MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

MAY 8, 1969

CLOSTRIDIA TOXINS

1. Botulism

Case Report:

[redacted], a 25-year-old male [redacted] developed the sudden onset of dizziness at work on the morning of [redacted]. He described this as true vertigo of an intense severity. By the evening of [redacted] he could not swallow and his vision was blurred. At 3:00 a.m. on [redacted] he experienced difficulty of breathing. In a few hours he could not move his eyes, swallow saliva, nor move his facial muscles. Later he developed weakness of arms and then the legs. He was admitted to an osteopathic hospital on the afternoon of [redacted] where a lumbar puncture revealed no cells and a protein of 54. During the early morning of [redacted] he had progressive respiratory difficulty so a tracheostomy was performed. The only past history of significance was the occurrence of a car accident two weeks earlier in which he sustained a mild whiplash injury.

On admission to [redacted] on [redacted] he was a fully conscious, healthy male who was severely paralyzed. Vision was intact if the examiner held the patient's eyes open, but he had complete paralysis of extraocular muscles. Pupils were 5 mm and both reacted normally. He had more upper facial weakness than lower, but he had complete paralysis of the palate, tongue and sternocleidomastoid muscles. His mouth was rather moist. Proximal muscles in upper extremities were completely paralyzed; the distal groups were more severely impaired on the right than on the left. He had moderate paralysis of both lower extremities. Biceps reflex were 1+, knee jerks were 3+ and he had ankle clonus. No sensory changes were noted. His paralysis worsened over the next 48 hours until the only muscle groups he could move were his toe dorsiflexors. The possibility of botulism was entertained by the neurology service and attempts were made to obtain botulinum antitoxin. The NCDC was informed of the possibility of botulism and an E.I.S. officer was dispatched to Dallas with A, B, and E antitoxin. Serum was obtained, and mice injected with the material developed progressive muscular paralysis and death in all save those given Type A botulism antitoxin. On the basis of the suspected presence of botulism, antitoxin was administered. On [redacted] he had some transient increase in strength of the ankles and toes. His pupils eventually dilated on [redacted] and were sluggishly reactive to light.

He developed a rapidly progressive staphylococcal pneumonia on [redacted]. He remained hypoxic despite the administration of 70% O_2. By [redacted] he would lose consciousness if the O_2 delivered was dropped to 60%. Because of the rapid progression of the pneumonia from the RML and RLL to all other lobes over the next two days, kanamycin was added to cephalothin. He developed gastrointestinal bleeding with a falling hematocrit. Attempts to maintain adequate ventilation were largely unsuccessful despite the use of a number of types of ventilators and high pressures. Eventually he became hypotensive and unresponsive even on 80% O_2. He expired on the a.m. of [redacted]. Blood cultures on [redacted] were positive for Pseudomonas species.

Autopsy revealed no abnormalities of the nervous system save scattered petechiae

of certain lung nerves. Microabscesses with liquefactive necrosis were present in all lobes of the lung with a confluent fibrino-purulent exudate compatible with staphylococcal pneumonia. There was bilateral cortical adrenal hemorrhage which was likely less than 1 day old.

No source of the botulism toxin has been found. He and his wife ate spaghetti and drank wine with a couple on the evening of [redacted]. Both were nauseated that evening, but she had no further symptoms. He ate a sandwich away from home that his wife didn't eat; otherwise, they had eaten the same foods. He had eaten nothing that was home canned. This is, unfortunately, a case of botulism for which no contaminated foodstuff has been determined. Hopefully, it will be a sporadic case.

Botulism is a disease which results from the ingestion of exotoxins produced by Clostridium botulinum, a spore-forming, anaerobic, gram-positive rod. Six types of toxin have been distinguished which have been designated A, B, C, D, E, and F. The toxin of one type is not neutralized by the antitoxin of a heterologous type. Man is affected mainly ty Types A and E, less frequently by Types B and F, and never by C and D. Case-fatality rates very from 20 to 70%, depending upon type and amount of toxin ingested. The importance of the disease is not the numbers of individuals affected, but in the fear of the potential of the toxin, the most potent one known to man.

The natural habitat of the organism is in the soil, and it prefers virgin soil to cultivated, fertilized soil. In the United States it is more commonly found in the western states and is less commonly present in the soil in the middle western states and the Great Plains (1, 2). Type E spores have been demonstrated primarily in lakeshore mud, coastal sand and seabottom sludge; hence, Type E botulism has a predilection for fish as vehicle (3).

