

Botulism and Mimicking Disorders

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Latin botulus, "sausage"



Sausage Poisoning in Würtemberg



Justinus Kerner
Physician and poet
1786-1862

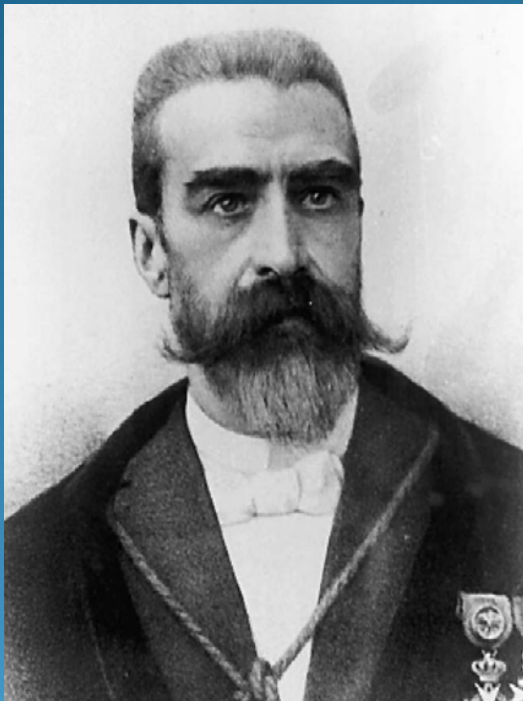
(1820- clinical Report 155 cases)
J Neurol Transm 2008; 115:559-63

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

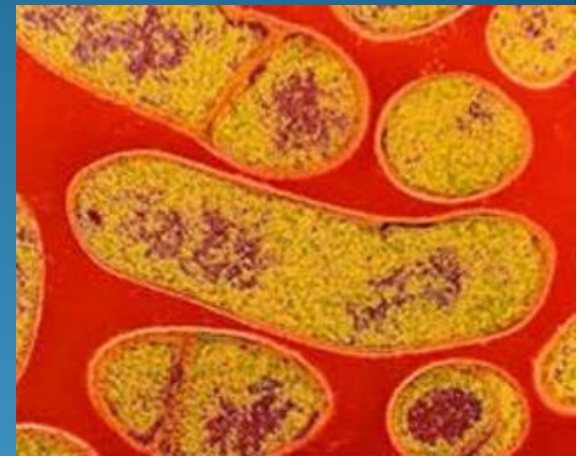


Emile Pierre van Ermengem
1851-1922
Professor of Microbiology,
University of Ghent

Used with permission from Professor Erbguth of the Nurnberg University

34 cases from pickled smoked ham

- Diplopia
- Dysphagia
- Dysphonia
- Dysarthria
- Progressive paralysis



Clostridium botulinum

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

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

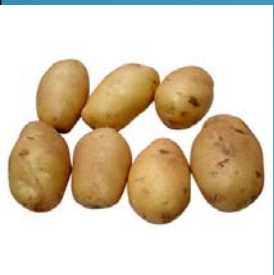
Semin Neuro 2004; 24:153-63

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



A-38%

B, E - ~15% each

B spores more in East;

A spores West soil

Vegetables - 42%

Fish/marine - 20%



Two European countries where meat is the most common vehicle

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 gram 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
Bacterial Protease: peripheral nervous system
-50 kD light chain cholinergic synapses,
-100 kD heavy chain binding irreversibly to
presynaptic receptors

- 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

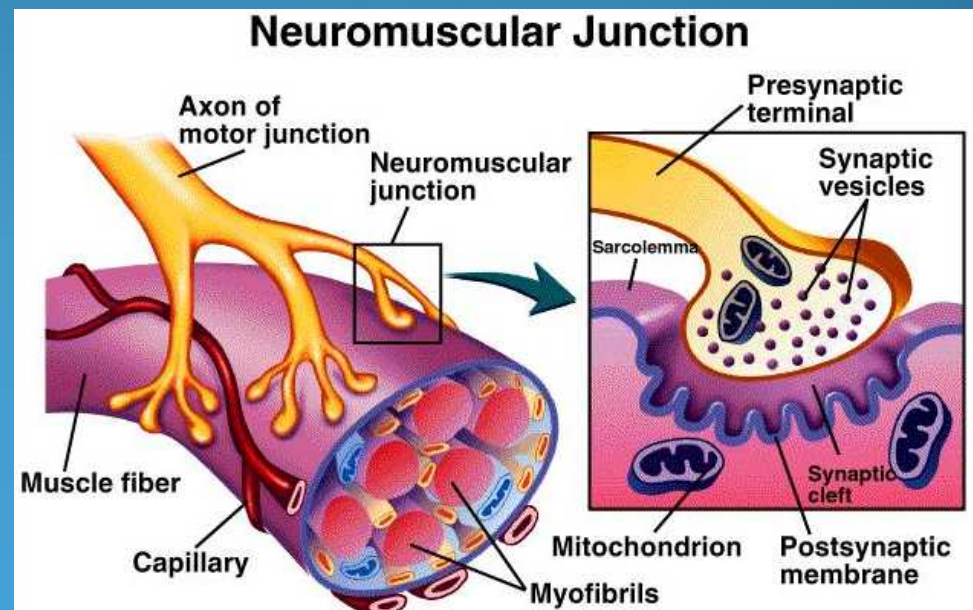
C. argentinense – G (associated with sudden death, but not paralysis)

