16 per cent, died of tetanus. Similar conditions obtained in Stockholm, Paris, Vienna and other hospital centers. As late as 1846, 4 per cent of all deaths in Charleston and 3.7 per cent of all deaths in New Orleans were due to tetanus of the newborn. *Tetanus neonatorum* still occurs with some frequency among the Negroes of our southern states. Hines reports 5,767 deaths from tetanus in infants under 1 month of age from 1906 to 1927 in the United States, an average of about 275 cases annually.

The former frequency of *tetanus neonatorum* focused attention on the fact that the disease almost never occurred among the well-to-do, but only among the poor; thus, in turn, attention was directed to the importance of hygiene and to the infectious nature of tetanus.

"There is, however, another point to be considered here . . . on which I should be inclined to lay special stress for the production of trismus neonatorum. I mean bad hygiene, which would set up infection in the newborn infant all the more readily that the umbilical surface offers an easy way of entrance to infective matters. Among the authorities on lockjaw in the newborn, there is but one opinion, that the disease is almost confined to the crowded and filthy dwellings of the poor, or to badly kept boundling and lying-in hospitals."  

*Tetanus* was a warm-weather disease.

The statistics of Bruce on the incidence of tetanus during the World War also showed that it was more common from April to October than during cold weather.

It is, however, as has been stated, a rare disease in the temperate zone. In the United States tetanus caused 1,226 deaths in 1934 and 1,057 in 1935. From 1915 to 1924 the mean annual number of deaths of civilians from tetanus in England and Wales was 157.7 (Topley and Wilson).
Modern History:

The modern concept of tetanus started with the experimental observations of two Italians, Carle and Rattone, in 1884. They studied a patient who died of typical tetanus after scratching an acne pustule under the chin. Within two hours after his death, matter obtained from the wound was injected into a series of twelve rabbits. In four the material was injected into the sciatic sheath; in six, it was injected into the muscles of the back; and in two, into the spinal canal. All but one died of tetanus. Material obtained from the dead animals was injected into four more rabbits. Two which were injected with sciatic nerve emulsion died, whereas two which were injected with blood of the dead rabbits remained well. No tetanus-like symptoms were obtained from eight rabbits injected with ordinary septic material. This was the first recorded transfer of the disease.

In the same year, 1884, Arthur Nicolaier, who was working at Flügge's Hygienic Institute at Göttingen, injected garden soil under the skin at the root of the tail of house mice, rabbits, guinea pigs, and dogs. With the exception of the dogs, all the animals developed typical symptoms of tetanus. Examination of the local inflammatory exudate showed cocci and various bacilli. Histologic section of the local lesions showed similar bacilli without invasive tendencies. Nicolaier was only partly successful in obtaining pure cultures in the depth of a blood-serum medium at body temperature. Such cultures produced tetanus. Nicolaier showed that tetanogenic soil was unable to produce tetanus after it was subjected to a temperature of 100°C for one hour. Of eighteen samples taken from different places he was able to show that earth from certain particular sources, and only in the upper layers of soil, was able to produce lockjaw. He observed that the bacilli were not disseminated throughout the body of inoculated animals, and concluded that death was caused by a strychnine-like poison elaborated by the bacilli.

In 1886-87, another surgeon in Göttingen, J. Rosenbach, inoculated guinea pigs with particles of tissue taken from a case of frost bite. He successfully transmitted disease through many generations of guinea pigs and mice. Although he was not able to produce pure cultures, he observed the "drum stick" appearance of the bacilli. In 1886, Flügge described the terminal oval spores of the bacillus. In 1887, Nocard and Shakespeare separately demonstrated tetanus in horses; and in 1889, Shibaura Kitasato, then a young man working in the Hygienic Institute of the University of Berlin, allowed his contaminated cultures to grow for several days until spores formed. He recognized their anaerobic qualities. He therefore purified this tetanogenic mixture by placing it in a water bath at 80°C for thirty minutes to one hour in order to kill the more labile bacteria. Gelatin and agar plates were then inoculated and incubated in a special apparatus under an atmosphere of hydrogen. Under these anaerobic conditions the unheated spores germinated. The pure cultures thus obtained produced typical tetanus in animals. But, since the organism could not be recovered from the blood, or from any part of the experimental animal other than at the point of inoculation, he also deduced the presence of a potent toxin as the cause of symptoms.

In 1890, K. Faber reproduced the disease with cultures filtered free from gross materials and demonstrated the toxic nature of the culture.

During the same year (1890), Kitasato and Behring demonstrated the toxic nature of culture filtrates and showed that rabbits could be immunized by the injection of successive small doses of toxin. The serum of immunized, but not of normal, animals was found to have the power of neutralizing the toxin both in vitro and in vivo. The significance of this momentous discovery has been discussed in the section on diphtheria.

Bruschettini, in 1891, demonstrated the presence of toxins in the central and peripheral nervous systems. Up to this time it was known that the disease was produced by specific organisms generated in the wound region but the path by which the toxins traveled remained obscure and, up to the present time, has not been perfectly elucidated.

Etiology:

The etiologic agent of tetanus is Clostridium tetani. It is a motile, spore-bearing, gram-positive, obligate anaerobe which exists in animal-fertilized soil and in the intestinal tract of man, horses, cattle, hogs and birds. When isolated in pure culture and examined before twenty-four hours old, Cl. tetani is seen as a bacillary form, 0.5 to 0.6 micron wide and often several microns in length. In young cultures the ends may be rounded but no spores can be distinguished. Within two to ten days, depending on the conditions of cultivation, oval or spherical spores develop at one end, giving the bacillus the "drum stick" appearance described by Rosenbach. As the spore matures, the body of the bacillus undergoes degenerative changes and loses its staining characteristics. It grows best at a temperature of 37°C, grows slowly at lower temperatures, and fails to grow at temperatures below 14°C. Growth occurs in media with a pH ranging from 5.0 to 8.5 in the absence of oxygen. The optimum tension of oxygen is below 10 mm. Hg; no growth occurs if the tension is above 15 mm. Hg. Spores, however, are not destroyed by a higher oxygen tension.

Growth of the tetanus bacillus in broth is visible within twenty-four hours and continues from seven to fourteen days, causing turbidity and imparting a "cheesy" odor. After a few days broth filtrates become highly toxic.

In gelatin and agar stab cultures, growth first becomes visible about the center...
of the stab. From the central stem growth radiates in all directions, the radial lines becoming shorter toward the bottom of the stab.

Biochemical characteristics

Gelatin is liquefied after four to seven days but coagulated serum does not undergo liquefaction. The organism hemolyzes red blood cells. It produces indol in media containing tryptophan. It ferments none of the sugars.

Several variants have been described. Some of these are morphologically typical, but do not produce toxin. Others are morphologically atypical, but produce toxin. Some strains are nonmotile. By means of agglutination tests several distinct strains can be identified, but no differences exist in the toxin produced.

Therefore, antitoxin produced in response to the injection of toxin from one strain neutralizes the toxins of all strains. In this respect the tetanus bacillus and the diphtheria bacillus are alike, and differ from the bacillus of botulism.

The vegetative form is destroyed by heat and by chemicals as easily as other bacteria, but the spores are extremely resistant. Spores can resist boiling but are destroyed in the autoclave at a temperature of 115°C. maintained for fifteen or twenty minutes. Exposed to direct sunlight, spores survive for eighteen days; but when protected, as in soil, they may live for years. Resistance of the spores to sunlight and drying means that they may survive in street dust and thus be blown about by the wind. From two steel nails dipped into a tetanus culture in 1891, a growth of virulent organisms was obtained from one in 1902 and from the other in 1909. The resistance of spores renders the use of ordinary wound antiseptics useless. As shown by Corbitt, spores can survive for two weeks immersed in ether.