Pathogenesis:

Toxins elaborated by Cl. botulinum are the most poisonous substances known to man (4). The disease is most often caused by the oral ingestion of toxin, although parenteral administration can lead to disease also. Although the molecular weight of crystalline toxin is in the order of 900,000, toxin crosses the intestinal tract and reaches the general circulation via the lymphatics. It is one of the few toxins not destroyed and indeed activated by the acid conditions and by proteolytic enzymes in the gastrointestinal tract. This is particularly true of Type E toxin. Russian investigators have claimed that toxin elaborated by Cl. botulinum during growth within the GI tract is important in the disease. Most investigators disagree with this contention and consider that the disease is secondary exclusively to orally ingested toxin.

After absorption, toxin can be found circulating in the blood. In fact, tests performed in animals with serum obtained from individuals suspected of having botulism provide the best means of diagnosis (5). The toxin acts very widely on all those portions of the peripheral nervous system that are cholinergic including pre- and postganglionic autonomic fibers and the somatic nerves supplying the skeletal muscles. In experimental animals, the toxin produced a progressive impairment of the ability of the vagus nerve to induce cardiac slowing, the chorda tympani to evoke salivary secretion, and the oculomotor nerve to produce a constriction of the pupil. The toxin has no effect on the contractile power of muscle fibers or of motor nerves to conduct impulses. The toxin inhibits the release of acetylcholine from its binding sites at the poisoned nerve terminals. This is in contrast to the action of curare which prevents the action of acetylcholine; thus, direct application of acetylcholine to poisoned nerve preparations will elicit muscle contraction. The botulinal toxin is unique in causing

presynaptic block through the inhibition of the release of transmitter substance. No evidence exists that indicates the toxin is directly injurious to the cells of the brain or spinal cord. Death is usually a result of respiratory paralysis or of infection which develop following paralysis. It has been shown that toxin injures the efferent inspiratory fibers of the brainstem.

Epidemiology:

Botulism emerged as a significant public health hazard in the United States with the development of the canning industry and the increased home processing of foods encouraged by the war conditions of 1917-1918. As a result of research by Meyer and others and as a result of the controls instituted by the commercial canning industry, the controls instituted by the commercial canning industry during the folowing 10 years, few outbreaks of botulism were reported from commercial canned goods from 1925 until 1963 in the United States. Most Americans with cases follow the ingestion of home canned vegetables and fruits which have been under-sterilized or inadequately preserved and most of these outbreaks have been Type A. The case-fatality rate through 1960 was 64%, which has been attributed to the greater lethality and toxigenicity of Type A. However, the case-fatality in the 60's has been improved so that it is 21% in the period 1960-1967, and in particular is 20% for Type A. This improvement is presumably a reflection of the use of intensive care of acute respiratory failure. In European countries, pork products, especially sausage, have been implicated most often. Type E has been the most significant type in Russia, Japan, and Canada due to the outbreaks secondary to the ingestion of fish products.

The growth of Cl. botulinum within canned meats is associated with a foul odor; however, the odor may not be so noticeable in acid foods such as canned string beans (the leading cause of outbreaks in the United States). The strains of Cl. botulinum producing disease in Europe and Type E strains are non-proteolytic and probably give less evidence of spoilage. An important potential factor at the present time is the packaging of meats and fish in air-permeable pouches. Previously, cured meat allowing entrance of air would become spoiled secondary to the growth of aerobic microorganisms before Cl. botulinum could grow and produce toxin. With the use of air-permeable pouches, a cured meat could be held at room temperature for days without spoiling, but Cl. botulinum could grow and elaborate toxin (6). Therefore, it is imperative that such products be maintained at 4°C. This is particularly true for fish products, since Type E Cl. botulinum is widely distributed in fish and shellfish of the Pacific Northwest. Mud samples from the Pacific coast demonstrate a 50 to 90% incidence of positive cultures of Type E.

Prior to 1963, few cases of botulism each year were reported to the Public Health Services. However, in 1963, 46 cases were reported, 22 of which were Type E strains. Twenty-four of these were traced to commercially prepared products, and most of these were traced to a single shipment of a contaminated smoked whitefish chub (7). This product had been vacuum packaged in pliofilm bags and individuals had eaten the fish without cooking. Hence, this outbreak of botulism in that year was characterized as a "disease of technical progress."

