# Botulism and Mimicking Disorders

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Latin botulus, "sausage"

## Sausage Poisoning in Würtemberg

Justinus Kerner
Physician and poet
1786-1862

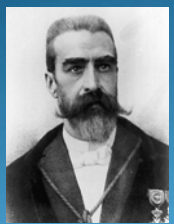
*(1820- clinical Report 155 cases)*
*J Neurol Transm* 2008; 115:559-63

Sausage extracts fed to birds, cats, frogs, etc: created botulism model

"The capacity of nerve conduction is interrupted in the same way as an electrical conductor by rust"

## Discovery of *Bacillus botulinus* in Belgium

Among musicians playing at funeral of 87 y old Antoine Creteur- 1895



Emile Pierre van Ermengem
1851-1922
Professor of Microbiology,
University of Ghent

34 cases from pickled smoked ham

- Diplopia
- Dysphagia
- Dysphonia
- Dysarthria
- Progressive paralysis

*"Highly probable... poison in ham was produced by anerobic growth of specific microorganisms..."*

Used with permission from Professor Erbguth of the Nurnberg University

# Botulism

Preformed Toxin

*Food-borne*

Spores germinate => later produce toxin

*Infant* – 10% honey sold in US contaminated with spores!

*Wound* – black tar heroin

*Hidden* – prior GI surgery, Crohn's, recent antibiotics

Proliferates at pH>5, high water content

low salt, low sugar

Heat 85 ° C inactivates toxin; 120 ° C to kill spores

Note: boiling renders solutions more anaerobic

*Semin neuro* 2004; 24:155-63
*Ann Intern Med* 1996; 125:558-63
*J Environmen Health* 2003; 65:51-2

# Botulism Outbreaks in Colorado

Boiling food prior to canning at high altitudes may not provide enough heat to kill all spores.

Water boils at 85° C at 10,000 feet

*Semin Neuro* 2004; 24:153-63

Add lemon juice (↓ pH) if canning tomatoes

*NEJM* 1997; 337:184-90

Baked potatoes wrapped in aluminum foil hazardous: spores not killed by baking in foil wrap. Baking aids spore germination. Foil wrap provides anerobic environment. Dip not reheated prior to serving after days at room temp. 86% attack rate! - Colorado

*JID* 1998; 178:1727

# Foodborne Botulism 1899-1996 in US



Two European countries where meat is the most common vehicle

A-38%
B, E - ~15% each
B spores more in East;
A spores West soil

*J Clin Neuromusc Dis* 2003; 4:139-49
*Health Lab Sci* 1978; 15:74-80

## Substance Abuse and Botulism

3 cases after tea from Peyote previously covered in closed jar 2 months

Ages 40, 42, 72 / Religious ceremony

*NEJM* 1998; 339:203-4

Botulism and *C. botulinum* sinusitis after intranasal cocaine

25 male (2nd use 10 days earlier)

Classic presentation but no GI Sx

Ventilator-dependent 6 mo

*AIM* 1988; 109:984-5

## Botulism and Bioterror

Toxin: 100,000 more toxic than sarin

1 grm toxin aerosolized: potential to kill 1.5 million

LD 50 0.7-0.9 µg inhaled

Gulf War I


Iraq produced 19,000 liters of concentrated BTX – 3x amount needed to kill entire world's people

*JAMA* 2001; 285:1059-70
*JAMA* 1997; 278:433-5

## Action of BoNT: Absorbed in Duodenum, Jejunum

Toxin -> Circulating system → Cranial and peripheral nervous system cholinergic synapses, binding irreversibly to presynaptic receptors

Bacterial Protease:
-50 kD light chain
-100 kD heavy chain

- From receptor, toxin transmitted into nerve cell
- LC endoproteases selectively target, cleave 3 components of synaptic fusion complex
- Inactivation of SNARE proteins leads to neurotransmitter blockade

