Lecture № 9

DIPHTHERIA
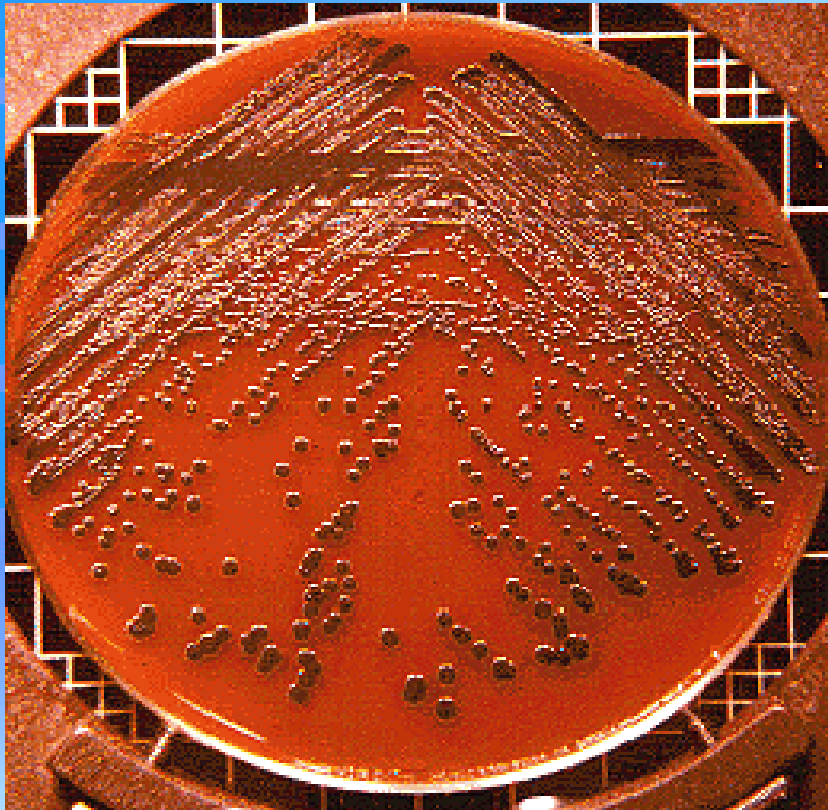# TETANUS

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Diphtheria – definition

- **Severe acute infectious disease manfested by:**
- **<u>fibrinous inflammation</u> of the throat, nose, larynx, trachea, eyes, skin, genitals and**
- **<u>specific intoxication</u> with a damage of the <u>nervous system, myocardium and kidneys.</u>**
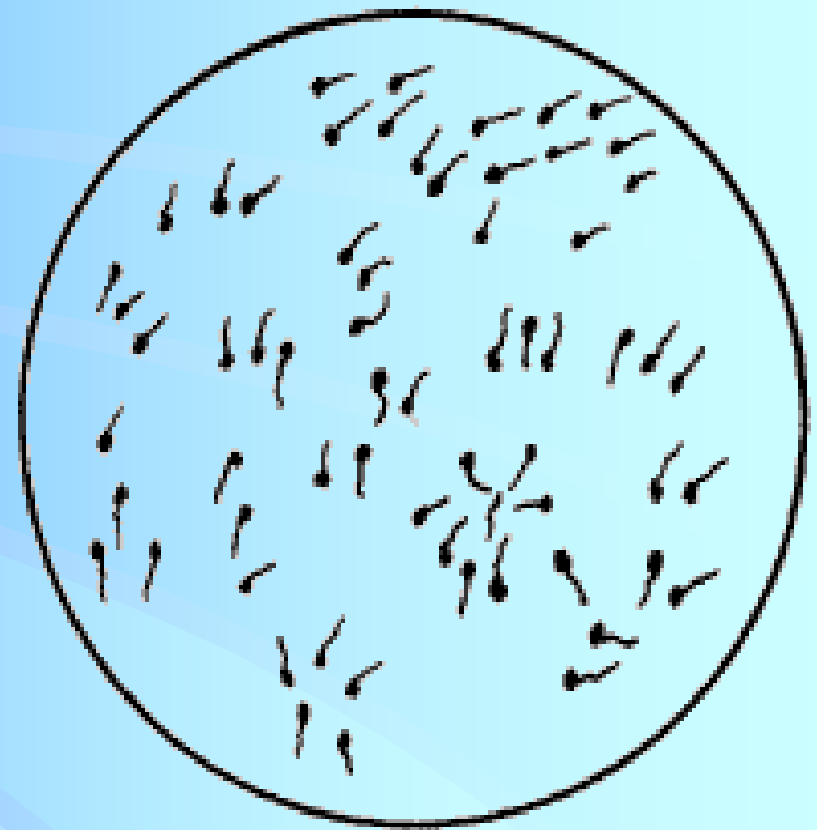
Diphtheria – etiology

- **Causative agent – Corynebacterium diphtheriae** – in shape of rods, producing a potent exotoxin. Gram (+).

Corynebacterium diphtheriae

Corynebacterium diphtheriae, mitis
Chocolate tellurite agar

Diphtheria – epidemiology

- **Source of infection – human – a case or a carrier.**
- **Anthroponosis.**
- **Rout of transmission – respiratory, seldom inhalatory or by feeding.**
- Susceptibility – high, contagious index – 10-12%.
- Sporadic diseases, rare epidemics.
- Autumn-winter seasonal peak.
- Facilitating factors – poverty, insufficient health culture, lack of immunizations.

Diphtheria – pathogenesis

- **_C. diphtheriae_ is not a very invasive organism, ordinarily remaining in the superficial layers of the respiratory mucosa and skin lesions,** where it can induce a mild inflammatory reaction in the local tissue.

- **The major virulence of _C. diphtheriae_ results from the action of its potent exotoxin,** which inhibits protein synthesis in mammalian cells but not in bacteria. The polypeptide toxin is comprised of two segments: B, which binds to specific receptors on susceptible cells, and A, the active segment. Following proteolytic cleavage of the bound molecule, segment A enters the cell, where it **catalyzes inactivation** of the transfer RNA (tRNA) translocase, "elongation factor 2", present in eukaryotic cells but not in bacteria. **Loss of this enzyme prevents the interaction of messenger RNA and tRNA, stopping further addition of amino acids to developing polypeptide chains.**

- The toxin affects all cells in the body, but **the most prominent effects are on the heart (myocarditis), nerves (demyelination), and kidneys (tubular necrosis).** Diphtheria toxin is extremely potent: a single molecule can stop protein synthesis in a cell within several hours, and 0.1 µg/kg will kill susceptible animals.

Diphtheria – pathogenesis

❖ Within the first few days of respiratory tract infection, <u>toxin elaborated locally induces a dense necrotic coagulum</u> composed of fibrin, leukocytes, erythrocytes, dead respiratory epithelial cells, and organisms. <u>Removal of this adherent gray-brown "pseudomembrane" reveals a bleeding edematous submucosa.</u>

❖ <u>The membrane can be local (tonsillar, pharyngeal, nasal), or extend widely, forming a cast of the pharynx and tracheobronchial tree.</u> The <u>underlying soft tissue edema and cervical adenitis can be intense,</u> and, particularly in the proportionally smaller airways of children, can cause <u>respiratory embarrassment and a "bull neck" appearance.</u> In both adults and children, a common cause of death is suffocation following aspiration of the membrane.

Diphtheria involving a pharyngeal tonsil. The membrane-tissue junction is clearly marked by intense cellular infiltration.