Prevention of the disease is independent upon proper preparation and sterilization of canned goods (1, 2). The spores of Cl. botulinum are resistant to heating at 100°C for 360 minutes, although heating to 120° for 4 minutes destroys all spores. Hence, canning with a pressure cooker is necessary. The toxin is more heat-labile than spores, and cooking prior to eating will destroy toxigenic activity. Type A toxin is destroyed in 30 seconds to 6 minutes at 80°C, and Type E is even more heat-labile and is destroyed by heating to 60°C for several minutes. Hence fish products containing Type E toxin

will produce disease only if they are not heated prior to ingestion (5).

Clinical Features (1, 5, 7, 8):

The onset of symptoms may occur from 12 to 100 hours after ingestion of the toxin. Nausea and vomiting usually heralds the onset. It has been stated that gastrointestinal symptoms are less frequent with Type A than with Type E. Diarrhea may occur early, but constipation is present later. In a majority, an early symptom is a peculiar lassitude or fatigue. The neurological symptoms appear progressively with descending weakness. First, the person notices postural dizziness or vertigo (as in this case) and blurred vision next. Difficulty swallowing occurs early, followed soon by difficulty speaking (dysphonia). Weakness of somatic muscle groups, especially girdle muscles and of the neck muscles develop, and sometimes, as in this case, generalized profound weakness of all muscles ensues. Finally, diplopia and respiratory muscular paralysis complete the picture of paralysis. Physical examination reveals a mentally alert but often somnolent individual. Ocular abnormalities are noted in virtually all patients, including extra-ocular muscle paralysis, ptosis, impairment of accommodation, and dilated, fixed pupils. The latter may develop quite late, as was true with our case. Dry tongue and mouth have been noted in most, although this was not helpful in this case. Pharyngeal erythema and edema have been noted. Cranial nerve weakness is present and proximal shoulder girdle and neck weakness is prominent in many. The muscle weakness is not associated with impairment of deep tendon reflexes. Sensory abnormalities are not present.

In general, symptoms are more severe and mortality higher in those individuals in whom symptoms appear early after ingestion of toxin. Also, the signs of botulism persist longer in the patients who have more severe toxemia (8). A return to normal of the eyes, such as pupils becoming reactive, may not occur for 2 weeks. Objective respiratory impairment and postural hypotension may persist for 2 to 3 weeks.

Botulism must be considered in the differential diagnosis of any neurological disorder with cranial nerve involvement, especially eye muscle involvement, and in those with a descending form of paralysis. The list of possible diagnoses in cases reviewed in Reference 5 serves as a group of diseases with which one should keep one's mind open to possibility of botulism.

Diagnosis	Feature Present in Botulism
Basilar artery thrombosis	Cranial nerve signs, especially IX and X
Poliomyelitis or Guillain-Barre syndrome	Cranial nerve plus somatic muscle involvement
Myasthenia gravis	Ptosis, dysphagia, respiratory muscle impairment
Acute intoxication (arsenic, etc.)	Quadriplegia or proximal girdle weakness
Small bowel obstruction	Vomiting, followed by constipation with signs of ileus
Streptococcal sore throat	Pharyngeal pain and hyperemia

Koenig and associates have emphasized the fact that certain individuals do not develop symptoms after ingesting food which produces botulism in other individuals (5, 8). The attack rate with Type E was 44% and with Type B 50%. They also demonstrated Type botulinum toxin circulating in the serum in an individual with no clinical manifestations of botulism. Most previous investigators have suggested that such attack rates are due to the focal distribution of toxin in contaminated foodstuffs. However, Koenig

raises the possibility that susceptibility to the action of botulinum toxin may relate to biochemical differences in enzyme systems present at tissue-binding sites.

Laboratory Studies and Treatment:

Routine laboratory studies do not aid in establishing the diagnosis. The most effective way to confirm the diagnosis of botulism is to demonstrate toxicity of the patient's serum for mice and to prove specificity of the toxin by neutralization tests with botulinum antitoxins (5, 8). Serum from patients with botulism should contain a mouse-lethal substance. It has been demonstrated as late as 3-1/2 weeks after the ingestion of contaminated food. Although it has been stated that such tests are only helpful in diagnosing Types B and E botulism, other cases and the present one clearly demonstrate that Type A botulism is associated with circulating toxin.