- Soluble –N – ethylmaleimide-sensitive Attachment protein Receptor

## Botulism Toxins – mostly

## *C. botulinum*: 150 kDa Polypeptides

All inhibit Acetylcholine release at neuromuscular junction

*C.baratii* – only F

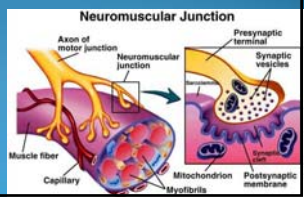
*C. butyricum* – E

*C. argentinense* – G (associated with sudden death, but not paralysis)

ID 50 estimates:

Oral - 70 µg

IV .09-.15 µg




*Disaster Med Pub Hlth Preparedness* 2007; 1:122-134 *JID* 1992; 166:1281-6

## Natural History of Botulism

## Usual Incubation 2-36 hours

Nausea
Vomiting
Abdominal cramps
Diarrhea

Diplopia
Dysphagia
Dysphonia
Dysarthria
Blurred Vision
Ptosis
Ophthalmoplegia
Tongue weakness

Acute Descending Flacid muscle Paralysis (resp.muscles)
can be abrupt

Cholinergic Parasym Autonomic Nerves } **inhibited**

Constipation – Pupillary abnormalities

Dry mouth, Postural hypotension

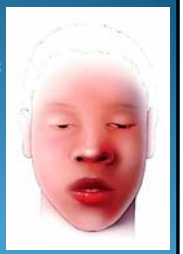
Alternations in resting heart rate

*Semin Neuro* 2004; 24:155-63
*J Neurol Neurosurg Psych* 1992; 55:844-5
CBC news Feb 20, 2008

## Key Clinical Aspects of Botulism

- Patients are completely alert
- No (rarely) sensory changes
- Symmetrical C.N./*Descending* Paralysis
- Preserved Deep tendon reflexes (progressively disappear)
- No fever
- Normal/slow heart rate

Note: the absence of cranial nerve palsies rules out botulism!



Ptosis, facial paralysis, youthful, unlined, inexpressive

*CID* 2005; 41:1167-73

## Botulism – 50% Require Respiratory Assistance

- Sudden, unexpected respiratory arrest common
- Respiratory failure – almost all early deaths
- Median time: symptoms to intubation – 1 days
- Intubation: 2 to 8 weeks: A>B
- Case fatality> 5%; if age >60-30%
- 1st case of outbreak 25% subsequent cases 4%

Hughes *Infections of CNS* 1994

- Cost of care $340,000 – 1989

Int J Food Microbiol 1989; 9:313-26

## Severe Botulism with Prolonged Toxemia Caused by Commercial Carrot Juice


All 6 – required intubation
5 – Dysphagia
4 – Blurred vision
3 – Dysphonia
3 – Diplopia
3/6 antitoxin within 24 h
5/6 survived
At 1 year: 2 still on vent!

pH 6.8
Low salt
Low sugar

Patient *1 - * 100 mouse intraperironeal $LD_{50}$
Patient *2 - * 100,000 $MIPLD_{50}$ highest ever reported

*CID* 2008; 47:1245-51

## Severe Botulism with Prolonged Toxemia Caused by Commercial Carrot Juice

SERUM SAMPLE

Botulinum toxin < 18 h
After exposure – 160 MIPLD 50/ml
Day 8 – 1800 MIPLD 50/ml!

Day 12 – still > 200 MIPLD 50/ml
Two patients given antitoxin at Day 13, 46 respectively

CLINICAL LESSONS

* Collect serum 24 h after antitoxin Rx to determine if toxin still present

* Consider antitoxin Rx even Weeks after exposure if high toxin exposure suspected