Diphtheria –
clinical manifestations

- **Incubation period** – <u>2-14 days.</u>
- <u>Clinical manifestations and respectively clinical form depend of the portal of entry.</u>
- <u>The membranes appears in all clinical forms.</u>

Diphtheria –
clinical manifestations and clinical forms

- Symptoms of infection with *C. diphtheriae* occur **locally** in the respiratory tract and skin secondary to noninvasive infection of these two organs, and **at distant sites secondary** to absorption and dissemination of diphtheria toxin. Occasionally, *C. diphtheriae* disseminates from the skin or respiratory tract and causes systemic infections including bacteremia, endocarditis, and arthritis.

- **Respiratory Tract Diphtheria**

- Asymptomatic upper respiratory tract carriage of the organism occurs commonly in areas where diphtheria is endemic and is an important reservoir for maintenance and spread of the organism in a population. However, in the developed world, throat colonization has become exceedingly rare except in individuals associated with pockets of infection such as the inner city (e.g., homeless people) and rural poverty areas.

- Following an incubation period averaging 2 to 4 days, local signs and symptoms of inflammation can develop at various sites within the respiratory tract.

- **Anterior Nasal Infection**

- Infection limited to the anterior nares presents with a serosanguineous or seropurulent nasal discharge often associated with a whitish mucosal membrane, particularly on the septum. The discharge can excite an erosive reaction on the external nares and upper lip, but symptoms generally are quite mild, and signs indicating toxin effects are rare.

Diphtheria –
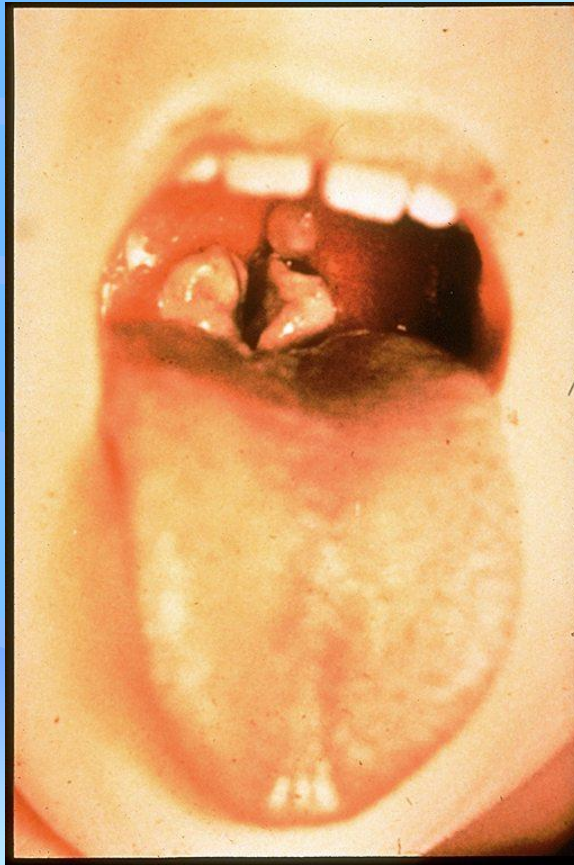# clinical manifestations and clinical forms

- **Faucial Infection**

- ❖ **Including the posterior structures of the mouth and the proximal pharynx, this area is the most common site for clinical diphtheria.** Onset is usually abrupt, with low-grade fever, malaise, sore throat, mild pharyngeal injection, and development of a membrane typically on one or both tonsils, with extension variously to involve the tonsillar pillars, uvula, soft palate, oropharynx, and nasopharynx. The membrane initially appears white and glossy, but evolves into a dirty gray color, with patches of green or black necrosis. **The extent of the membrane correlates with the severity of symptoms:** localized tonsillar disease is often mild, but involvement of the posterior pharynx, soft palate, and periglottal areas is associated with profound malaise, weakness, prostration, cervical adenopathy, and swelling. The latter can **distort the normal contour of the submental and cervical area, creating a "bull neck" appearance and causing respiratory stridor.**

Diphtheria of the throat

Diphtheria of the throat

Pharynx of a 39-year-old woman with bacteriologically confirmed diphtheria. The photograph was taken 4 days after the onset of fever, malaise, and sore throat. Hemorrhage caused by removal of the membrane by swabbing appears as a dark area on the left.

Diphtheria – toxic form

10 y/o boy with
severe diphtheria
- conjunctivitis
- pharyngeal membrane
- bull neck
- severe myocarditis
- all vaccines contraindicated

CDC

Diphtheria – toxic form

Diphtheria –
clinical manifestations and clinical forms

- **Laryngeal and Tracheobronchial Infection**

❖ Pharyngeal infection may spread downward into the larynx, or occasionally the disease may begin there. Symptoms then include **dyspnea, respiratory stridor, and a brassy cough.** Edema and membrane involving the trachea and bronchi can embarrass respiration further, and a child so afflicted will appear **anxious and cyanotic, use accessory muscles of respiration, and demonstrate inspiratory retractions of intercostal, supraclavicular, and substernal tissues.** If this state is not relieved promptly by intubation and mechanical removal of membrane, patients become exhausted and die.

❖ Systemic complications are due to diphtheria toxin, which, although toxic to all tissues, has its **most striking effects on the heart and nervous system.**

Diphtheria –
clinical manifestations and clinical forms

- **Cardiac Toxicity**

❖ Subtle evidence of myocarditis can be detected in as many as two thirds of patients, but 10% to 25% will develop clinical cardiac dysfunction, with the risk to an individual patient correlating directly with the extent and severity of local disease. **The first evidence of cardiac toxicity occurs after 1 to 2 weeks of illness, often when the local oropharyngeal disease is improving.** Changes in electrocardiograph (ECG) pattern, particularly **ST-T wave changes and first-degree heart block, can progress to more severe forms of block, atrioventricular (AV) dissociation, and other arrhythmias, which carry an ominous prognosis.** Clinically, myocarditis can present acutely with **congestive failure and circulatory collapse, or more insidiously with progressive dyspnea, weakness, diminished heart sounds, cardiac dilatation, and gallop rhythm.** Because patients without clinical evidence of myocarditis may have significant electrical changes, **it is important to monitor their cardiograms routinely. Elevations of serum AST concentration closely parallel the intensity of myocarditis, and so may be used to monitor its course!!!**

❖ From a **prognostic standpoint**, patients with ECG changes of myocarditis have a mortality rate three to four times higher than those with normal tracings. In particular, AV and left bundle branch blocks carry a mortality rate of 60% to 90%. Patients with prolonged P-R interval and minor T-wave changes generally do well, and these abnormalities ordinarily resolve with time. **Patients with bundle-branch blocks and complete AV dissociation have a much higher incidence of death, and survivors may be left with permanent conduction defects.**

Diphtheria – clinical manifestations and clinical forms

- **Neurologic Toxicity**
- ❖ This complication is also proportional to the severity of the primary infection: mild disease only occasionally produces neurotoxicity, but up to three fourths of patients with severe disease can develop neuropathy. <u>Within the first few days of disease, local paralysis of the soft palate and posterior pharyngeal wall occurs commonly, manifested by regurgitation of swallowed fluids through the nose.</u> Thereafter, **cranial neuropathies causing oculomotor and ciliary paralysis are also common, and dysfunction of facial, pharyngeal, or laryngeal nerves, although rare, can contribute to the risk of aspiration.**
- ❖ **Peripheral neuritis develops later, from 10 days to 3 months after the onset of disease in the throat.** Principally a <u>motor defect, it begins with proximal muscle groups in the extremities and extends distally,</u> affecting particularly the dorsiflexors of the feet. <u>Dysfunction varies from mild weakness with diminished tendon reflexes to total paralysis.</u> Occasionally motor nerves of the trunk, neck, and upper extremity are involved, as are sensory nerves, resulting in a glove-and-stocking neuropathy. Microscopic examination of affected nerves shows degeneration of myelin sheaths and axon cylinders. Although slow, total resolution of all diphtheritic nerve damage is the rule.
- ❖ The frequency of complications such as myocarditis and neuritis is directly related to the time between onset of symptoms and administration of antitoxin, and to the extent of membrane formation.