Patients suspected of having botulism should receive material containing A, B, and E antitoxin until laboratory tests demonstrate which toxin is responsible. A number of preparations are available, but A, B and E must be obtained from the NCDC. A commercially available preparation containing antitoxin to A and B can be obtained. Experience in treatment of Type E botulism has demonstrated efficacy (3). In outbreaks in Japan, case-fatality rate in untreated cases was 29% and only 3.5% in treated patients. In two patients with Type E botulism treated in Reference 5 severe muscular paralysis was rapidly reversible. In contrast, patients with Type A and B disease do not show dramatic improvement (1, 8). Experimental studies in monkeys have demonstrated that antitoxin is of value after administration of toxin and before symptoms have appeared, but it is not effective after the appearance of symptoms (1). In spite of this, if one suspects botulism, serum should be drawn for studies of toxin and antitoxin administered. Since the antitoxin is derived from horses, skin testing should be done before administration.

Neither clinical botulism nor ingestion of toxin results in a detectable antibody response. One attack of botulism should not confer immunity, and individuals have been reported with repeat attacks of botulism.

II. Tetanus

Case Report:

[redacted], a 67-year-old [redacted] male, was admitted on [redacted] 1969, with congestive heart failure and gangrene of right foot. He had been having pain in the right foot for 1 year, and the foot was noted to be tender when seen in urology clinic 1 month prior to admission. He was treated for urinary retention at that time and was referred to medicine clinic. In the 2 weeks prior to admission, he developed more pain in the foot and it became darker in color. In addition, he noted increasing dyspnea, paroxysmal nocturnal dyspnea, orthopnea and edema.

Physical examination on admission demonstrated a BP 180/90, P-120, T-101. He was obese, edematous, and in moderate respiratory distress. His neck was supple. He had scattered expiratory wheezes without rales, left ventricular hypertrophy and enlargement and a G ⅗ holosystolic murmer at the apex. The right foot was gangrenous, but no purulent exudate was noted. Pitting edema was present to the knees. He was treated with digitalis, diuretics and had rapid improvement in respiratory symptoms. Cephalothin 8 grams/day was given for infection. On the morning of [redacted], he was noted

to bite his tongue when his temperature was taken; then he was unable to swallow KCl and later unable to open mouth. At 1200 while eating, he fell over and quit breathing. He was resuscitated, but EKG revealed idioventricular rhythm. Isuprel therapy led to sinus tachycardia. He was comatose thereafter, but he had spontaneous tonic movements and would develop spasms with stimulation. A BK amputation was done at 1630 and he was transferred to recovery room. He had a tracheostomy and required ventilation with IPPB. Initially he had mild spasms controlled by nembutal IM, but gradually the spasms worsened and on [redacted] he had breathholding spells. Valium was given intermittently IM and later by IV drip, but by April 7 he escaped from a response to it. On [redacted] Robaxin was given IV, but he had more severe spasms and even convulsions with breathholding. Curare was added, and the seizures seemed better controlled, although he continued to have some. He continued to run a low-grade temperature, and on [redacted] minimal pulmonary infiltrates were noted. Other therapy consisted of 2500 units hyperimmune human globulin, penicillin, tetracycline and kanamycin. He had a moderate respiratory alkalosis (pH 7.49 to 7.56), the pO_2 ranged from 100 to 200, and he was adequately ventilated as determined by physical exam. His BUN and creatinine gradually rose to 73 and 3.7, his urinary output fell and by [redacted] his serum potassium was 6.5. Peaked T waves were noted on [redacted] and pH was 7.15. Treatment for hyperkalemia and metabolic acidosis was initiated, but early the next morning he developed hypotension, bradycardia and died.

Tetanus continues to be a serious health problem, especially in the southern states, although the incidence of tetanus has declined during the last 20 years (9). Texas is a leading state from which both neonatal tetanus and tetanus in other age groups are reported. Factors contributing to the geographic localization in the southern states are the low immunization levels in the non-white, low socioeconomic groups and the distribution of Cl. tetani spores in the soil (10, 11). In spite of advances in the intensive care of patients, the case-fatality ratio in the United States and at Parkland remains high (9). One definite reason for this is that with widespread toxoid vaccination programs, tetanus now affects the elderly and the neonate, two groups with the highest case-fatality ratios. A second possible explanation that must be strongly considered is that hyperimmune human globulin may not be as efficacious (at least in the quantity recommended) as equine antitoxin (12).