Resistance

Tetanus toxin is more poisonous than strychnine.

When precipitated by ammonium sulfate and dried in vacuo, it can be heated to 120°C. without loss of toxicity. It is destroyed also by air and sunlight, and by both organic and inorganic chemicals. Thus it is destroyed by acids, alkalies, soaps, and even by certain enzymes such as ptyalin and trypsin, but not by pepsin alone. Its oxidation by air and light is said to be hastened by the addition of photodynamic substances such as eosin.

It may be absorbed without destruction by a great number of substances such as kaolin, alumina, barium sulfate, or charcoal, and by tissues and tissue extracts. When neutralized by tissues it can again be released by extraction methods.

Toxin:

Toxin begins to form in broth cultures within twenty-four hours and increases in amount up to ten days or two weeks. The composition of tetanus toxin is unknown, since chemical methods of analysis result in its destruction. It is readily destroyed by boiling and by temperatures of from 50°C. to 70°C. maintained for a couple of hours.

As with the toxin of the diphtheria bacillus, tetanus toxin is detoxicated without loss of antigenic power by 0.5 per cent formalin for fifteen days at 36°C. forming tetanus anatoxin or toxoid.

Although the chemical formula of tetanus toxin is unknown, on the basis of biologic tests it can be regarded as consisting of two fractions. One of these is a hematoxin (tetanolysin) which is slightly less stable than the other, a neurotoxin (tetanospasmin).

A specific antitoxin can be produced for each fraction. But since tetanolysin is of little pathogenic importance, the term tetanus toxin is generally used with reference to tetanospasmin, the fraction responsible for all the clinical phenomena of the disease. Some strains of Cl. tetani produce only tetanolysin, some only tetanospasmin, some both and some neither.

Pathogenesis of Tetanus:

Tetanus can be induced in susceptible animals either by inoculation with living cultures or by administration of sterile broth filtrates containing the toxin. Among larger animals the horse is most susceptible. The hog is also susceptible, as are cattle to a lesser degree. In certain parts of the world the economic loss caused by the death of valuable horses following accidental wounds or following castration, tail-docking, and other operations has been appreciable and has led to the adoption of prophylactic immunization. Similarly, the castration of boars in certain localities has resulted in the death of from 10 to 15 per cent of animals operated on. In bull calves, however, castration is much less likely to result in tetanus than in the case of horses and hogs. Among small animals, the mouse, guinea pig and rabbit are susceptible, and are therefore used for experimental work. It is significant that the spores of the tetanus bacillus can be recovered from the stools of all these animals in a high percentage of cases, indicating that the mere presence of the organism in the intestinal tract does not confer immunity. Bauer and Meyer found that 24.1 per cent of 530 specimens of human stools contained tetanus spores.

Man, apes, and monkeys are highly susceptible; cats and dogs are resistant; birds and “cold-blooded” animals, such as tortoises and alligators, are totally immune.

Toxin combines with nerve tissue of susceptible animals.

It would seem that birds and turtles do not develop the clinical symptoms of tetanus following administration of the toxin because their nerve tissue shows no affinity for union with the toxin. On the other hand, the brain and spinal cord of susceptible animals show a marked capacity for binding toxin. If toxin be well mixed with rabbit or guinea pig brain, the resultant
mixture can be introduced into susceptible animals without inducing symptoms. The liver, spleen, kidneys, lungs, and bone marrow of susceptible animals have only a slight capacity for binding toxin. The union of toxin and brain tissue is firm, but separation can be effected without destruction of the toxin. The union of brain tissue and toxin resembles adsorption or a physical combination which can be broken by disintegration of the nerve cells. That susceptibility is related to the capacity of the nerve cells of a given species to combine with toxin, is indicated by the length of time during which toxin can be recovered from the blood of animals given large amounts intravenously. In rabbits the toxin disappears from the plasma within a few hours; in hens it persists for several days. Hens are therefore not resistant because of a special capacity for destruction of toxin. In susceptible animals the affinity of nerve tissue for toxin is so great that a high antitoxic titer of the blood plasma will not protect them from the effects of an injection of toxin directly into the brain. A balanced mixture of toxin and antitoxin however can be introduced intravenously without danger, or the toxin and the neutralizing dose of antitoxin can be given separately, but simultaneously, without danger. Delay of a few hours between the introduction of toxin and the administration of antitoxin will not prevent the appearance of tetanus, even though many times the amount of antitoxin necessary for complete neutralization in vitro be given. The delay permits passage of toxin from the plasma into the tissues of the nervous system, where it becomes bound in a union from which it cannot be displaced.

Tetanus toxin administered to an animal never results in immediate signs of intoxication. If a dose several thousand times the minimum lethal dose for a given species is administered, the incubation period can be shortened a few hours but it cannot be abolished entirely. In the rabbit, the incubation period following administration of a lethal dose is about eighteen hours. Following administration of 30,000 lethal doses the incubation period is reduced to about fourteen hours. In other words, a 30,000 per cent increase in the dose of toxin results in a 22 per cent decrease in the period of incubation. Here again, tetanus toxin resembles diphtheria toxin, which also shows an incubation period. In general the period of incubation following injection is in proportion to the size of the animal. Very small animals show a short period of incubation, larger animals a longer one.

The length of the incubation period is modified also by the method of administration. The most rapid action follows injection into the brain or cord; a longer period is required when the toxin is introduced intravenously, subcutaneously, intramuscularly or into a peripheral motor or mixed nerve. When the toxin is introduced into the cerebrospinal fluid, it does not reach the nervous system directly, but passes first into the blood and thence to the nervous system.

The most natural assumption would be that toxin passes directly from the blood plasma into the tissues of the central nervous system. This theory is supported by Abel and his associates, but a large number of investigators reject it and advance a nerve-transport hypothesis, of which there are three variations. One of these is that toxin is conveyed up the nerve in the perineural lymphatics. Without exception, all lymphatics drain into lymph glands. From the glands, drainage is into either the thoracic or the right lymphatic duct, and then into the general circulation. Furthermore, there is no evidence to indicate that the central nervous system itself has a lymphatic circulation, the circulation of cerebrospinal fluid taking its place.

The second variation of the neural-transport theory is that the toxin ascends the nerve in the tissue spaces by diffusion instead of in the lymphatic current. This theory can also be dismissed, since the tissue spaces are in close relation to venules capillaries in the nerve and are also in communication with the cerebrospinal fluid in the subarachnoid space. As is well known, the cerebrospinal fluid, like the lymph, drains into the venous circulation; therefore, when toxin is injected directly into the subarachnoid space, it does not pass into the brain and consequently does not cause any acceleration in the onset of symptoms.

The third variation of the neural-transport theory is that toxin is absorbed from the blood by the motor nerve endings, thence it passes up the axis-cylinder to the cells in the anterior grey matter of the spinal cord. This theory has many adherents and has been presented by Ransom as follows:

"When tetanus toxin is injected subcutaneously it begins at once to pass from the lymph spaces into the lymph vessels and can, after a few minutes, be recognized in the lymph of the thoracic duct. By this route it reaches the blood stream, not much being taken up by the blood-vessels direct from the seat of injection. The distribution then goes on till, in about 24 hours, the lymph and blood contain per cubic centimetre about the same amount of toxin. If the toxin is given intravenously it soon begins to pass into the lymph, and again after some 24 hours the thoracic lymph and blood serum contain per cubic centimetre nearly equal quantities of toxin. Neither after subcutaneous nor after intravenous injections can toxin be detected in the cerebrospinal fluid, not even when very large doses of toxin far exceeding the minimal lethal dose have been given. If by means of lumbar puncture the toxin is injected into the subarachnoid space without injury to the pia or cord it passes rapidly into the blood stream, and after the usual period of incubation general tetanus ensues. If, however, the toxin is injected intravenously and immediately afterwards the spinal cord is injured by the injection of a drop of normal salt solution, the general tetanus which ensues is preceded by a local tetanus corresponding to the injured cells, and the period of incubation is greatly shortened. If an animal is first protected by the..."
administration of a large dose of antitoxin so that no free toxin can exist in the blood, and then a small dose of toxin is injected into a motor nerve, a local tetanus corresponding to the distribution of the injected nerve results. Injection of toxin into a purely sensory nerve does not cause either local or general tetanus.