Diphtheria – clinical manifestations and clinical forms

- **Cutaneous Diphtheria**

- ❖ It has long been recognized that, particularly in the tropics, *C. diphtheriae* can cause clinical skin infections characterized by **chronic nonhealing ulcers with a dirty gray membrane**. The presentation is **indolent and nonprogressive**, and is only rarely associated with signs of intoxication. Nonetheless, **these infections can induce high antitoxin levels, and thus appear to act as natural immunizing events**. They also serve as a **reservoir for the organism under conditions of both endemic and epidemic respiratory tract diphtheria**: cutaneous sites of *C. diphtheriae* have been shown both **to contaminate the inanimate environment and to induce throat infections more efficiently than does pharyngeal colonization, and bacterial shedding from cutaneous infections continues longer than from the respiratory tract.**

- ❖ Despite these facts, the clinical significance of isolating the organism from an individual skin lesion is often unclear. Most lesions from which *C. diphtheriae* is isolated are indistinguishable from other chronic dermatologic conditions (eczema, psoriasis, etc.). Moreover, because *C. diphtheriae* is usually isolated in association with other known skin pathogens, and because the ulcers do not respond to antitoxin therapy, there is debate as to whether or not the isolates are actually causing clinical disease.

Diphtheria of the skin

Diphtheria –
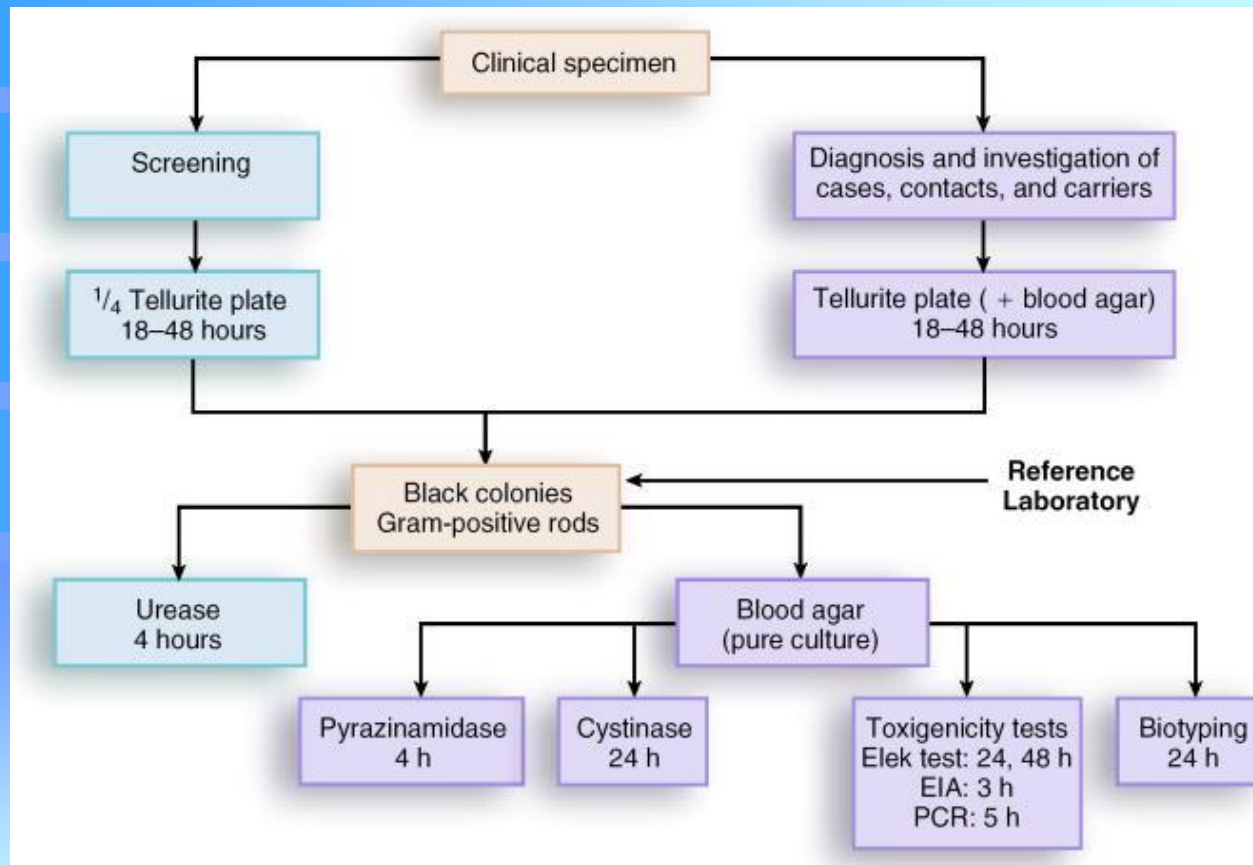# clinical manifestations and clinical forms

- **Invasive Disease**
- ❖ **Endocarditis, mycotic aneurysms, osteomyelitis, and septic arthritis have been described recently in clusters of drug addicts, alcoholics, Australian Aboriginals, and young adults, all caused by nontoxigenic** *C. diphtheriae.* Ribotyping has indicated that these outbreaks have been caused by **unique epidemic strains, and both skin and throat colonization have been implicated as portals of entry.** These illnesses have been characterized by **aggressive course, a high proportion of endocarditis, arterial embolization, metastatic sites of infection (joints, spleen, CNS), and high mortality!!!** **Why these nontoxigenic strains are so virulent remains a mystery.** Coincident with these outbreaks of invasive disease, examples of non-toxin-producing strains causing clinical pharyngitis and even fatal respiratory tract diphtheria have been published since 1990.
- **Other Sites**
- ❖ On rare occasions, clinical infection with *C. diphtheriae* can be seen in other sites such as **the ear, conjunctivae, or vagina.**

Diphtheria – diagnosis

- It is a result of clinical and epidemiologic data.
- **Microbiology** – culture and isolation of the agent.

Algorithm for laboratory diagnosis of diphtheria. *Abbreviations:* EIA, Enzyme immunoassay; PCR, polymerase chain reaction. *(From Efstratiou A, Engler KH, Mazurova IK, et al. Current approaches to the laboratory diagnosis of diphtheria. J Infect Dis 2000;181[Suppl 1]:S138–S145.)*

Diphtheria – management and treatment

- **Diphtheria antitoxin (DAT), hyperimmune antiserum** produced in horses, has been the cornerstone of therapy for diphtheria. **The antibodies only neutralize toxin before its entry into cells, and so it is critical that DAT be administered as soon as a presumptive diagnosis has been made.** The degree of protection is inversely related to the duration of clinical illness preceding its administration.

- ❖ The **recommended doses** are:

- ➢ **20,000 to 40,000 units of antitoxin for pharyngeal or laryngeal disease** of less than or equal to 48 hours' duration;

- ➢ **40,000 to 60,000 units for nasopharyngeal lesions;**

- ➢ and **80,000 to 120,000 units for extensive disease** of 3 or more days' duration **and for anyone with brawny swelling of the neck.**

- ❖ Administration by **intravenous infusion over 60 minutes** to inactivate toxin as rapidly as possible, **or intramuscular injection of antitoxin for moderate disease,** and **combined intramuscular/ intravenous administration for severe disease. Repeated injections are of no additional benefit!**

- ❖ Even very sick patients **must be questioned first concerning known allergy** and evaluated first with **a "scratch test" (a drop of 1:1000 dilution of serum applied to a superficial scratch on the forearm), followed in 15 minutes if no wheal develops with 0.02 mL of a 1:1000 dilution injected intracutaneously, with epinephrine available for immediate administration!!! If an immediate reaction occurs, the patient should be desensitized with progressively higher doses of antiserum.**

Diphtheria – management and treatment

- **Antibiotic therapy, by killing the organism,** has three benefits: (1) termination of toxin production; (2) amelioration of the local infection; and (3) prevention of spread of the organism to uninfected contacts. Although several antibiotics, including **penicillin, erythromycin, azithromycin, clarithromycin, fluoroquinolones, clindamycin, rifampin, and tetracycline, are effective in vitro, only penicillin and erythromycin have been studied in controlled trials!!!**

- **Intramuscular administration of procaine penicillin G (300,000 to 600,000 units) at 12-hour intervals** is recommended until the patient is able to swallow comfortably, when **oral penicillin V (125 to 250 mg quarter in day) or erythromycin estolate or succinate (125 to 500 mg quarter in day) may be substituted for a recommended total treatment period of 14 days.** Both drugs are equally effective in resolving fever and local symptoms, and in time to disappearance of membrane.