Pathogenesis (13):

Tetanus is a toxemia due to an infection with Cl. tetani following the introduction of organisms (spores) subsequent to an injury. Such an injury may be insignificant in appearance. The incubation period in man is 5 to 14 days following the introduction of the spores of this anaerobic, gram-positive organism. During this time, spores germinate, and a neurotoxin is produced. The mechanism by which this toxin spreads from the site of infection to the susceptible sites in the central nervous system remains controversial.

The toxin is the second most potent one known (following botulinum toxin). It is a simple protein of a single antigenic type with a molecular weight of 67,000. In the highly purified state, the toxin loses its toxicity but retains its antigenicity (it toxoids). A potentiation of toxicity occurs in the presence of certain chemicals and proteolytic enzymes (14).

The toxin is specifically and avidly bound to the gray matter of the nervous tissue (brain gangliosides) (13). However, there is no proof that this fixation is a

necessary part of the lethal action of the toxin. The toxin acts both in the central nervous system and upon peripheral cholinergic nerve endings. The site of the central paralytic action is between the specific interneurons of the inhibitory pathway and the motoneuron (15). Toxin diminishes and then abolishes all five types of spinal inhibition. This action, similar to strychnine, is due to the prevention of the release of transmitter substance from inhibitory presynaptic terminals. The peripheral neuromuscular effect of the toxin is due to depolarization of motor nerve terminals (16). As a result, spontaneous miniature end-plate potentials increase in frequency. Thus without the effects of the spinal inhibitory pathway and with depolarization of motor nerve terminals, paroxysmal motor spasms of muscles occur spontaneously and when induced by stimuli.

EPIDEMIOLOGY:

Peak incidence of tetanus occurs in the very young and the elderly. Striking changes have occurred in the age distribution of tetanus over the past 70 years. In 1900, the mortality rates per 100,000 for age groups over 1 year of age was the same. Since 1910, mortality rates have decreased in all age groups, but the factor of decrease has been 50 in groups under 30 years of ge, but the death rate in those over 60 has decreased by only a factor of 5. These decreases are due to the widespread use of antitoxin after WWI, the adoption of routine toxoid immunization of infants after WW II, and improved obstetric techniques. However, the southern states lag considerably in immunization programs. Furthermore, the continued poor obstetric care of a considerable rural population in Texas is demonstrated by the fact that 56% of all cases of neonatal tetanus in the United States in 1966 were in Texas. Most of these cases follow home delivery unattended by an M.D.

Mortality rates are greater in rural than urban areas and in non-whites than whites. The peak incidence occurs in midsummer. It has been demonstrated that tetanus neonatorum is more prevalent during warm, moist months than in hot, dry months, presumably because Cl. tetani spores increase in number under the former conditions (11).

CLINICAL CHARACTERISTICS:

Source and site of injury: Infection can develop following insignifcant appearing wounds, and the infection itself can be relatively insignificant without purulent discharge. Puncture wounds and lacerations account for a majority of the wounds associated with tetanus (9). Tetanus following surgery has been emphasized (9, 17). In particular tetanus can follow operations or manipulations some length of time after the Cl. tetani were introduced (17). Three patients with compound fractures 4 to 12 weeks before had tetanus following remanipulation of their fracture. One patient developed tetanus upon the spontaneous breakdown of an ankle wound injured 3 years previously, and another developed tetanus 12 days after grafting skin at a site of a wringer injury five months previously. These cases demonstrate the prolonged viability of Cl. tetani within tissue.

Other less frequent groups but ones associated with high case-fatality rates are tetanus related to abortion, injection related tetanus, primarily in drug addiction (18), and tetanus resulting as a sequel to wounds. Such wounds included individuals with infected decubiti and varicose ulcers, frostbite, chronic skin ulcerations, and, as in our fatal case, gangrenous extremities. Tetanus following these wounds are uniformly fatal (9). Injuries occurring in garden work are common in those over 50 years.