"From these and other facts we have drawn the conclusion that the transport of toxin to the central nervous system takes place along the motor nerves. The cells of the central nervous system do not pick up the toxin from the blood or the lymph; the only route by which cells can be attacked is via the motor nerves. Under this condition the motor nerves of the infected area are at an advantage, and the toxin traveling along them reaches their centers before the rest of the toxin, which has first to be absorbed and distributed, has time to be effective. The consequence is that, other things being equal, the first symptoms of tetanus occur in the area supplied by the motor nerves about the point of injection—a local tetanus arises."

The facts as advanced by Ransom, however, are subject to other interpretations. Ransom shows that toxin concentration in the blood and lymph becomes equalized, irrespective of the method of administration. This can only mean that upon intravenous administration it passes from the blood stream into the tissue spaces and thence to the lymph of the thoracic duct; also that the process continues until equalization between blood, lymph, and tissue spaces has been attained. That it is not found in the cerebrospinal fluid does not disprove this assumption, since cerebrospinal fluid is not a mere transudate. Many substances normally present in blood plasma are absent from cerebrospinal fluid. A barrier exists between the arterial circulation and the cerebrospinal fluid, which permits passage of certain substances in one direction only while holding back others more or less successfully. This barrier, however, may break down as a result of disease or injury. According to Ransom's own statement, transportation of toxin to the cord by way of motor nerves is not essential for the development of tetanus. All that is necessary is to break down the barrier by injuring the cord by an injection of salt solution, and tetanus ensues following intravenous administration of toxin.

Ransom stresses the fact that antitoxin given intravenously does not protect an animal from the effect of toxin injected into a motor nerve. The injection of antitoxin intravenously induces humoral immunity. Cellular immunity, however, is dependent on the chemical composition of the cells, which determines their affinity for substances normally present or artificially introduced into the blood plasma, and on the size of the molecules of these substances, which determines their capacity for diffusion through membranes. It does not follow, therefore, that the cells of the nervous system will be immune merely because immune bodies are present in the plasma. The injection of a motor nerve in an immunized animal, resulting in the development of local tetanus, merely shows that the nerve did not contain enough antitoxin (if any) to neutralize the amount of toxin injected into it. Although it suggests the possibility it certainly does not prove that toxin ascended the nerve to the cord. Ransom also points out that

animals can be grouped in three classes according to the sequence of symptoms induced by the toxin.

After subcutaneous or intramuscular injections, guinea pigs and mice develop a focal reaction consisting of tonic rigidity of the muscles in the immediate neighborhood of the injection. This precedes general symptoms. With intravenous injection, however, the first reaction is tetanic rigidity, usually being spasm of the jaw and neck muscles.

In man and in the horse the first symptoms involve the jaw and neck muscles, and in the horse the tail muscles as well, regardless of the site of the injection.

In the frog and in fowls the symptoms do not affect specific nerves or muscles, but involve the general musculature from the outset.

It is significant that Ransom's grouping of animals according to the initial symptoms following administration of toxin, conforms to the grouping according to susceptibility: man and the horse being most susceptible; the guinea pig and mouse are less susceptible, while the frog and hen are least susceptible.

Just as there are varying degrees of susceptibility to tetanus toxin between different species of animals, and just as there is an evident selectivity of toxin for the motor cells of all animals in preference to the cells governing transmission of common and special sensations, so there may be in some animals a heightened susceptibility of certain groups of motor cells as compared to others. Thus the motor cells of the trigeminal and facial nerves may be more susceptible to the effects of tetanus than the motor cells of the brachial and lumbar nerves. The tendency of tetanus toxin to induce spasm in muscles with short motor nerves could thus be explained without the assumption of transport in the axis-cylinder. It is significant that spasm of the ocular muscles, which also have short motor nerves, is never emphasized as a major sign of tetanus, although it sometimes occurs. The muscles involved early are those concerned with mastication and deglutition, governed by cells in the medulla and the lower part of the pons. Diseases of the central nervous system offer numerous illustrations of selectivity of pathologic processes, as in pernicious anemia, poisoning by arsenic, lead, diphtheria, nerve, or botulism, or infections such as poliomyelitis, encephalitis, and syphilis.

That neither tetanus dolorosus nor cerebral tetanus occurs following intravenous injection of tetanus toxin, may also be explained on the basis of selectivity, while neither can be explained on the basis of transportation of toxin in the axis-cylinder of a motor nerve. While they have no clinical counterparts, the conditions induced experimentally by the injection of toxin into the dorsal spinal roots or into the cerebrum are of interest.

If tetanus toxin be injected into a dorsal spinal root, the symptoms are exclusively sensory. The animal shows symptoms of hyperesthesia and finally of extreme pain in the region supplied by the injected root; but muscular spasms do
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*Tetanus dolorosus* does not occur, apparently because the toxin is bound by the nerve tissue into which it is injected and therefore cannot diffuse into the motor cell columns. Section of the root does not relieve the pain. However, when toxin is injected into a peripheral sensory nerve, no symptoms appear until the toxin is absorbed into the general circulation; then the spasms of general tetanus appear.

When tetanus toxin is introduced directly into the brain of a rabbit, it causes symptoms in eight to twelve hours, even though the animal has previously been immunized. These symptoms of so-called cerebral tetanus are of a nature never seen upon intravenous injection. They consist of restlessness and running about in a wild, clumsy and disoriented manner. The animal bungs into objects, dashes against its cage, and finally dies in convulsions, but at no time is muscular rigidity seen. Similar phenomena are observed in rats and guinea pigs, but with less regularity.

These two conditions illustrate the affinity of the nerve tissue of susceptible animals for tetanus toxin, even in the presence of humoral immunity, when the two substances are brought into intimate contact. They also indicate that its effect is primarily one of stimulation.

Under natural conditions, functionally related groups of cells vary in susceptibility. Variation in susceptibility and the presence of a barrier between the arterial blood and the cells of the nervous system explain many of the former objections to the theory of distribution of tetanus toxin by way of the blood. On the basis of very careful experimental work, Abel and his associates have come to the conclusion that the theory of carriage of tetanus toxin to the central nervous system by way of the peripheral nerves is no longer tenable; and that instead of this poison reaching the central nervous system, it can do so only by being brought to it by arterial blood. The occurrence of local tetanus has been one of the main supports of the nerve transport theory. Abel, however, finds that tetanus toxin acts directly on voluntary muscles whose motor nerve terminals are intact, and that the action of the toxin is as strictly peripheral as is that of curare. If future research confirms a local muscular, as well as a specific central, effect, the theory of nerve transport of toxin will have to be completely abandoned. In the meantime, it should be regarded as one of the possibilities.