*CID* 2008; 47:1245-51

## *C. Botulinum* Type G: Sudden Unexpected Death

| Age/sex | Prodrome | Pathology |
|---|---|---|
| 24 M | looked pale 10 pm<br>7:30 am found dead | |
| 29 M* | nausea midday<br>dry mouth<br>found dead in bed | Hemorrhagic edema<br>Congested brain |
| 33 M | 3 d abd pain<br>1 d – thirsty, dry mouth<br>found dead 9:30 a.m. | |
| 18 wks M* | SIDS | Interstitial Pneumonia |
| 45 M* | cough, loss appetite<br>found dead 3:40 am | bronchopneumonia |

* **Toxin G found in blood**

*JID* 1981; 143:22-7

## *C. Botulinum* toxin in 15% SIDS (n=70)

| Age(d) | Toxin serum | Sm bowel | Colon |
|---|---|---|---|
| 192 | A | NT | NT |
| 136 | G | G | - |
| 122 | - | - | F/F toxin |
| 337 | - | - | C/C toxin |
| 254 | G | G/G tox | - |
| 70 | - | G/G tox | - |
| 267 | - | - | F/F toxin |
| 71 | - | B/B tox | B/B tox |
| 198 | F | - | F/F tox |

*Lancet* 1985; (Feb)237-41

## Confirming Botulism

Demonstrate toxin: serum (10 ml red top)
Gastric contents, stool (sterile water enema), food
Refrigerate – not freeze
Bioassay in mice – most reliable
Sensitivity: 60% - if within 2 days
**0.03 nanograms** 44% - if within 3 days
23% - if within 4 days
Some culture/toxin-neg cases may be due to not screening for non-botulinum species

*JAMA* 2001; 285:1059-70

## Antitoxin Therapy

| Product | FDA approved? | Availability |
|---|---|---|
| Bivalent (A/B) equine antitoxin | Yes | CDC |
| Monovalent (E) equine antitoxin | No | CDC |
| Trivalent A, B, E | Yes | CDC |
| Heptavalent (A-G) antitoxin | | |
| Fc portion cleaved –"despeciated" | No | USAMRIID, CDC |
| Baby-BIG | Yes | CDHS |
| Human botulinum immune globulin E | No | CDHS |

**CDC:404-329-2888**

**770-488-7100**

USAMRIID, US Army Medical Research Institute of Infectious Diseases
CDHS California Department of Health Services

*Disaster Med Pub Hlth Preparedness* 2007; 1:122-34

## Treating Botulism

Early antitoxin therapy essential
T ½ 5-8 days
2% anaphylaxis; 4% serum sickness
If wound associated: Penicillin or Metronidazole
Benefit not proven
If infant botulism: no antibiotics!
(toxin released after bacterial lysis)
Plasmapheresis – Mixed results
Guanidine, aminopyridine – may improve muscle strength in recovery phase
Meds to avoid: aminoglycoside, clindamycin, Mg-containing meds – aggrivate neuro-muscular disorder

*Ann Intern Med* 1998; 129:221-8 *Intensive Care Med* 2002; 28:814
*Muscle Nerve* 1998; 21:701-10

## Electrophysiological Dx Botulism

- Compound muscle action potential (CMAP)
  Low amplitude – 85%
  Mostly proximal muscles
  not predictive
- *Decremental* response on 2-HZ stimulation – defect in N-M transmission, but inconsistent
- Tetanic stimulation (20-50 HZ) shows *incremental* response reflecting presynaptic defect. Not reliable
- CMAP following 10 sec max contraction> 20% baseline, lasting minutes. Most consistent

*J Clin Neuromusc Dis* 2001; 1:121-2

- A patient with suspected botulism should be treated ASAP
- Deliver the antitoxin
- Call state health department to investigate (CDC has supplies in quarantine stations around the country)

CID 2009; 48;1874-5

## Differential Diagnosis - Botulism

**Guillian Barre Syndrome:**

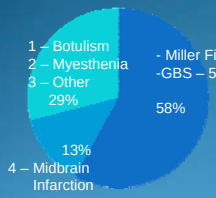
*Ascending* Paralysis
Sensory Abnormalities/Paresthesias Common
Loss of DTRs; No altered pupillary activity
90% autoantibodies (GQ1b)
Elevated CSF protein
Miller Fisher variant may have ocular, bulbar abnormalities (5% ) but usually prominent ATAXIA!
EP studies –peripheral nerve, not neuromuscular junction
May be history of recent diarrhea (*C. jejuni* in 25% of GBS) *CID* 2005; 41:1167-73