- Because **erythromycin is marginally superior to penicillin in eradicating the carrier state,** some authorities prefer it for initial treatment, despite a significant incidence of thrombophlebitis when it is given intravenously, and of gastrointestinal irritation when given orally.

- **Patients should be maintained in strict isolation throughout therapy and, following therapy, should have two consecutive negative cultures at 24-hour intervals to document eradication of the organism.**

- **The carrier state has a slow rate of spontaneous resolution** (12% after 1 month) and so should be treated to prevent spread of infection. **Erythromycin orally for 7 days is the treatment of choice because of several reports demonstrating its greater efficacy in comparison with penicillin. It is necessary to obtain cultures at least 2 weeks after completing therapy to assure eradication of the organism!!!** A single intramuscular dose of benzathine penicillin G (600,000 to 1,200,000 units) is prudent when compliance with oral therapy is uncertain.

Diphtheria – management and treatment

- **Supportive care** is also important.
- **Bed rest** is recommended during the acute phase of illness.
- Early in the disease, <u>**respiratory and cardiac complications are the biggest threats:**</u> airway obstruction can result from aspiration of dislodged pharyngeal membrane, its direct extension into the larynx, or from external compression by enlarged nodes and edema. For this reason, many experts recommend <u>**tracheostomy or intubation as an early measure, particularly when the larynx is involved, thereby providing access for mechanical removal of tracheobronchial membranes and avoiding the risk of sudden asphyxia!!!**</u>
- Vigilance must be maintained to detect the development of <u>**primary or secondary bacterial pneumonia.**</u>
- <u>**Cardiac complications**</u> can be minimized by <u>close ECG monitoring and the prompt initiation of electrical pacing for conduction disturbances, drugs for arrhythmias, or digitalis for heart failure.</u>
- <u>**Physical therapy**</u> should preserve range of motion in paretic extremities while awaiting return of neurologic function. <u>**A recent study has shown that treatment of acute diphtheria with prednisone did not reduce the incidence of carditis or neuritis!!!**</u>
- <u>**Treatment of systemic infection such as endocarditis and arthritis**</u> has not been studied systematically, but most reports describe administration of <u>**intravenous penicillin or ampicillin, usually with an aminoglycoside(???), for 4 to 6 weeks.**</u> Mortality rates of 30–40% occur with bacteremic disease, and valve replacement is often necessary in cases of endocarditis.

Diphtheria – prophylaxis

- *For children from 6 weeks to 7 years of age:* Three 0.5-mL intramuscular injections of (DTaP) vaccine should be given at 4- to 8-week intervals, beginning at 6 to 8 weeks of age, followed by a fourth dose 6 to 12 months after the third.

- *For persons 7 years or more of age:* 0.5 mL Td (toxoid-adult) is given twice at a 4–8-week interval, with a third dose 6 to 12 months later. Because the pertussis component of DPT is responsible for most of its side effects, and the risk of pertussis is much less after age 6, that component of the vaccine is omitted. If the recommended sequence of primary immunizations is interrupted, normal levels of immunity can be achieved simply by administering the remaining doses without need to restart the series.

- *Booster immunizations:* Children who have completed their primary immunization before age 4 should receive a booster dose of DTaP at the time of school entry. Persons above 7 years of age should receive booster immunization with Td at 10-year intervals. As a help to memory, this should be done at decade or mid-decade intervals (e.g., ages 15, 25, 35, etc., or 20, 30, 40, etc.). Careful attention to this adult booster strategy is important to assure population protection in areas with excellent childhood immunization programs. Travelers to areas where diphtheria is still endemic should be particularly careful to be sure their immunization is current. The recommended booster dose is 1.5 to 2.0 Lf units.

- Patients should receive **toxoid immunization in the convalescent stage of their disease** because clinical infection does not always induce adequate levels of antitoxin. **Close contacts whose immunization status is incomplete or unclear** should promptly receive a **dose of toxoid appropriate for their age, and complete the proper series of immunizations.** In addition, they should receive **prophylactic treatment with erythromycin or penicillin,** pending the results of pretreatment cultures. Given these preventive measures, the prophylactic use of antitoxin is considered unwarranted.