Incubation Period (9): Median incubation period is 7 to 8 days, and 90% began within 14 days of injury. In the age group over 50, no difference in case-fatality ratio has

been noted in relation to incubation period, whereas the ratio was significantly less in individuals under 50 who had a prolonged incubation period. Thus, the age group of a particular series must be known to compare case-fatality ratios. In neonatal tetanus, the greatest number became symptomatic on the sixth or seventh day, and an incubation time of greater than 10 days is associated with better survival.

Symptoms: Trismus is the most dependable sign, being present in 80% (9, 17). Local symptoms occur in approximately one-third, and consist of pain at the extremity of site of injury and stiffness of local muscle groups. Localized symptoms often follow Trismus. "Risus sardonicus" or the distorted grin, with peaking of the eyebrows, is common in tetanus, although it may not be as evident in tetanus neonatorum patients (19). The presence of convulsions bears an ominous sign, since it is associated with a higher case-fatality ratio. Other early symptoms and signs may include fever (if wound is infected), malaise, headache, dysphagia, dysphonia, spasticity of the skeletal muscle, which often leads to the maintenance of opisthotonus, increased salivation, and abdominal rigidity (often mistaken for a local abdominal problem). The spasms are both tonic and clonic, are extremely painful, and are easily precipitated by noise, movement, or even touch. Severe spasms may interfere with breathing.

The differential diagnosis is important since treatment of tetanus is potentially hazardous. Other diagnoses to consider include meningitis, retropharyngeal and peritonsillar abscesses, osteomyelitis of the mandible, streptococcal pharyngitis, strychnine poisoning, phenothiazine toxicity, acute surgical abdomen, rabies and hypocalcemia. Patients with these may have Trismus, but they should not have Risus sardonicus. Cerebrospinal fluid examination will reveal no cells nor any increase in protein.

Clinical course and treatment: The natural history of clinical tetanus follows a rather characteristic pattern (20). There is an initial buildup phase of about 2-7 days in which the signs may worsen. Following the buildup, the signs stabilize and remain relatively stable for 1 to 2 weeks. It is during the early stage and the early plateau phase that therapy is so difficult and hazardous. The clinical care and treatment necessary in this disease is best described in the monograph by Dr. Jenkins (19). At present, sedation and antispasmodic therapy is begun with nembutal or diazepam (Valium). Robaxin IM or IV has been utilized if these fail. However, in severe cases, large dosages of 3 to 6 grams per day may be required, but toxicity as manifested by metabolic acidosis, renal failure and occasionally convulsions is a considerable threat. These are secondary to the polyethylene glycol used as the vehicle in Robaxin. Since other agents, especially curare, are available for the treatment of tetanus, it would seem appropriate not to consider Robaxin for the treatment of severe tetanus.

Debridement of the wound (and hysterectomy if tetanus follows an abortion) is critical. Antibiotics, either tetracycline or penicillin, should be administered since either is effective against Cl. tetani. If, as in our case, gangrene has developed, and infection with gram-negative rods, is a possibility, kanamycin should be administered.

Immune therapy: The use of antitoxin has been an accepted part of treatment of tetanus since WW I. Equine antitoxin in quantities of 20,000 to 100,000 units had been the accepted mode of therapy of proven tetanus until the 1960's (19). Since complications, especially serum sickness, in addition to anaphylaxis, are frequent with this large dosage, the availability of hyperimmune human globulin after 1963 provided an alternative to equine material. This homologous antitoxin is devoid of side effects in man (21). Experimental work has indicated that homologous antitoxin persists longer than heterologous type (21, 22); thus the material appeared to have clear advantages in tetanus prophylaxis. However, the rationale given for its use in tetanus

is the same as that for tetanus prophylaxis, since "in man the human product has a half-life 2 to 3 times longer than horse serum antitoxin, and for this reason (it) may be used in smaller quantity" (4). However, experimental studies of tetanus have demonstrated that any form of therapy which prevents death must be initiated prior to the development of clinical signs or early in the course of tetanus (23). Also, with the intravenous route of administration in man, a high level is achievable at a much earlier time (6 hours versus 48-72 hours for intramuscular route) and the high level persists just as long (7 days). Hence, intravenous injection has greater theoretical advantages than the intramuscular administration, if antitoxin is to make a difference. The equine antitoxin can be given IV, but hyperimmune human globulin must be given IM.