## Guillian-Barre* variants

- Acute inflammatory demyelinating polyneuropathy – 85-90%
- Miller-Fisher – ophthalmoplegia, ataxia, areflexia 5% U.S./25% Japan
- Acute Motor Axonal neuropathy. Most – prior campylobacter, esp. Japan and China
- Acute sensori motor axonal neuropathy 5-10% U.S. more in China, Japan, Mexico
- Bickerstaff brainstem encephalitis
- Other
  - Pharyngeal-cervical brachial: arm weakness, swallowing difficulties
  - Paraparesis
  - Acute pandysautonomia (responds to IVIG) diarrhea, vomiting, abdominal pain, dizzy, orthostritic, urinary retention, pupils abnormal, decreased sweating, salivation, tearing
  - CAN IF CSF cell count ≥ 10 -> screen for HIV!

up-to-date 2010

## Bilateral Ocular Paralysis (n=31) – over 13.000 Neuro/Nsgy Cases screened




- 42 pts with MFS. Thus, 31% Miller-Fisher had ophthalmophegia
- 18/31 involved nerves vs NM Junction (4), brainstem (S) or Cavernous sinus(4)

- Only 1 % with myasthenia and 6% with Botulism had complete ocular paralysis

*Arch Neurol* 2007; 64:178-80

## Myasthenia Gravis/Eton Lambert

Fluctuating, fatiguable weakness

1 mg test dose
Wait 1 min
2-3 mg bolus
Repeat in 1 min if no response

MG

Dramatic (<60 sec) response to Edrophonium Chloride
Autoantibodies (Acetylacholine receptor AB – 80-90%)
EMG differentiates
5% pernicious anemia, RA, SLE
1% thyroid disease
No myalgia. No autonomic features

*Seminars in Neurol*; 2001; 21:425-440

EL

Usually preexisting lung CA
Improve with repeated/sustained exercise
Squeeze hand – modest squeeze → more forceful over next 5 seconds – Lambert's sign
No deep tendon reflexes
Usually No cranial nerves involved
EMG does mimic botulism

## Autoimmune Myasthenia Gravis

Target of attack:

1) skeletal muscle acetylcholine receptor
2) muscle-specific receptor Tyrosine kinase (occasionally)

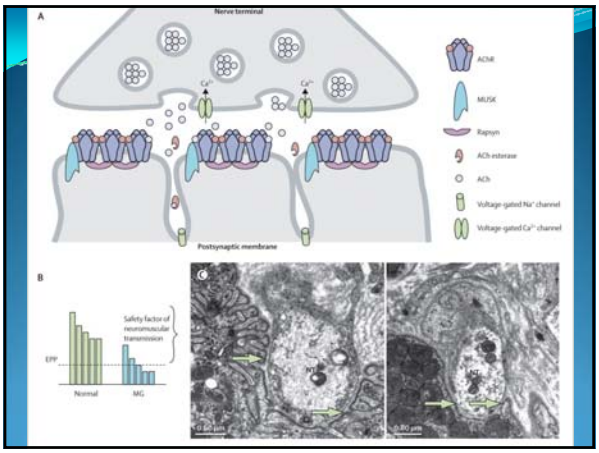
< age 40: Women:Men 3:1

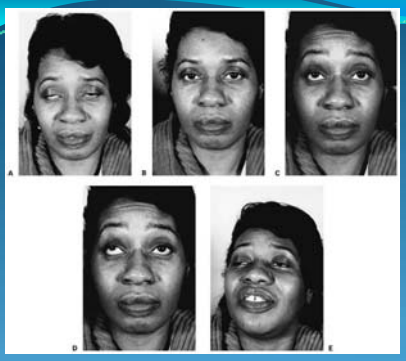
>age 50 Men >> Women ->

10-15% Thymoma Ptosis
peak onset age 50

Diplopia ->
Dysarthria fatiguable weakness
Dysphagia 15% initial symptoms ->
Dysphonia