Tetanus – definition

- **Tetanus is a disease of the nervous system characterized by persistent tonic spasm, with violent brief exacerbations. The spasm almost always commences in the muscles of the neck and jaw, causing closure of the jaws (trismus, lockjaw), and involves the muscles of the trunk more than those of the limbs. It is always acute in onset, and a very large proportion of those affected die.**
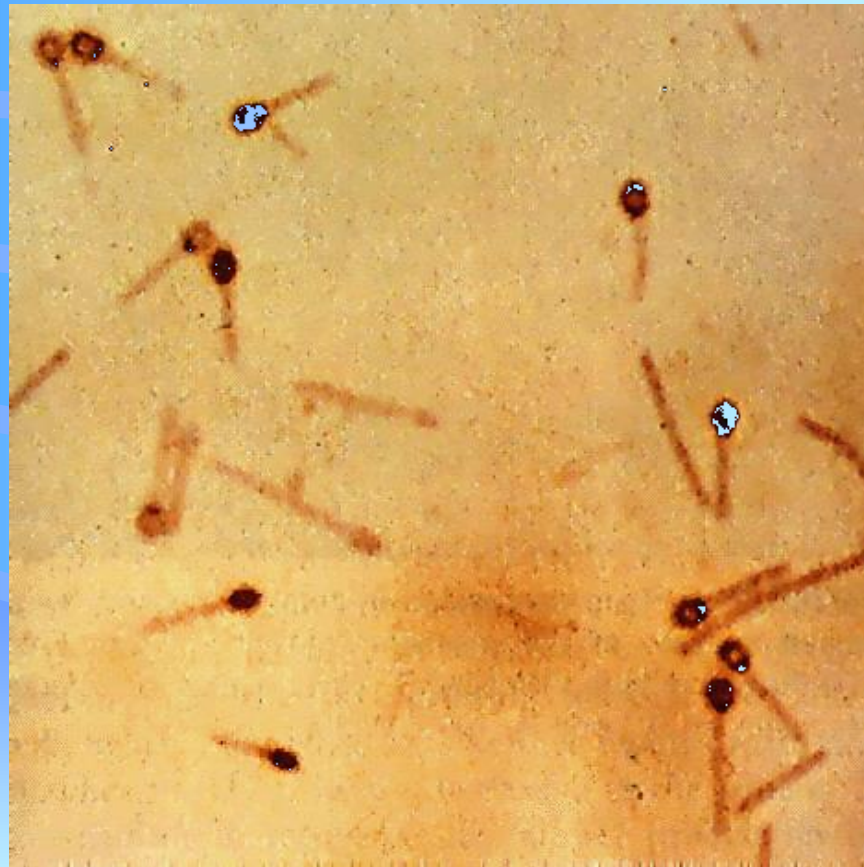
"Opisthotonus" by Sir Charles Bell (1809) (Essays on the Anatomy and Physiology of Expression. 2nd ed. London: J. Murray; 1824.)
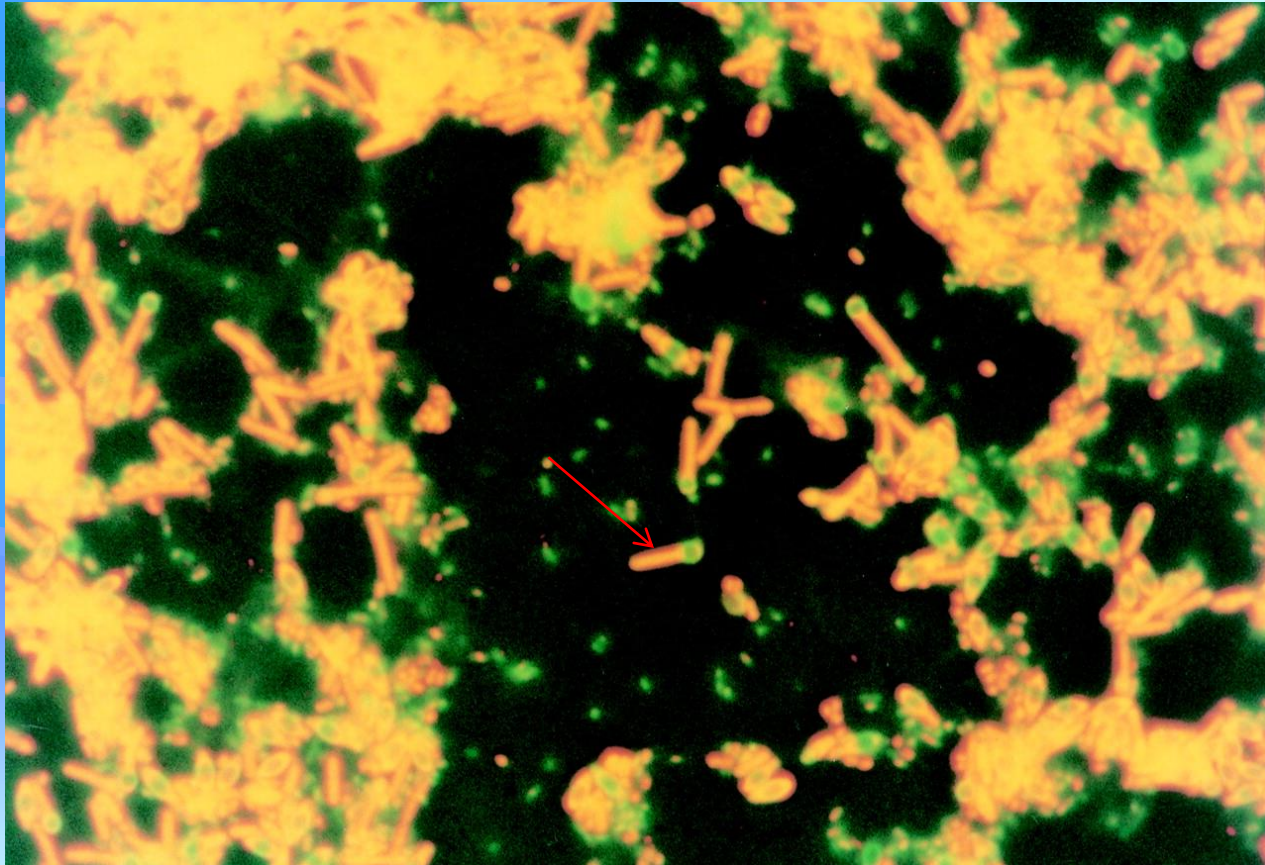
Tetanus – etiology

- *Clostridium tetani* is an **obligately anaerobic bacillus** that is <u>gram positive</u> in fresh cultures but that may have variable staining in older cultures or tissue samples.

- ❖ During growth, the bacilli possess abundant flagellae and are sluggishly motile.

- ❖ **Two toxins,** *tetanospasmin* (commonly called *tetanus toxin*) and *tetanolysin*, are produced during this phase. Tetanospasmin is encoded on a plasmid that is present in all toxigenic strains. Tetanolysin is of uncertain importance in the pathogenesis of tetanus.

- ❖ **Mature organisms** lose their flagellae and develop a **terminal spore,** and begin to resemble a squash racquet. The spores are **extremely stable in the environment,** retaining the ability to germinate and cause disease indefinitely. They withstand exposure to ethanol, phenol, or formalin, but can be rendered noninfectious by iodine, glutaraldehyde, hydrogen peroxide, or autoclaving at 121° C and 103 kPa for 15 minutes.

- ❖ Growth in culture is optimal at 37° C under strictly anaerobic conditions, but **culture results are of no diagnostic value!!!**
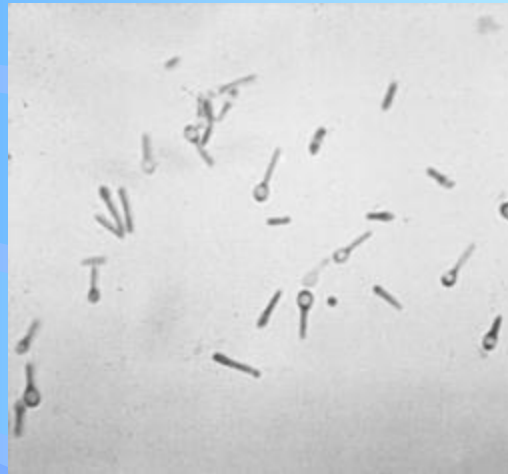
Clostridium tetani

Clostridium tetani

Gram stain of a culture of C. tetani. *(From Bleck TP. Tetanus. In: Scheld WM, Whitley RJ, Durack DT, eds. Infections of the Central Nervous System. New York: Raven Press; 1991:603–624, with permission. Courtesy of Paul C. Schrechenberger, PhD and Alex Kuritza, PhD.)*

Tetanus – epidemiology

- The global incidence of tetanus is thought to be about <u>1 million cases annually, or about 18 per 100,000 population.</u> The majority of reported cases are in <u>patients older than 60 years;</u> this is one of several indicators that **waning immunity is an important risk factor.** Injection drug abuse and other unsterile practices place patients at risk for tetanus.

- In developing countries, mortality rates are as high as 28 per 100,000, while in North America the rate is less than 0.1 per 100,000.

- Neonatal tetanus accounts for about half of the tetanus deaths in developing nations. The World Health Organization reported that <u>Somalia had the highest rate in 1999, with 16.5 neonatal tetanus deaths per thousand live births.</u> Immunization programs clearly decrease neonatal tetanus deaths, and some recent evidence suggests progress in prevention. Neonatal tetanus still occurs rarely in developed countries, usually in <u>individuals who avoid standard practices of immunization and obstetric care.</u>