An analysis of patient groups given both homologous and heterologous antitoxin has been done recently by the NCDC (12). A case-fatality ratio of 55% was observed in 97 patients receiving 50,000 or more units of animal antitoxin, but a substantially higher ratio (70%) was noted in 77 patients receiving less than 50,000 units. However, the case fatality-ratio for 58 patients receiving more than 3,000 units of hyperimmune human globulin was 78%, which was no different than that found in 70 patients receiving no serological therapy for tetanus (81%). They argue that 1 unit equals 1 unit in terms of protection, and they conclude that larger quantities of hyperimmune human globulin may not be necessary.

It has been our impression that the case-fatality ratio at Parkland is higher now than the 13% reported by Dr. Jenkins through 1962 (19). Hence a review of the cases of tetanus since hyperimmune human globulin has been utilized at Parkland might be instructive.

NO. OF PATIENTS - 8

Date [redacted] 1966 - Present

Age Group	Neonatal	1-50	> 50	Total
Number	4	1	3	8
Died	4	0	3	7 (88% case-fatality ratio)

Type of injury:

3) Cord tied with string
1) Cord tied with rag
Splinter in arm
1) Gangrene
1) Burn
1) Unknown - greenhouse employee

Complications:

GI bleeding	6
Pneumonia	4
Renal failure	4

1952 - 1962	Neonatal	1-20	21-50	> 50	Total
Number	10	39	10	3	62
Died	4	2	2	0	8 (13%)

Hence, our record is not as good at the present time as it was in the period through 1962. Part of the reason may be that the majority of our patients are in age groups with high case-fatality ratios.

In addition, the use of large dosages of equine antitoxin may have been a factor, although this is hard to prove.

Complications: As noted in the review of recent tetanus cases, significant gastrointestinal hemorrhage is a problem. The use of atropine and antacids might be of value, although this is not proven to be of value in preventing Cushing's ulcers. Renal failure has been a problem, particularly in the elderly. It was secondary to Robaxin in one patient, since this patient developed renal failure and metabolic acidosis soon after receiving large quantities IV. Compression fracture of the vertebrae is a possibility and x-rays of dorsal and lumbar vertebra should be obtained (19). Some patients will have a prolonged period of gait difficulty and jerky arms. Escessive weight loss and muscle wasting are considerable problems in those that survive, as illustrated by a 40-lb. weight loss and the requirement of prolonged physical therapy in the one patient who survived. The most dreaded complication is that of getting tetanus again. One attack does not confer immunity to a second attack (24). In a review of the problem in India, a 0.5% rate of recurrence was noted (25). Hence, any patient who survives must be given adequate immunization with tetanus.

Prevention:

The best approach to the prevention of tetanus is to provide immunization programs for all. The success of the program in the United States since WW II is illustrated by the mortality rates which reveal a problem primarily in the neonate and the elderly. Yet, there exists a large population of young mothers in the rural south, especially in Texas, and of elderly who are unimmunized. It has been demonstrated that immunization programs in pregnant females in underdeveloped countries decreases the incidence of tetanus neonatorum (26). We should develop a statewide program for rural areas to immunize the mothers and the young.

In addition, at Parkland, we could initiate in earnest an immunization program for our clinic population, since we serve the elderly from the socioeconomic group with the lowest immunization history. It has been demonstrated recently that if one adequately immunizes individuals with toxoid, one can provide protective levels of antitoxin which persist for a duration of 30 years (27). It has been calculated that the risk of developing tetanus at the end of 12 years is 1 per 300,000,000. Therefore, if the basic immunization program for adults of two doses of Td (which includes small quantities of diptheria toxoid) toxoid 4 to 6 weeks apart following by a reinforcing dose 1 year later, booster injections would not have to be given with each wound or laceration. Considering the cost of hyperimmune human globulin, this is an inexpensive project. An appropriate beginning would be in our clinic population.

Once individuals have this course of immunizations, it would no longer be necessary to give booster doses with injury. In fact, a number of studies indicate that harm may be done by giving too frequent boosters (28, 29). The reaction that occur include local reactions with swelling, pain and malaise, urticarial reactions and angioneurotic edema.

For those individuals presenting with a wound and no history of previous immunizations, passive prophylaxis should be employed. Because of the advantages of hyperimmune human globulin (persistent levels for longer periods and lower reaction rate), it should be employed rather than equine antitoxin. The dose recommended is 250 units (30). However, just as 3,000 to 5,000 units of equine antitoxin were not completely protective,

the hyperimmune human globulin is not either, as demonstrated by the case report of tetanus developing following passive prophylaxis with human globulin (31).