High titers anti-AchR antibody
of those without anti-ACHR antibody 40% have antibodies to MUSK



The patient has several months of fluctuating diplopia, dysarthria, and dysphagia.The exam shows bilateral ptosis, dysconjugate gaze, and a weak myopathic facies. (B) Thirty seconds after administration of 3 mg of intravenous edrophonium, the patient's deficits are markedly improved.This response would be considered positive, and supportive of the diagnosis of myasthenia gravis. (C) One minute later, with the patient looking up. (D) Three minutes later, as medial rectus weakness becomes apparent. (E) Five minutes after infusion, not only has the baseline weakness returned but also the patient now has increased difficulty controlling oral secretions.

*Seminars in Neurol* 2001; 21:425-40

MYASTHENIA GRAVIS – RESPONSE TO 3 MG EDROPHONIUM

## Lambert-Eaton Paraneuroplastic Neurological Syndrome

1/10,000 with cancer

1% with small cell CA lung

Must: occur **before** cancer diagnosis

Onconeural antibodies: against tumor and nervous system

Almost all have VGCC-Ab

Mechanism: Reduced AcH release

Lower limb weak 100%  weight loss 24%

Upper limb weak 78%  Myasthenia Sx

Excessive eyelid elevation after sustained upgaze

VGCC – Voltage Gated Calcium channel

Orphanet J Rare Dis 2007; 2:22 doi:10.11 86/1750-1172-2-22

## Tick Paralysis

Symmetric *ascending* paralysis – over 1-2 days
Tendency to fall
Trunchal Instability
Parathesias common, fatigue, myalgias
Cranial nerves – usually normal
Dilated pupil – U.S. – no; Australia - yes
Find the tick!
No fever
Nystagmus
DTRs – absent, diminished

Neurotoxin in saliva
43 tick species

*Infect Dis Clin N Amer* 2008; 22:397-413

## Case History: 33 y old male

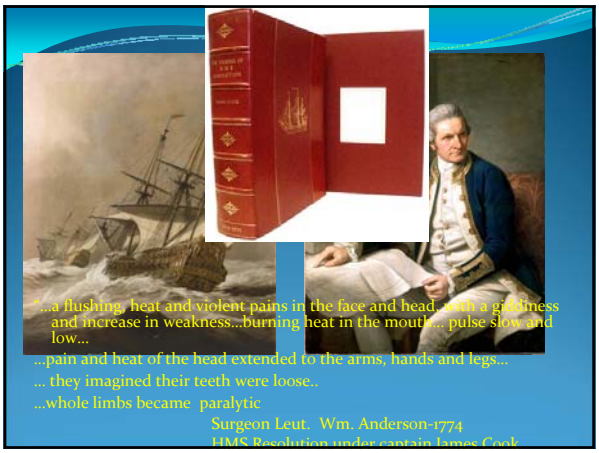
2-days:fever, sore throat, ITA
Watery diarrhea, photophibis
39˚, rigid masseters, slowed speech
Difficulty eating, drinking, xs salivation
Brief periods: agitation and lucid calm
WBC 12,000 (85% ℗)
LP: 1120 (85% ℗), P-95; Sug – 70
Day 2: L facial weakness (UMN), bilat ptosis
Incomplete ophthalmoplegia
Normal motor, sensory, DTRs

*CID* 2010; 50:77-9

## Differential Diagnosis

1. Tetanus
2. GBS – Miller-Fisher variant
3. Bickerstoff-brainstem encephalitis – GBS variant
4. Paralytic Rabies

*CID* 2010; 50:77-9



"...a flushing heat and violent pains in the face and head...with a giddiness and increase in weakness...burning heat in the mouth... pulse slow and low...