Unlike the toxin of diphtheria, the toxin of tetanus does not cause organic changes in the central nervous system fairly chargeable to a direct effect. The changes observed following administration of lethal doses to animals are nonspecific and consist of minute hemorrhagic areas and chromatolysis of the pyramidal cells; they are of a nature that could equally well be caused by anything capable of producing similar interference with physiologic functions. The toxin of tetanus, however, resembles that of diphtheria: with sublethal doses complete restitution to normal occurs. Despite its profound effect in inducing a state of hyperexcitability in motor nerve cells, it does not destroy them. A temporary paralysis of the facial nerve is occasionally seen as a complication of tetanus originating from wounds of the head, but with this one exception paralysis is rarely observed. An increased toxicity amounting to rigidity may persist for weeks or months, but eventual complete recovery is the rule with cessation of the stage of spasms and general convulsions.

To cause any effect, tetanus toxin must be introduced parenterally. With the exception of botulin, bacterial toxins (including those of tetanus and diphtheria) are practically harmless when given by mouth. This is also true of living cultures of the tetanus bacillus. Tetanus toxin, if absorbed at all by a normal mucous membrane, is rendered inert, or destroyed before absorption occurs, by enzymes and chemical substances in the stomach and bowel. It has been shown that proteins, such as egg albumin, can be absorbed unchanged from ulcerated mucous membranes. Conceivably the same thing might occur with tetanus toxin. This view is supported by experiments on mice, which succumb following oral administration of toxin if the intestinal mucosa has previously been injured.

It has been shown that all the constitutional effects of tetanus can be induced by the parenteral administration of tetanus. Natural tetanus, however, is due to the effects of tetanus toxin produced by tetanus bacilli growing in the tissues. In order that tetanus bacilli may survive, grow, and elaborate toxin, certain conditions must be fulfilled. It is not sufficient for the development of tetanus that spores merely gain entrance to a traumatized area of tissue. Tulloch and others have repeatedly isolated virulent bacilli from wounds of patients who at no time presented symptoms of tetanus. Spores washed free of toxin can be inoculated into experimental animals with impunity, if care be taken not to destroy the local resistance of the tissues (Vaillard and Vincent, 1891). The tetanus bacillus is therefore a saprophyte capable of growing only where tissues are dead or dying; it does not grow in normal circulating blood, hence there is no such thing as tetanus septicemia, except perhaps occasionally as a terminal event. The spores, however, are highly resistant; although conditions in normal tissues are unfavorable for their germination, they need not result in death of the organism. That spores can be recovered from wounds, in the absence of signs of tetanus, is a fact of as evidence. Another proof is that typical tetanus may develop when normal tissues which have been inoculated with washed spores are subsequently injured. Tetanus may also occur months or years after an initial wound has healed as the result of secondary trauma.

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Tissues at a distance from the original site of inoculation may become infected by spores transported by wandering phagocytes. Thus it has been observed that the injection of calcium chloride into one leg of an animal and of spores into one of the other legs results in growth of the organism only at the
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site of the calcium injection. Since viable spores have been found in lymph glands, in the liver, the spleen and in other tissues, without being present in the blood stream, it would appear that they must be transported to distant points by phagocytes, there to await conditions suitable for their germination or eventual destruction. It may be regarded, therefore, as an established fact that the saprophytic tetanus bacillus requires dead tissue in which to grow. In causing tissue injury, tetanus toxin plays an important part, for while washed spores are innocuous, spores plus toxin induce tetanus. Tetanus toxin, therefore, exerts a local tissue-debilitating effect as well as generalized constitutional effects. The local action of tetanus toxin, however, is entirely nonspecific, since the toxins of other organisms such as the Welch bacillus and the bacillus of malignant edema are equally effective. Furthermore, many chemical and physical agents such as calcium chloride, formalin, lactic acid, splinters of wood, pieces of metal or cloth, sterile earth, and many pathogenic and nonpathogenic bacteria produce local conditions favorable for growth of the tetanus bacillus, when introduced prior to, simultaneously with, or subsequent to inoculation with spores.

The great variety of substances which favor germination of spores and multiplication of the bacillus suggests interference with the normal oxidation-reduction reaction of the tissues as the mechanism that is disturbed. Under certain circumstances anything may debilitate the tissues sufficiently to bring about conditions suitable for saprophytic growth. It is not the size of a wound, therefore, that is important, but the extent to which normal tissue metabolism is disturbed. The wound need be neither large in extent nor recent in origin.

In spite of their present rarity, it is interesting to note some of the unusual conditions which have given origin to tetanus. The disease has followed the use of contaminated vaccine, bacterins, catgut, kangaroo tendon, gelatin by injection and, as a local application, diphtheria antitoxin, morphine, quinine and cocaine hypodermically. It has complicated simple varicose ulcers, frostbite, burns, intestinal obstruction, appendicitis, ringworm infections, insect bites, tooth extractions, and aseptic operations both of a primary and secondary nature. At one time it was common among children as a result of July 4th injuries. Fatal tetanus may be caused by the scratch of a pin, a sliver beneath the finger nail, or by a blister on the hand or foot. It is not even necessary that there be a wound in the ordinary sense, that is, a traumatic injury. Tetanus developed among British soldiers as a complication of trench foot. Bruce says: "One day it was found that, within a fortnight, 15 cases of tetanus originated in cases of trench foot in which no one thought that prophylactic antitoxin was necessary. The 15 cases made the surgeons open their eyes." All the predisposing causes of tetanus are in the same way, by destroying or lowering the resistance of tissues to which spores have access.

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Injury of the tissues and the presence of spores, however, are in themselves insufficient for the genesis of tetanus. The bacillus is not only a strict saprophyte but it is also a strict anaerobe incapable of multiplication in the presence of molecular oxygen with a pressure of more than 15 mm. Hg.

At sea level the partial pressure of the atmosphere due to oxygen (20.96 per cent) is 15.825 mm. Hg. The organism therefore could not multiply on a normal mucous or cutaneous surface. Although it cannot multiply in the presence of atmospheric oxygen, it need not be buried deep in the tissues. All that is necessary is the exclusion of oxygen, and this can be effected by a thin sable, a blood clot, a layer of exudate, a coating of the wound with ointment, paraffin, collodion, adhesive tape, court plaster, picric acid coagulum, or any more or less impervious substance. Thus a nurse died of tetanus four days after sustaining a mere scratch on her forehead by contact with a rear-view automobile mirror, the scratch being treated at once with an antiseptic and sealed with collodion, which also sealed in tetanus spores and excluded oxygen.

Tetanus has also followed vaccination, the scarified area having become infected with spores which germinated because of the use of a vaccination shield. Sealing of vaccination wounds with shields is such a dangerous practice that it is everywhere condemned. In summary, tetanus develops only when viable tetanus spores are planted in dead tissue and oxygen is excluded.

The Symptoms of Tetanus:

In a minority of cases, mild prodromal symptoms consisting of irritability, headache, restlessness, and slight stiffness of the jaw or neck muscles exist for a day or two; but much more frequently the first symptom is trismus, or lockjaw. The term is appropriate because tonic spasm of the masseters becomes so extreme that opening of the mouth is impossible.

The stage of tonic spasm

When trismus was the first symptom and closure of the jaws was complete within twenty-four hours, the mortality rate in Bruce's cases was 71.4 per cent; with complete closure after twenty-four hours, 50 per cent; with incomplete closure, 24.9 per cent. Thus this symptom has both diagnostic and prognostic value.