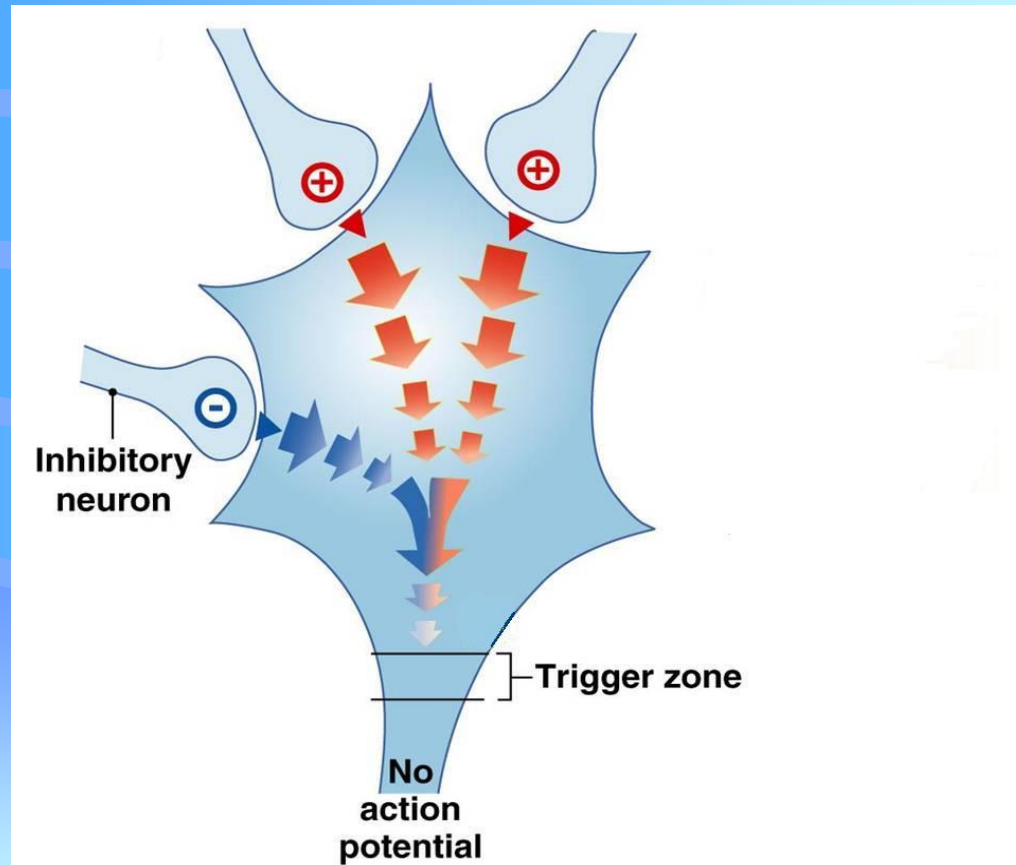- Acute injuries account for about 70% of U.S. cases.

Tetanus – pathogenesis

- The clostridial toxins that produce both tetanus and botulism are very similar in structure and function despite the almost diametrically opposed clinical manifestations of the diseases. **These toxins are zincdependent matrix metalloproteinases**.

- ***Tetanospasmin*** is synthesized as a single 151-kDa chain that is cleaved extracellularly by a bacterial protease into a 100-kDa heavy chain and a 50-kDa light chain (fragment A), which remain connected by a disulfide bridge. The heavy chain can be further divided into fragments B and C by pepsin. The heavy chain appears to mediate binding to cell surface receptors and transport proteins, while the light chain produces the presynaptic inhibition of transmitter release that produces clinical tetanus.

- The nature of the receptor to which tetanospasmin binds, previously thought to be a ganglioside, remains debated. **The toxin enters the nervous system primarily via the presynaptic terminals of lower motor neurons, where it can produce local failure of neuromuscular transmission. It then exploits the retrograde axonal transport system, and is carried to the cell bodies of these neurons in the brain stem and spinal cord, where it expresses its major pathogenic action.**
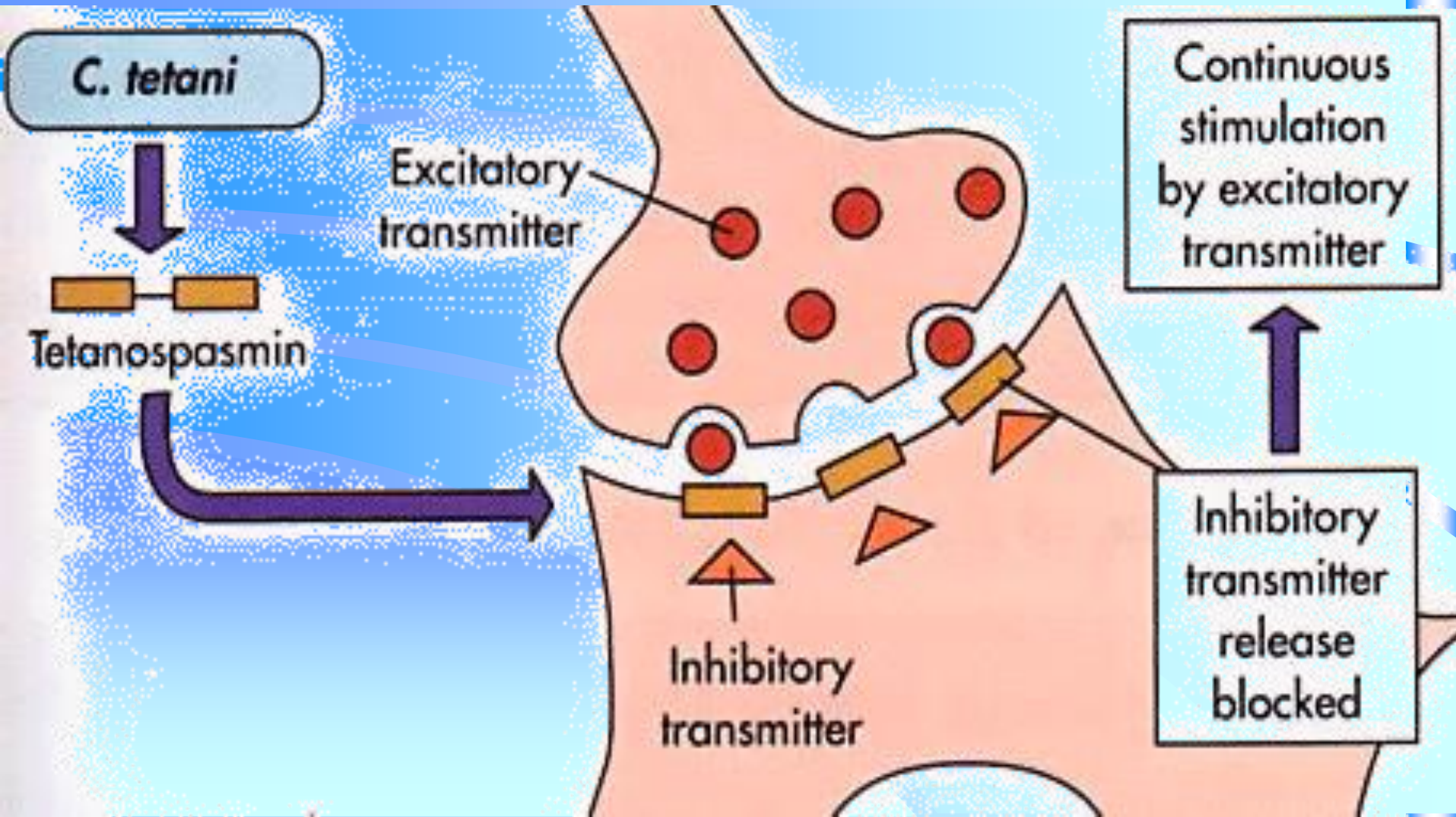
Tetanus – pathogenesis

- Once the toxin enters the central nervous system, it diffuses to the terminals of inhibitory cells, including both local glycinergic interneurons and descending γ-aminobutyric acid-ergic (GABAergic) neurons from the brain stem. The toxin **degrades synaptobrevin,** a protein required for blocking of neurotransmitter vesicles with their release site on the presynaptic membrane. **By preventing transmitter release from these cells, tetanospasmin leaves the motor neurons without inhibition.** This produces **muscular rigidity by raising the resting firing rate of motor neurons, and also generates spasms by failing to limit reflex responses to afferent stimuli.** Excitatory transmitter release in the spinal cord can also be impaired, but the toxin appears to have greater affinity for the inhibitory systems. **The autonomic nervous system is affected** as well; this is manifested as a hypersympathetic state induced by failure to inhibit adrenal release of catecholamines.