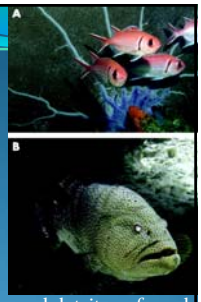
...pain and heat of the head extended to the arms, hands and legs...

... they imagined their teeth were loose..

...whole limbs became paralytic

Surgeon Leut. Wm. Anderson-1774
HMS Resolution under captain James Cook

## Ciguatera Poisoning



Worldwide 50,000 cases annually

90% - acute – within 12 hours of ingesting toxic fish

*Pract Neurol* 2007; 7:316-22

Herbivorous small fish graze on microalgae and detritus of coral reefs containing dinoflagellates (*Gambierdiscus toxicus*)

Larger reef fish feed on smaller fish – barracuda, grouper, red snapper, amberjack

Outbreaks after storms ; Increased Frequency with global warming?

*W J Med* 1995; 163:1-5

## Ciguatoxins – Polyether Toxins

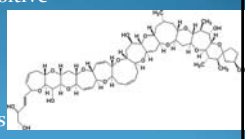
Higher Concentrations in viscera, liver, head of fish

No taste or smell

Not deactivated by heat/freezer for 6 mo/cooking/gastric juice

Bind to and modulate voltage –sensitive Na+ channels

→Membrane depolarization → decreasing conduction velocity of sensory and motor nerve fibers



*J Pub Health* 2006; 28:343-6

## Ciguatera Poisoning

Usual Incubation ≤ 12 hours (i-30)

Acute
GI Sx
N, V, D
abd pain

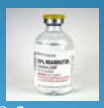
Cirumoral, limb paresthesias
Reversal of Thermal sense
Itching
Perception of loose teeth

Headache
Myalgia → polymyositis
Arthralgia
Rash – palms/soles
Tingling – tongue
Dysphagia
Ataxia
Tremor
Dysarthria
Paralysis

## Treatment of Ciguatera Poisoning

IV 20% mannitol (5-10 ml/Kg)
infused slowly over 30-45 minutes
(maybe cause decrease edema in Schwann cells, nodal swelling)

*Pract Neurol* 2007; 7:316-22
*JAMA* 1998; 259:740-2



Atropine for Symptomatic Bradycardia
*Arch Intern Med* 1982; 142:1090-2

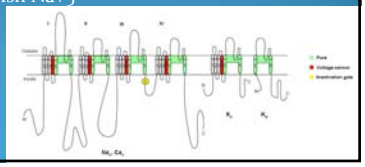
Case report: 2 patients responded well to gabapentin
*NEJM* 2001; 344:692-3

## Neurotoxins from Marine Dinoflagellates

Caused by diverse specific interaction with Ion Channels Included with Neurotransmission

- Ciguatera fish Na+ 5
- Paralytic shellfish Na+ 1
- Neurotoxic shellfish Na+5

*Marine Drugs*
2008; 6:349-71



## Neurotoxic symptoms

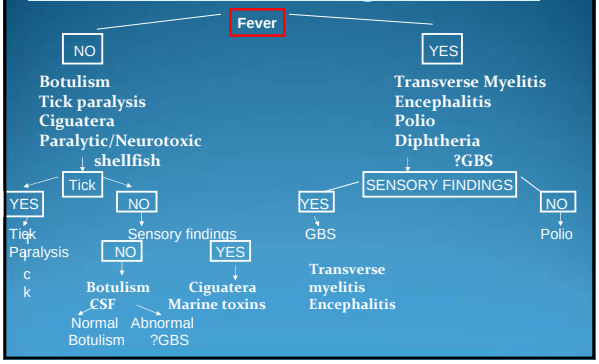
Paralytic SP – Tickling sense of lips, mouth, tongue
numb extremities, GI Sx
Difficulty breathing, sense of dissociation
→ complete paralysis
→ Respiratory failure And CV shock, death