Coincident with spasm of the masseters there is spasm of the facial and neck muscles. Spasm of the facial muscles causes wrinkling of the forehead, raising of the eyebrows, elevation of the cheeks, retraction of the corners of the mouth and protrusion of the lips, the whole giving to the face a highly characteristic malignant, derisive or sneering expression, technically termed risus sardonius. One of the muscles involved in the spasm draws out the angle of the mouth and compresses the cheek, and is normally brought into action during smiling and laughter. It is therefore known as the risorius, the name being
derived from risus, the Latin term for laughter, from which the English word risible is also derived. It is stated that the term sardonic is derived from sardone, the name of a plant found on the island of Sardinia, the juice of which causes puckering of the lips. But it is quite likely that the root of the word is more ancient; it may be derived from the Greek term σαρκός, meaning to grin like a dog.

The muscles of the back of the neck are also involved early in the course of the disease, their tonic contraction causing the head to be drawn backward. The clenched teeth, the fixed sneering expression of the face, and the rigid neck are therefore the first and most characteristic signs of tetanus.

"The muscles of the eye are sometimes, but not generally affected. When this occurs, as in Case 27, the eyeball is fixed and drawn slightly inwards, the patient being unable to direct it toward particular objects. It more commonly happens, however, that these muscles are free, the eyelids being semi-closed, as in this case the contractions of the orbicularis are unopposed by spasm in the levator palpebrarum." 4

The back muscles next become rigid.

The back muscles next become rigid. After a couple of days the anterior abdominal muscles become more rigid. Their contraction may cause a forward bowing (emprosthanos), although this is much less frequent than opisthotonos.

Finally the arms and legs become involved in the general rigidity, the hands and forearms escaping longest. Swallowing, urination, and defecation are rendered impossible by the generalized rigidity. The surface of the body is drenched with perspiration. Throughout the development of these symptoms the anxiety of the patient is intensified by retention of full consciousness. If tonic spasm of all the voluntary muscles were the only cause of suffering, tetanus would still be one of the most distressing sights, but the suffering of the patient is aggravated by the appearance of reflex clonic convulsions early in the course of the disease. All the tendon reflexes are tremendously exaggerated, and the slightest touch may precipitate a generalized muscular spasm not attended by loss of consciousness. The spasm of the muscles is attended by agonizing pain, so that attempts to increase the patient’s comfort only serve to aggravate his distress. Slight noises, attempts to furnish nourishment, to catheterize, to bathe, to cover him, or to straighten the bedding, bring on attacks of spasm. During the spasms the diaphragm and chest muscles become fixed, breathing is dyspneic, and cyanosis develops. The bronchial secretions can neither be expectorated nor swallowed. The laryngeal muscles are also frequently affected. With such inter-

4 Curling, Thomas Blizzard: Jacksonian Prize Essay on "Tetanus." 1834.

ference with the muscles of respiration it is not surprising that asphyxia should be the chief cause of death. This usually occurs on the third or fourth day of illness. Intoxication, exhaustion, and aspiration pneumonia are other common causes of death.

The temperature generally ranges between 101 and 103° F. but may be higher. There is a moderate leukocytosis of from 12,000 to 15,000. The cerebrospinal fluid is normal. The heart rate is rapid. In severe cases sleep is impossible. In mild cases it is observed that the tonic rigidity disappears completely during sleep, indicating the existence of a cerebral component and giving a clue to the treatment that should be followed.

**Head Tetanus:**

Most cases of tetanus develop as the result of wounds of the feet, legs, hands, and arms. Only about 5 per cent of the incidence of tetanus follows injuries to the face and head. Head tetanus differs from general tetanus in that it has a shorter incubation period, a more rapid course, and a higher mortality rate. The wound is often trivial, as in the case of the nurse cited. Paralysis of the facial nerve on the side of the injury is usually associated with spasm of the masticators, the larynx, the pharynx, and the esophagus. As mentioned by Curling, the ocular muscles also may be involved. Occasionally a localized hypoglossal involvement is observed.

**Local Tetanus:**

Of 23,835 cases of tetanus among British wounded during the World War, 201 were classified as local tetanus. In this series there were no deaths. Local tetanus is ordinary tetanus modified and restricted to a limited area as the result of immunization. The only muscles involved are those in the immediate vicinity of the infected wound. They become rigid; the reflexes are increased; pain proportional to the amount of spasm occurs. Local tetanus may develop weeks or months after the primary injury and is most frequently seen as a complication of osteomyelitis.

**Differential Diagnosis:**

The diagnosis of tetanus must be made on clinical evidence. Bacteriologic confirmation by anaerobic cultures from the site of injury might be required to sustain the diagnosis in court, but treatment is of little avail unless action is promptly taken. The history of injury, probable contamination of the wound with soil, the onset of increased reflexes and tonic rigidity of the jaw and neck muscles should arouse a suspicion of tetanus. Rigidity of the abdominal muscles may lead to errors in diagnosis. Other conditions requiring consideration include strychnine poisoning, rables, meningitis, hysteria, arthritis of the temporomandibular joint, and tetany.

In tetany, there is an absence of tonic rigidity of the jaw and neck. Spasms in-
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volve the hands and feet. The patient is relaxed in the absence of stimulation.

Arthritis of the temporomandibular joint is usually the result of a blow on the chin or of forcibly opening the jaws of a patient who is only partially anesthetized. It is associated with tenderness over the joint, local pain on movement of the jaw, and rigidity of the masseters; but rigidity of the neck is lacking. Pain is referred to the ear, and a point of tenderness can be detected by placing the finger in the auditory canal while the patient opens and closes the mouth.

Hysteria may simulate any disease; but careful examination, a sympathetic attitude, and the use of suggestion will usually produce symptoms foreign to the condition being considered. Thus, if sensory symptoms or paralysis are produced by suggestion, tetanus can be excluded.

Meningitis is accompanied by extreme headache, stupor or coma, rigidity of the neck, and increased pressure of the cerebrospinal fluid which contains an excess of protein and white blood cells. The spinal fluid in tetanus is normal.

Rabies resembles tetanus in the ease with which convulsions are produced, the clenching of the jaws, and the presence of laryngeal spasm; but it differs in the marked evidence of cerebral irritation. The patient is restless, agitated or maniacal, suffers from delirium, anger, or is delusional. There is hyperesthesia of the skin, and a tenacious, copious mucus issues from the mouth.

Strychnine poisoning can duplicate all the symptoms of tetanus with one exception—between the clonic convulsive seizures there is complete muscular relaxation instead of tonic rigidity.

Prognosis:

Favorable indications are: late onset, limited muscular spasm, absence of laryngeal symptoms, infrequency of clonic spasms, ability to take food and drink, ability to sleep, and a normal temperature. According to Vener, the patient with tetanus who can be kept alive for nine days has at least a 90 per cent chance of recovery. Anders, in an earlier series of cases, gives the mortality rate for patients surviving beyond the tenth day as 30 per cent.

Acute tetanus developing within ten days of injury is accompanied by a mortality rate of over 75 per cent; if it develops more than fifteen days after injury, the rate falls rapidly, and in certain series of cases has been less than 10 per cent.

Prophylaxis:

The fundamental principles governing the pathogenesis of tetanus have been known for many decades. Despite this knowledge, methods of prevention prior to the World War were very inadequate. Too much reliance was placed on the protection afforded by antitoxin; insufficient attention was given to the fact that effective passive immunity rarely lasts longer than a week; wounds were often cauterized or flooded with antiseptics in futile attempts to destroy tetanus spores.

Since the World War, however, there has been a distinct improvement in the application of preventive measures. It is now recognized that primary care of the wound is the most important prophylactic measure, and that the administration of large amounts of antitoxin will not compensate for faulty surgical care.