- Toxin binding appears to be an irreversible event. At the neuromuscular junction, initial recovery from botulism depends on sprouting a new axon terminal; this is probably the case at other affected synapses as well. Later, the new synapses are removed when the original ones reestablish their connections.

Physiology of neurotransmission

Tetanus – a blockage of inhibitory transmitters

Tetanus –
clinical manifestations and clinical forms

- Incubation period – 4-14 days (from 24 hours to 50-60 days).

- Tetanus is classically divided into four clinical types: **generalized, localized, cephalic,** and **neonatal.** These are valuable diagnostic and prognostic distinctions, but reflect host factors and the site of inoculation rather than differences in toxin action. Terms describing the initial stages of tetanus include the **incubation period** (time from inoculation to the first symptom) and the **period of onset** (time from the first symptom to the first generalized spasm). **The shorter these periods are, the worse the prognosis is. Certain portals of entry (e.g., compound fractures) are associated with poorer prognoses.**
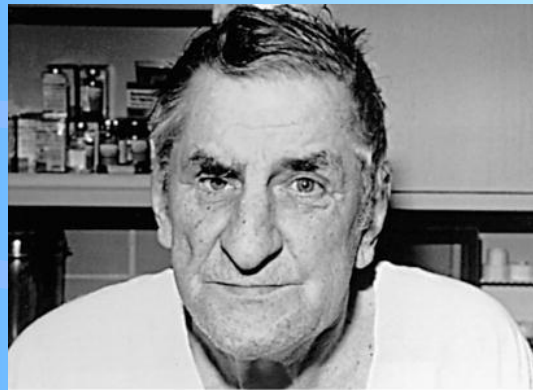
Tetanus – clinical manifestations and clinical forms

- **Generalized tetanus** is the most commonly recognized form, and often begins with *trismus* ("lockjaw"; masseter rigidity) and a *risus sardonicus* (increased tone in the orbicularis oris). *Abdominal rigidity* may also be present. The *generalized spasm* resembles decorticate posturing, and consists of *opisthotonic posturing with flexion of the arms and extension of the legs.* The patient *does not lose consciousness, and experiences severe pain during each spasm.* The spasms are often triggered by sensory stimuli. *During the spasm, the upper airway can be obstructed,* or the diaphragm may participate in the general muscular contraction. Either of these compromise respiration, and even the first such spasm may be fatal.

- The illness can progress for about 2 weeks, reflecting the time required to complete the transport of toxin, which is already intra-axonal when antitoxin treatment is given. Recovery takes an additional month. Lower motor neuron dysfunction may not be apparent until spasms remit, and recovery from this deficit in neuromuscular transmission may take additional weeks. Recurrent tetanus may occur if the patient does not receive active immunization, as the amount of toxin produced is inadequate to induce immunity.

A,Risus sardonicus. Note the straightened upper lip at rest.
B,Trismus. The patient is opening his mouth as fully as possible.
(From Bleck TP. Tetanus. In: Scheld WM, Whitley RJ, Durack DT, eds.
Infections of the Central Nervous System. New York: Raven Press;
1991:603–624, with permission.)

Risus sardonicus

Risus sardonicus

Opisthotonus

Opisthotonus

Tetanus –
clinical manifestations and clinical forms

- **Localized tetanus** involves <u>rigidity of the muscles associated with the site of spore inoculation.</u> This may be mild and persistent, and often resolves spontaneously. Lower motor neuron dysfunction (weakness and diminished muscle tone) is often present in the most involved muscle. This chronic form of the disease probably reflects partial immunity to tetanospasmin. However, <u>**localized tetanus is more commonly a prodrome of generalized tetanus, which occurs when enough toxin gains access to the central nervous system.**</u>

Tetanus –
clinical manifestations and clinical forms

- **Cephalic tetanus** is a special form of localized disease affecting the cranial nerve musculature, almost always following an apparent head wound. Although earlier reports linked cephalic tetanus to a poor prognosis, more recent studies have revealed many milder cases. A lower motor neuron lesion, frequently producing facial nerve weakness, is often apparent. Extraocular muscle involvement is occasionally noted.

Cephalic tetanus

Tetanus –
clinical manifestations and clinical forms

- **Neonatal tetanus** follows infection of the umbilical stump, most commonly caused by a failure of aseptic technique if mothers are inadequately immunized. Cultural practices may also contribute.

❖ The condition usually presents with <u>generalized weakness and failure to nurse; rigidity and spasms occur later.</u> The mortality rate exceeds 90%, and developmental delays are common among survivors.

❖ <u>**Poor prognostic factors** include age less than 10 days, symptoms for fewer than 5 days before presentation to hospital, and the presence of risus sardonicus or fever.</u>

❖ <u>**Apnea is the leading cause of death**</u> among neonatal tetanus patients in the first week of life, and sepsis in the second week. Bacterial infection of the umbilical stump leads to sepsis in almost half of infants with neonatal tetanus, which contributes to the substantial mortality despite treatment.

Neonatal tetanus – risus sardonicus and generalized muscle rigidity

Neonatal tetanus –
generalized muscle rigidity

Neonatal tetanus – "symptom of the trunk"

Tetanus – complications

- Spasms of larynx or respiratory muscles.

- Fractures of bones or vertebras

- Increased sympathetic tone → hypertension and tachycardia

- Nosocomial infections – sepsis, pneumonia, trophic wounds of the skin

- Pulmonary embolism

- Aspiration

- Cardiac arrest in severe seizure.

Tetanus – laboratory investigations

- Without specific laboratory findings.

- If a secondary bacterial infection appears – leucocytosis.

- Severe metabolic acidosis due to muscle hypoxia resulting of the increased muscle tone and the seizures.

Tetanus – diagnosis

- **<u>From clinical and epidemiologic data.</u>**

Tetanus –
management and treatment

- **Tasks:**
- ❖ **<u>Treatment in ICU!!! The patient is not contagious!!!</u>**
- ❖ <u>The patient is in a isolated quiet and dark room.</u>
- ❖ <u>Control and support of vital functions!!!</u>
- ❖ <u>Minimal manipulations!!!</u>
- ❖ <u>Neutralizin of tetanic exotoxin</u>
- ❖ <u>Antimicrobial treatment</u>
- ❖ <u>Increasing of active immunity</u>
- ❖ <u>Sedation</u>
- ❖ <u>Parenteral nutrition.</u>

Tetanus – management and treatment

- **The patient with tetanus requires simultaneous attention to several concerns.**

- ❖ Tetanic spasms sometimes demand that **the airway be secured before other lines of therapy are possible.** An orotracheal tube can be passed under sedation and neuromuscular junction blockade; a feeding tube should be placed at the same time. Because the endotracheal tube may stimulate spasms, an early tracheostomy may be beneficial.

- ❖ **Benzodiazepines** have emerged as the mainstay of symptomatic therapy for tetanus. These drugs are $GABA_A$ agonists, and thereby indirectly antagonize the effect of the toxin. They do not restore glycinergic inhibition. The patient should be kept free of spasms, and may benefit from the amnestic effects of the drugs as well. Diazepam has been studied most intensively, but lorazepam or midazolam appear equally effective.

- ❖ The intravenous formulations of both diazepam and lorazepam contain propylene glycol; at the doses required to control generalized tetanus, this vehicle may produce lactic acidosis. Nasogastric delivery of these agents is often possible, but some tetanus patients develop gastrointestinal motility disorders and do not absorb drugs well. Intravenous midazolam (5 to 15 mg/hour or more) is effective and does not contain propylene glycol, but must be given as a continuous infusion because of its brief half-time. When the symptoms of tetanus subside, these agents must be tapered over at least 2 weeks to prevent withdrawal.

- Neuroleptic agents and barbiturates, previously used for tetanus, are inferior for this indication and should not be used. Magnesium infusion may emerge as a useful therapeutic technique in generalized tetanus.