Neurotoxic SP – Nausea, tingling and numbness of perioral area
Loss of motor control
Severe muscular pain

## Botulism – Pattern Recognition

| Botulism: | Ascending Paralysis: |
|---|---|
| 4 Ds | GBS |
| Diplopia | Tick paralysis |
| Dysphagia | |
| Dysphonia | If weakness/Paralysis + sensory findings: |
| Dysarthria | |
| *Descending* paralysis | Ciguatera |
| Fully alert | Marine toxins |
| | GBS |

## Disorders Mimicking Botulism



## Summary – Botulism Recognition

Descending Paralysis
Symmetrical Cranial Nerve Defects
Alert and Afebrile
Slow/Normal Heart Rate
Preserved DTRs
No sensory Changes

## Approach to Diseases Mimicking Botulism

| | |
|---|---|
| History: | Food, travel, tick bites, fever, rate of progression |
| | Pain, sensory problems |
| PE: | Vital signs, 4Ds, neuro exam – Cranial Nerve disorder? |
| | Look for tick! |
| LAB: | CSF, MRI spine, brain EEG, |
| | nerve conduction |

## Botulism and Mimicking Disorders

| | Botulism | GBS | Tick paralysis | Transverse myelitis | Viral Enceph. or polio |
|---|---|---|---|---|---|
| Fever | no | rare | no | variable | yes |
| Sensory Findings | no | yes | no | yes | prominent |
| Pain | no | rare | rare | yes | variable |
| Dilated Pupils | yes | rare | US-rare Austral-occ. | no | no |
| CSF Protein | normal | elevated | normal | usually elevated | elevated |
| MRI | normal | usually normal | normal | abnormal | abnormal |

*Infect Dis Clinics N Am* 2008; 22:397-413

## Diphtheric Toxin

Penetrates into Schwann cells
binding quickly – progressive deteriotarion of myelin sheath

Equine antitoxin must be given on day 1 to have effect
Need to call CDC:
1-404-639-2889

1) 1:100 dilution of scratch test
2) 0.02 ml 1:1000 injection
3) Then therapeutic dose
If disease <48 h 20,000-40,000 n
nasopharyngeal 40,000-60,000 n

## Diphtheric Polyneuropathy

32 Patients with Severe Illness

1990-95 – 125,000 cases (4000 deaths)
Former Soviet Union

*Arch Neurol* 2001; 58:1438-42
*J Neurol Neurosurg Psych* 1999; 67:433-8

| 100% Cervical SC Fat edema To clavicle 30/32 -myocarditis | Numbness gingivae, tongue Face Pareses of soft palate Paresthesias fingers toes Dysphasia, dysphagia | All CN invol??? IX-X – 100% VII – 88% II, IV, VI – 84% XI – 84% XII – 72% V – 53% | Prox Quadriparesis Quadriplegia Areflexia Improve ? Vibration ↑CSF Protein – 33% Normal protein ≤ 12 cells |
|---|---|---|---|
| ONSET | 3-5 weeks after onset diphtheria | weeks 4-7 sudden decrease blood pressure | motor disturbances peaked – day 51 |


National
The New York Times
Ash Flood in Tennessee Is Found to Be Larger Than Initial Estimates

Elevated levels of thallium found

## Thallium Poisoning from Eating Contaminated Cake – Iraq, 2008

Thallium: odorless, tasteless heavy metal – rodenticide
10/12 who ate cake were ill (83%)
4/10 died (40%)

- ABD pain
- Vomiting
- Dysphagia
- Within hours -

→ 4 days

5/10(50%) neuro Δs
- paresthesias
- painful, ascending neuropathy
- beginning hair loss

→ 6 survivors had lower limb spasticity

Rx: Prussian blue (ferric hexacyanoferrate)

*MMWR* 2008; 57:1015-8