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Care of the Wound:

In the treatment of a wound in which the objective is the prevention of tetanus, one should aim toward the removal of dirt and foreign bodies. To prevent further contamination, the wound should be covered at once with several thick pads of sterile gauze. There should be no preliminary investigation; fingers, dressings, gauze, antiseptics and instruments should be kept out of the wound. After the surface has been protected from further contamination by the application of sterile gauze, a wide area of surrounding skin should be scrubbed with soap and water until the last vestige of dirt has been removed. Effective cleansing may require shaving of the hair and the use of grease solvents such as benzine or ether. After the surrounding area of skin has been thoroughly cleansed, the protective pads over the wound may be removed. Gross dirt and foreign bodies should be lifted, not wiped, from the surface of the wound and sent to the bacteriologic laboratory for cultural examination. If possible, the tissues affected should be excised en bloc. If this is not possible, the surface of the wound should be irrigated with sterile water. The deeper recesses of the wound should be protected from further contamination by placing the injured part on a vertical plane, if possible, and by avoiding the use of water under pressure, since irrigation may wash dirt into the deeper recesses, if the wound is kept in a horizontal position. Loose particles of dirt should be floated instead of forced away.

Blood clots and adherent particles of dirt may then be removed by gentle friction with pledgets of cotton moistened with liquid soap, irrigating the area from time to time with sterile water. The surface of the wound may then be inspected.

Dead, mutilated tissue should be removed and rough uneven edges should be trimmed back to normal tissue. The deeper portions of the wound may now be investigated and cleansed, enlarging the opening as necessary to permit removal of all dirt, foreign bodies and dead tissue. Under this treatment, properly performed, most tetanus spores will be removed from the wound and such as are missed will be unable to germinate in the presence of normal healthy tissue. Tetanus spores have many times the resistance of animal cells to antiseptic chemicals. It is therefore sheer nonsense to introduce ether, iodine, phenol, peroxide of hydrogen, or any other chemical substance into the wound. To do so may actually predispose to the development of tetanus by debilitating healthy tissues so laboriously exposed. If it is possible to do so, severed nerves and tendons should be sutured, and all "dead spaces" in the depths of the wound obliterated. No pockets in which serum may collect should be permitted to remain. If the size of the wound renders the coaptation of healthy tissues an impossible task, Carrel-Dakin tubes should be inserted, but gauze, simple wick, and rubber tube drains should be avoided. In the Carrel-Dakin treatment of infected
wounds, freshly prepared sodium hypochlorite solutions of from 0.45 to not more than 0.50 per cent strength are carried to the deepest pockets through rubber tubes with numerous lateral openings. Irrigation may be continuous or intermittent. If Dakin's solution is used continuously in full strength, the skin will require protection by vaseline. Dakin's solution dissolves sloughing tissue, but is more irritating than the more stable and practically nontoxic chloramine-T used in a 1 or 2 per cent strength. Chloramine-T is soluble in water, but dichloramine-T is soluble only in oils. Neither chloramine nor dichloramine exerts the strong solvent action of Dakin's solution on necrotic tissue; but being less irritating to the skin they are often preferred. Although Dakin's solution is irritating to the skin and destructive to the peritoneum, it does not interfere with wound-healing, being practically harmless to subcutaneous tissues. The great advantage of these compounds over ordinary antiseptics resides in their solvent action on exudates and necrotic tissue. Azo-chloramide is also frequently used as a substitute for Dakin's solution. When none of these preparations is available, hydrogen peroxide may be used.

The wound is finally covered with a layer of coarse mesh paraffin gauze and several thicknesses of ordinary sterile surgical gauze. The coarse-mesh paraffin gauze prevents adhesion of dry surgical gauze to the wound surface. During the lengthy primary care of the wound a general anesthetic is required. Local anesthesia should be avoided in the treatment of wounds in which tetanus is feared.

Subsequent care of the wound involves frequent changes of dressings and inspection for evidence of further necrosis.

Not all wounds require such meticulous attention. Deep puncture wounds, wounds associated with contusion and crushing of soft tissue, and compound fractures are particularly dangerous. Simple incised wounds made with a sharp cutting instrument are least dangerous. The presence in the wound of any sort of foreign body greatly augments the hazard of tetanus. The danger is further increased when the injury is sustained during warm weather. According to statistical studies by Wainwright, certain occupations are almost exempt. Industrial injuries account for only about 20 per cent of the incidence of tetanus, the larger number following street accidents, farm injuries, and stab and gunshot wounds. Children, farmers, hostlers, soldiers, automobile mechanics, and others particularly subject to injury and contact with street dirt or garden soil furnish most of the cases. Children under 15 years of age constitute about 30 per cent of the population, but 50 per cent of the deaths from tetanus are in this group. For these reasons, active immunization of these groups is now advocated.

Active Immunization with Tetanus Toxoid:

Active immunization with tetanus toxoid is now obligatory in the French army. In certain children's institutions combined active immunization for diphtheria and tetanus is a routine procedure. Immunity is established slowly, but a person previously immunized responds to a subsequent dose of toxoid with a rapid increase of antitoxin to a high level. Thus, increases of 6 to 200 times the previous level have been observed, so that the majority of cases show from 1 to 2 units of antitoxin per cubic centimeter of plasma. This is a greater concentration than can be maintained for a week by passive immunization with a prophylactic dose of antitoxin. A patient who has been immunized, and who subsequently sustains an ordinary injury, may safely be given another dose of toxoid instead of a prophylactic dose of antitoxin. Unfortunately there is as yet no effective skin test indicating the degree of immunity. For this reason, immediate passive immunization by the administration of 1,500–3,000 units of tetanus antitoxin or combined tetanus and gas gangrene antitoxin is advised when the nature of the injury or the degree of contamination inordinately increases the risk of tetanus. A dose of toxoid may also be given at the same time, in order to induce a more durable immunity, and to render subsequent doses of antitoxin unnecessary. Active immunization of pregnant women in areas where puerperal and infantile tetanus occurs, has been suggested. The subject of active immunization has recently been studied by Boyd and by Gold. In the French army wounded soldiers, in whom development of tetanus is feared, are given a prophylactic injection of serum and 1.5 cc. of modified toxin, followed in 20 days by 2 cc. and 30 days later by a third dose.

Passive Immunization:

The indiscriminate use of tetanus antitoxin may be dangerous if it causes neglect of other important prophylactic measures. Tetanus antitoxin does not give complete protection under any and all circumstances. Protection is relative and of short duration. Whether to give or not to give antitoxin is a question of estimating the risk of tetanus as compared with the risk of an allergic reaction or of sensitizing the patient. It is well known that tetanus may follow the most trivial injuries, but in most instances it will be found that the wound was neglected or improperly treated. In any event, such occurrences make a profound impression because of their extreme rarity. There are millions of minor injuries, but only 1,200 cases of tetanus annually in the United States.

Wainwright reports that only 14 per cent of industrial surgeons use tetanus antitoxin routinely as a prophylactic. He believes its use is necessary only in wounds soiled with dirt from street, barnyard or stable. Many industrial insurance companies will not authorize the administration of tetanus antitoxin as a routine measure, regarding the cost as prohibitive compared to the risk entailed.

If indicated at all, tetanus antitoxin should be given immediately in adequate dosage and repeated every 7 days until danger is past. For protection of persons not previously actively immunized, whose injuries are ordinary, the administration of 1,500 units is suggested. At the same time 1.5 cc. of toxoid
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should be given, followed in 20 days and again at the end of 50 days by doses of 2 cc. If danger of tetanus appears minimal, toxoid alone may be used. If the wounds are deep, extensive, crushing, necrotic, or badly contaminated with soil, skin dirt, pieces of clothing, or if foreign bodies of any kind are present in the wound, twice the usual prophylactic dose of antitoxin should be given. Re-immunization is indicated when secondary operations on such patients become necessary, unless a definite active immunity has been induced by toxoid injections. The combined tetanus and gas gangrene antitoxin is gaining in use in the prophylactic treatment of compound comminuted fractures and similar injuries.