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- Rare patients cannot be adequately controlled with benzodiazepines alone; **neuromuscular junction blockade** is then indicated. All of the available drugs have side effects, including the potential for prolonged effect after the drug is discontinued. Vecuronium (by continuous infusion) or pancuronium (by intermittent injection) are adequate choices. Electroencephalographic monitoring is a useful adjunct for this purpose.

- The majority of tetanus patients will still have the portal of entry apparent when they present. **If the wound itself requires surgical attention, this may be performed after spasms are controlled. However, the course of tetanus is not affected by wound débridement.**

- Passive immunization with **human tetanus immune globulin (HTIG)** shortens the course of tetanus and may lessen its severity. A dose of 500 units appears as effective as larger doses. There had been no apparent advantage to intrathecal HTIG administration. Intrathecal HTIG was ineffective in a study of neonatal tetanus. Pooled intravenous immune globulin has been proposed as an alternative to HTIG, although this should be approached with caution. Active immunization must also be initiated.

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- The role of **antimicrobial therapy** in tetanus remains debated. The in vitro susceptibilities of *C. tetani* include **metronidazole, penicillins, cephalosporins, imipenem, macrolides, and tetracycline.** A study comparing oral metronidazole to intramuscular penicillin showed better survival, shorter hospitalization, and less progression of disease in the metronidazole group. This may reflect a true advantage of metronidazole over penicillin, but it more likely corresponds to a negative effect of penicillin, a known GABA antagonist. Topical antibiotic application to the umbilical stump appears to reduce the risk of neonatal tetanus.

- Autonomic dysfunction generally reflects excessive catecholamine release, and may respond to combined **α- and β-adrenergic blockade** with intravenous labetalol. β-Blockade alone is rarely employed, because the resulting unopposed α effect may produce severe hypertension. **If β-blockade is chosen, the short-acting agent esmolol should be employed.** Other approaches to hypertension include morphine infusion, magnesium sulfate infusion, and epidural blockade of the renal nerves. Hypotension is less common, but if present may require norepinephrine infusion.

- **Nutritional support** should be started as soon as the patient is stable. The volume of enteral feeding needed to meet the exceptionally high caloric and protein requirements of these patients may exceed the capacity of the gastrointestinal system.

Management Protocol for Generalized Tetanus
Adapted from Bleck TP. Tetanus. In: Scheld WM, Whitley RJ, Durack DT, eds. Infections of the Central Nervous System. New York: Raven Press; 1991:603–624.

- ***I. Diagnosis and Stabilization: First Hour After Presentation***

- ❖ A. Assess airway and ventilation. If necessary, perform endotracheal intubation using benzodiazepine sedation and neuromuscular blockade (e.g., vecuronium 0.1 mg/kg).

- ❖ B. Obtain samples for antitoxin level, strychnine and dopamine antagonist assays, electrolytes, blood urea nitrogen, creatinine, creatine kinase, and urinary myoglobin determination.

- ❖ C. Determine the portal of entry, incubation period, period of onset, and immunization history.

- ❖ D. Administer benztropine (1 to 2 mg, intravenously) or diphenhydramine (50 mg, intravenously) to rule out a dystonic reaction to a dopamine blocking agent.

- ❖ E. Administer a benzodiazepine intravenously (diazepam in 5-mg increments, or lorazepam in 2-mg increments) to control spasm and decrease rigidity. Initially, employ a dose that is adequate to produce sedation and minimize reflex spasms. If this dose compromises the airway or ventilation, intubate using a short-acting neuromuscular blocking agent. Transfer the patient to a quiet, darkened area of the intensive care unit.

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- *II. Early Management Phase: First 24 Hours*
- ❖ A. Administer human tetanus immunoglobulin (HTIG), 500 units, intramuscularly; as an alternative, consider intravenous pooled immune globulin (see text).
- ❖ B. At a different site, administer adsorbed tetanus toxoid such as tetanus-diphtheria vaccine (0.5 mL) or diphtheria-pertussis-tetanus vaccine (0.5 mL), as appropriate for age, intramuscularly. Adsorbed tetanus toxoid without diphtheria toxoid is available for patients with a history of reaction to diphtheria toxoid; otherwise, the correct combination for the patient's age should be employed.
- ❖ C. Begin metronidazole 500 mg, intravenously, every 6 hr, for 7–10 days.
- ❖ D. Perform a tracheostomy after placement of an endotracheal tube and under neuromuscular blockade if spasms produce any degree of airway compromise.
- ❖ E. Débride any wounds as indicated for their own management.
- ❖ F. Place a soft, small-bore nasal feeding tube or a central venous hyperalimentation catheter, and begin feeding. Patients receiving total parental nutrition should also be given parenteral H_2 blockade or other gastric protection.
- ❖ G. Administer benzodiazepines as required to control spasms and produce sedation. If adequate control is not achieved, institute long-term neuromuscular blockade (e.g., vecuronium 6–8 mg/hr); continue benzodiazepines for sedation with intermittent electroencephalographic monitoring to ensure somnolence. Neuromuscular junction blockade should be discontinued daily to assess the patient's physical examination and to decrease the possibility of excessive accumulation of the blocking agent.

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- ***III. Intermediate Management Phase: The Next 2–3 Weeks***

- A. Treat sympathetic hyperactivity with labetalol (0.25–1.0 mg/min as needed for blood pressure control) or morphine (0.5–1.0 mg/kg/hr by continuous infusion; see text for other recommendations). Consider epidural blockade with a local anesthetic. Avoid diuretics for blood pressure control, because volume depletion will worsen autonomic instability.

- B. If hypotension is present, initiate saline resuscitation. Place a pulmonary artery catheter and an arterial line, and administer fluids, dopamine, or norepinephrine as indicated.

- C. Sustained bradycardia usually requires a pacemaker. Atropine or isoproterenol may be useful during pacemaker placement.

- D. Begin prophylactic heparin.

- E. Use a flotation bed, if possible, to prevent skin breakdown and peroneal nerve palsies. Otherwise, ensure frequent turning and employ antirotation boots.

- F. Maintain benzodiazepines until neuromuscular blockade, if employed, has been terminated, and the severity of spasms has diminished substantially. Then taper the benzodiazepine dose over 14–21 days.

- G. Begin rehabilitation planning.

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- *IV. Convalescent Stage: 2–6 Weeks*

❖ A. When spasms are no longer present, begin physical therapy. Many patients require supportive psychotherapy.

❖ B. Before discharge, administer another dose of tetanus-diphtheria vaccine or diphtheria-pertussis-tetanus vaccine.

❖ C. Schedule a third dose of toxoid to be given 4 weeks after the second.

Tetanus – prophylaxis

- **<u>Tetanus is preventable in almost all patients,</u>** leading to its description as the "inexcusable disease". A series of three monthly intramuscular injections of alum-adsorbed tetanus toxoid provides almost complete immunity for at least 5 years. Patients younger than 7 years of age should receive combined diphtheria-tetanus-pertussis vaccine, and other patients combined diphtheria-tetanus vaccine. Routine booster injections are indicated every 10 years; more frequent administration may increase the risk of a reaction. The Advisory Committee on Immunization Practices in the United States recommends visits at age 11 to 12 years and age 50 years for health care providers to review vaccination histories and administer any needed vaccine. Toxoid vaccination remains the standard.

- Older people may have waning tetanus immunity, related to either changes in immune function due to age or to a longer period since initial immunization.

Tetanus – prophylaxis

- **After injury –** tetanus toxoid 0.5 ml subcutaneously for people with regular immunizations. **For nonimmunized – obligate both tetanus toxoid 0.5 ml subcutaneously and HTIG 250 – 500 E subcutaneously, if has not HTIG – tetanic serum 1 500 – 3 000 E i.m.**

THANK YOU
FOR THE ATTENTION !