III. Diseases Caused by the Toxins of Clostridium perfringens

Toxins elaborated by Cl. perfringens produce wound infections (gas gangrene) enterotoxemia, and food poisoning. Gas gangrene and the toxemia are due to the alpha toxin produced by Cl. perfringens (13). This toxin is an extremely lethal toxin which has hemolytic and necrotizing features. The toxin (lecithinase C) is an enzyme which catalyzes the hydrolysis of phosphorylcholine. Since lecithin is widespread throughout the body, for example, in red cells, the enzyme can have multiple and devastating effects.

Gas gangrene (clostridial myonecrosis) is a rapidly spreading myonecrosis of healthy muscle following infection within severely injured muscle, particularly when the blood supply to the muscle has been interrupted. The clinical diagnosis can be made when there is sudden severe pain in the affected part, local swelling and edema and a profuse serohemorrhagic exudate. These symptoms and signs are frequently associated with a rising pulse rate and shock (32). At surgery, the muscle color will be altered to a pinkish-gray or a slate-blue color. Bubbles of gas may be seen, but there is not much odor (unless infection is present with other organisms. Surgical treatment is essential, and complete debridement the major consideration. Penicillin G in high dosages is the antibiotic of choice, especially when septicemia is associated, but it is only an adjunct to surgical debridement. Tetracycline has been recommended in the past, but a recent report demonstrated resistance of Cl. perfringens to tetracycline (33). Equine antitoxins have been utilized, but their value is questionable, and we do not recommend antitoxin therapy.

The clinical manifestations of toxemia in association with Cl. perfringens septicemia are primarily seen in cases of uterine gas gangrene. This may occur following manipulative procedures, such as induced septic abortion or caesarian section, and has been seen as a complication of choriocarcinoma (34, 35). The characteristics include the very rapid development of elevated temperature, jaundice, hemoglobinemia and hemoglobinuria, renal failure, and shock. As a result of intravascular hemolysis, the hematocrit can drop precipitously, and hematocrits of 2% have been recorded. In addition, the thromboplastic activity released from red blood cells can initiate intravascular coagulation, which in turn could activate the fibrinolytic system (36).

Even if the patient survives the onslaught of the acute hemolysis and intravascular coagulation, she will frequently have anuria for a long period. The differential diagnosis includes gram-negative bacteremia with shock and anuria developing as a result of greensoap used as the abortifacient (35). Treatment should include high dose penicillin, dilatation and curretage of the uterus and injection of 100,000 units of Cl. perfringens antitoxin. X-rays of the pelvis should be taken, and if gas is noted in the uterus, hysterectomy will be necessary.

We have recently reviewed septic abortions at Parkland with bacteremia (37). Cl. perfringens was an uncommon organism, but a significant cause of mortality.

	1966	1967
Septic abortion	-	140
Positive blood cultures	40	41 (29%)
Deaths	2	1
Organisms:		
Peptostreptococcus (anaerobic streptococcus)	13	17
Bacteroides	6	2
Both	2	5
E. coli	8 (2 deaths)	5
Pseudomonas	7	0
BH. Streptococcus, Non A or D	3	3
Cl. perfringens	1	5 (1 death)
Enterococcus	2	1
Engerobacteo	0	1
Mixed	0	2

The two deaths in 1966 were in patients with gram-negative bacteremia who developed shock, renal failure and intravascular coagulation. The death in 1967 was with Cl. perfringens and was associated with shock, hemolytic anemia, jaundice and renal failure. Both the organism from this patient and from another patient with Cl. perfringens bacteremia who did well produced large quantities of alpha toxin in vitro.

Food poisoning with Cl. perfringens occurs in a rather characteristic fashion. The incubation period may range from 8 to 24 hours (usually 10-14) following the ingestion of food heavily contaminated with Cl. perfringens (38). The symptoms include the sudden onset of abdominal pain with nausea but rarely with vomiting and diarrhea. The course is short and the patient is well within 24 hours. The heavily contaminated food is usually a meat dish or gravy prepared one day previously and served the following day after short warming. The food is usually not spoiled. The spores in the contaminated food may be converted to vegetative forms by boiling the food for 1 hour. The nature of the food poisoning factor is not known, but it is not alpha toxin (39).

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