Tetanus antitoxin containing a foreign protein derived from the blood plasma of horses may cause serious allergic reactions in sensitized subjects. Tests for sensitivity, as outlined elsewhere, should therefore be conducted. Antitoxin injected subcutaneously reaches a maximum concentration in the plasma in 1 to 3 days and disappears completely in from seven to fourteen days. It is found in the milk of lactating animals, and passes through the placenta with ease, but does not pass readily into the tissue spaces of the brain.

Effect of antitoxin on incubation period. About 10 per cent of the cases given a prophylactic injection of antitoxin show an incubation period of a week; about 30 per cent develop symptoms during the second week, while in fully 30 per cent the symptoms are delayed until after the fifth week. In cases not so protected, symptoms usually appear within from 9 to 12 days.

In the first year of the World War, during which antitoxin was not in general use, the incubation period among British wounded showed an average duration of 11.8 days; in 1915 it was 27.3 days; in 1916, 34 days; in 1917, 48 days, and in 1918-19, 50 days. This prolongation of the incubation period was due to: increasing recognition of mild cases of local tetanus; more general use of antitoxin; the administration of second, third and fourth doses in grave cases; improved surgical treatment, including removal of foreign bodies and necrotic tissue; and the development of the Carrel-Dakin irrigation treatment of wounds. Tetanus antitoxin unquestionably prolongs the incubation period when it fails to protect, but it is only one of several factors responsible.

In September 1914 the incidence of tetanus per 1,000 British wounded was 0.15; in October, 31.8. After October the use of antitetanic serum became general, and the rate thereafter until the end of the war never exceeded 2.8 per 1,000 wounded. From 1914 to 1918 there were 20,832,142 war injuries among British soldiers, of which 2,858 were followed by tetanus, an incidence of 1.17 per 1,000. In the army of the United States during the World War there were only 36 cases of tetanus with 5 deaths among 224,089 wounded. The rate of 0.16 per 1,000 wounded is the lowest ever recorded for war wounds and is attributed in large part to the early general use of antitoxin.

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The value of a prophylactic dose of tetanus antitoxin in establishing a temporary passive immunity is further supported by its effect in reducing the mortality rate in cases in which it fails to prevent the disease.

Of 839 British wounded given a prophylactic injection, 203 died, a mortality rate of 24.6 per cent. Of 559 unprotected wounded, 298 died, a mortality rate of 53.3 per cent. During the American Civil War there were 505 cases of tetanus among Union soldiers, who of course were also unprotected, of which 451 or 89.3 per cent terminated fatally. It is apparent, therefore, that the use of antitoxin was not the only factor operative during the World War in reducing the mortality rate. Bruce says:

A surgically clean wound just as important as antitoxin in prevention.

"The surgeon's knife, after all is said and done, is the best means of preventing the occurrence of tetanus. It stands in the first rank as prophylactic. Dead purifying tissue is the home, the favorite environment, of the anaerobe. Place washed tetanus spores among healthy living tissues and there is nothing doing. Add a trace of gas-gangrene toxin, or a chemical irritant, such as saponin, or a physical irritant, such as earth or any foreign body, and the tetanus bacilli have their tails up at once. At the beginning of the war the treatment of wounds was not thorough enough at the primary operation. It was thought sufficient to wash out the wound and apply an antiseptic. Lately, however, the thorough excision of wounds has come more and more into vogue."

Tetanus antitoxin is marketed in syringes and vials containing 1,500 units for prophylactic injections and in vials containing larger amounts for therapeutic use.

An antitoxin serum containing antibodies specifically neutralizing the toxins of other anaerobes is also available.

Polyanaerobic antitoxin. Antitoxins for Cl. tetani (B. tetani), Cl. welchii (B. welchii or B. perfringens), and Cl. oedematis maligni (Vibrio septique) are combined and marketed in syringes and vials containing 1,500 units of tetanus antitoxin, 2,000 units of Welch bacillus antitoxin and 2,000 units of Vibrio septique antitoxin. The product is also marketed in bottles containing 10,000 units of antitoxin for each of the toxins listed, but excluding tetanus. The respective preparations are intended for prophylactic and therapeutic use. In view of the local action of the toxins of other anaerobes in favoring the germination of tetanus spores, the use of polyanaerobic antitoxin is preferable to the use of tetanus antitoxin alone for patients with badly lacerated or badly soiled wounds.

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Death in tetanus usually occurs within the first three or four days, during a convulsion, or as a result of physical exhaustion caused by constant tonic rigidity and frequent repetition of generalized spasm. Therapy should therefore be directed toward the prompt control of this symptom, since there may be no opportunity to institute other therapeutic measures unless it is controlled. In view of the case with which convulsions may be precipitated by trivial stimuli, the patient should be placed in strict seclusion in a quiet, darkened room. Attendants should avoid all unnecessary manipulation of the patient. Blood counts, hypodermatic administration of drugs, intravenous infusions, dressing of wounds, bathing, shaving, and even feeding may well be postponed until reflex excitability has been reduced. To accomplish this, use has been made of various hypnotic drugs and anesthetics including morphine, morphia and magnesium sulfate, chloral hydrate, bromides, phenobarbital, sodium amytal, ether, chloroform, alcohol, and avertin. In a well-defined case, an anesthetic is indicated, but inhalation anesthesia either may precipitate laryngeal spasm; and prolonged administration of chloroform is dangerous, because of its toxic effect on the liver. Of all the anesthetics available, avertin (tribromothyl alcohol) in amylene hydrate appears most nearly to meet the requirements. It can be given by rectal injection; it is safe in the hands of experienced persons; its action is protracted; it is rapidly detoxicated in the liver by conjugation with glycuronic acid, and it is completely eliminated in the urine. Its use in tetanus was first suggested by Läwen in 1928. Avertin in amylene hydrate is administered rectally in 2.5 per cent solution in warm distilled water at body temperature. "The ordinary maximum dose for basal anesthesia is 80 mg. of avertin (40 mg. of amylene hydrate) per kilogram of body weight."—The total amount administered should not exceed from 6 to 8 cc. of avertin with amylene hydrate for women, or from 9 to 10 cc. for men, irrespective of weight. Avertin should not be given to patients suffering from liver or kidney disease or those whose respiration is already depressed. It should not be used by an inexperienced person. If improperly given or if given in excessive amounts, it can cause death, like any other anesthetic. Beecher regards it as more dangerous than chloroform.

Relaxation having been obtained, a tube may be passed through the nostril into the stomach. The tube may be left in place for the introduction of food, fluids, and sedative drugs used to supplement or replace the avertin. By this method intravenous and subcutaneous administration of fluids and drugs can be reduced to a minimum. If the patient can be kept in a sleepy or semistuporous, but not fully narcotized, state, morphine—which must be ad-

Complete narcosis may be fatal.

TETANUS

ministered hypodermatically, and is chiefly of value in abating the agonizing pain associated with spasm—may not be required. If it is not desirable to maintain relaxation with another dose of avertin, the bromides with their mild but prolonged sedative action may be given in combination with chloral hydrate, paraldehyde or one of the derivatives of barbituric acid. The barbiturates offer a wide choice between those, on the one hand, which act with great rapidity but short duration of effect, and those, on the other hand, which have a slow but prolonged action. Care must be taken to avoid barbiturate poisoning, characterized by a thin rapid pulse, shallow respiration, abolition of corneal and deep reflexes, cyanosis, hypotension, and coma. To control barbiturate poisoning, gastric lavage should be done at once. Oxygen and carbon dioxide should be given. Diuresis should be stimulated by parenteral fluids and sucrone. Picrotoxin, the specific antidote for barbiturate poisoning, should be given intravenously at the rate of 1 cc. per minute of 1:1000 solution continued until corneal and pupillary reflexes return. Picrotoxin is a powerful convulsant drug to be used with discrimination. "The drug is known to protect animals against chloral hydrate and to revive animals in deep coma from paraldehyde and sodium bromide." If preferred to the barbiturates, morphpine in a dose of 1/2 to 1/4 gr. may be given in combination with 2 cc. of 25 per cent magnesium sulphate solution, but because of its depressant effect on respiration the use of morphine should be avoided, if possible.

Magnesium sulphate alone, when given parenterally, has a pronounced antispasmodic action. It may be given subcutaneously every six to eight hours in a dose of 1 to 2 cc. of a 25 per cent solution. Calcium is a specific antidote for magnesium. The symptoms of magnesium intoxication, consisting of complete narcosis, abolition of reflexes, and disturbances in cardiac conduction, can be instantly controlled by the intravenous injection of 5 cc. of 5 per cent calcium chloride solution.

Whatever drug or combination of drugs is used, the object should be to keep the patient as completely and constantly relaxed as is possible without complete narcosis and without endangering respiration. Provision should be made for the emergency administration of oxygen and carbon dioxide, regardless of which sedative is used.

With the patient kept constantly relaxed, antitoxic serum can be administered as often as required, without distress to the patient, and with considerably less danger of initiating a convulsion. In recent articles, more emphasis has been placed

on serum therapy than on any other measure. The administration of very large doses subcutaneously, intramuscularly, intravenously, and intraspinally has been advised. Willard J. Stone advises 30,000 units of antitoxin intravenously and 30,000 units intraspinally, and states that the most important part of the treatment of tetanus is of course the administration of the specific antitoxin. However, he reports a mortality rate of 59 per cent in a series of 93 cases, a rate which is higher than that observed among 559 unprotected British wounded of whom 298 died, a mortality rate of 53.3 per cent. Vener and associates report 128 cases with 69 deaths, or 53.9 per cent. If antitoxin is the most important measure in the treatment of tetanus, why are the results of its use so poor? In the discussion of diphtheria antitoxin, it was stated that antitoxin to be most effective should be given early, and that it is practically worthless when given after the fourth day of illness. In diphtheria the physician can make a diagnosis on the basis of objective evidence in the throat, without waiting for the appearance of symptoms due to the action of toxin on the viscera and the central nervous system. In tetanus, however, the appearance of the wound does not indicate that tetanus toxin is being formed, being absorbed into the circulation, and being bound by the motor cells of the brain and cord. The diagnosis of tetanus, therefore, cannot be made until the effects of the toxin on the nervous system become apparent. In other words, treatment of tetanus with antitoxin is never started until after the toxin has been fixed by the cells in a union which cannot be broken by antitoxin or any other substance. Antitoxin therefore cannot cure tetanus. It can only prevent further development of the disease by neutralizing toxin in the plasma and lymph, which has not become fixed by cells. By thus preventing further damage, restitution of the cells already injured to a state of normal structure and function can be effected by normal metabolie processes, if the patient can be kept alive long enough. Even when antitoxin is given in adequate dosage upon the appearance of the earliest symptom, there is an inevitable delay in its action of neutralizing any unbound toxin in the nervous system, owing to the fact that the molecules of the serum proteins to which it is attached do not easily pass through the barrier between the plasma and the brain. Enormous amounts of antitoxin may be present in the plasma and lymph, without any being present in the tissue spaces of the brain. The daily administration of 100,000 or more units, therefore, cannot compensate for the unavoidable delay in instituting treatment. Ten thousand units given at the onset of toxin production, if that were possible, would be infinitely more valuable than 100,000 units two or three days later. The 128 cases reported by Vener and associates received varying amounts of antitoxin as shown in the table on page 381.

The figures seem to indicate that no deaths should occur if 350,000 or more units of antitoxin are given. It should be noted, however, that no corrections have been made to compensate for the errors introduced by a constantly diminishing number of cases as the amount of antitoxin increases. Under the handicap in treatment, imposed by a delayed start, it is certain that some deaths will occur in a large series of cases, regardless of the amount of antitoxin given. It is also certain that some recoveries will occur even if no antitoxin be given. In pre-antitoxin days, about 10 per cent recovered. In 112 cases of tetanus treated by Yodh with from 40,000 to 400,000 units of antitoxin given intramuscularly, intravenously, subcutaneously, and by cisternal puncture, the mortality rate was 47.3 per cent. Enormous doses of antitoxin administered by all possible routes, therefore, apparently reduce the mortality rate about 43 per cent, under the conditions imposed in the treatment of clinical tetanus which includes the use of other therapeutic measures.

Intraspinal administration of antitoxin does not solve the difficulty, since the direction of flow is from arterial circulation, to tissue spaces of brain and cord, to venous circulation. Statistics both supporting and disproving the value of serum intraspinally have been published. Theoretically there is no justification for its use. Wainwright objects to its use on statistical grounds and pitily remarks that the argument for intraspinal administration is based on propinquity and not on physiology. It should be noted, however, that serum is not an inert substance, but is a foreign protein which, when injected intraspinally, conceivably may produce sufficient reaction to permit penetration of tissue spaces by diffusion. If serum is to be given intrathecally, the evidence seems to show a slight superiority of administration by cisternal puncture over the lumbar route. From a practical standpoint the results do not justify the reflex stimulation incident to the procedure. It is suggested that from 25,000 to 50,000
units be injected intramuscularly and subcutaneously in the region of the wound, and 100,000 units be given intravenously, as soon as the diagnosis is made, and that 20,000 units be given intravenously daily thereafter.

In the discussion of diphtheria, attention is directed to the beneficial effects of intravenous glucose. The method is equally applicable in tetanus. From 1 to 2 liters of 10 per cent glucose may be given slowly by intravenous drip. The diet administered by tube should contain large amounts of glucose and water. If desired, alcohol can be given continuously by rectal drip in a 5 to 10 per cent solution. Strychnine, camphor and digitalis should not be used.

The methods described aim at the neutralization or elimination of toxin and at control of the symptoms of intoxication. They have little or no effect, however, on arresting the production of toxin by the tetanus bacillus. Unless such production can be arrested, a large proportion of cases (30 to 45 per cent) will end fatally, regardless of other measures used. In the past it has been considered inadvisable to attempt major surgical procedures in the presence of active tetanus. With newer and safer methods of inducing anesthesia and controlling shock, there is less reason for this extreme conservatism. When there is the certainty of death in at least one out of every three cases of tetanus, surgical measures, which under other conditions would be considered radical, may become justified. If the wound responsible is unhealed or is infected by pyogenic cocci, it can readily be opened to its depths without great danger to the patient. Dakin tubes can then be inserted, and continuous irrigation with one of the hypochlorites instituted. In other cases a finger or a toe can be amputated. The surgical measure that should or can be instituted in late tetanus originating in healed wounds or following elective aseptic operations will depend on the clinical condition of the patient and on the nature, extent, and location of the injury. In local tetanus the mortality rate is so low that radical surgery is not indicated. In head tetanus, death occurs so early and so generally that there is little opportunity to institute effective treatment. With Arataeus, then, we must agree that in certain cases the physician, though present and looking on, cannot furnish any assistance to preserve life.