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

	Diplopia	Acute
Nausea	Dysphagia	Descending
Vomiting	Dysphonia	Flacid muscle
Abdominal	Dysarthria	Paralysis
cramps	Blurred Vision	(resp.muscles)
Diarrhea	Ptosis	can be abrupt

Ophthalmoplegia

Tongue weakness

Cholinergic Parasymp

Autonomic Nerves

} inhibited

Constipation – Pupillary abnormalities

Dry mouth, Postural hypotension

Alternations in resting
heart rate

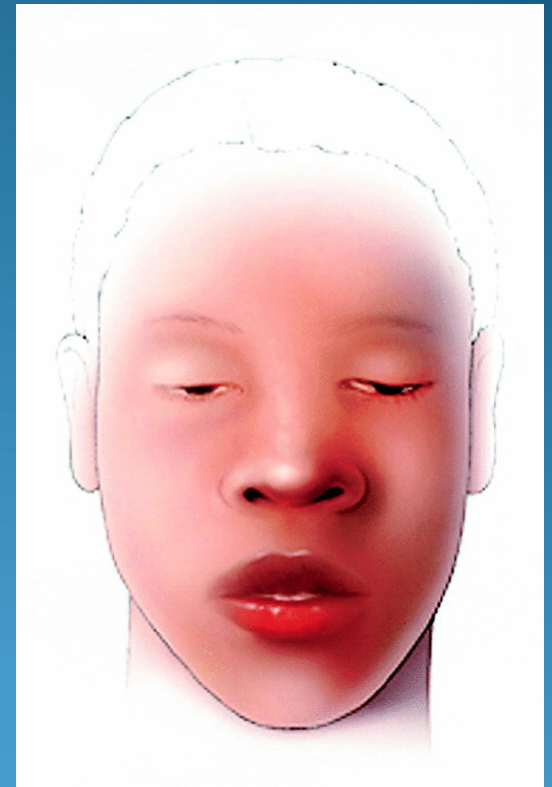
Semin Neuro 2004; 24:155-63
J Neurol Neurosurg Psych 1992;
55:844-5
CBC news Feb 20, 2008

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

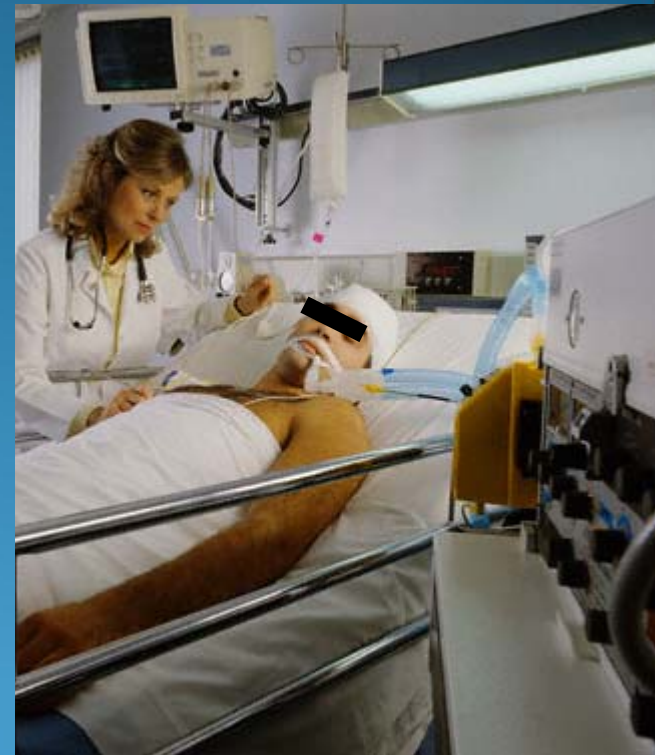
Case fatality > 5%; if age >60-30%

1st case of outbreak 25% subsequent cases 4%

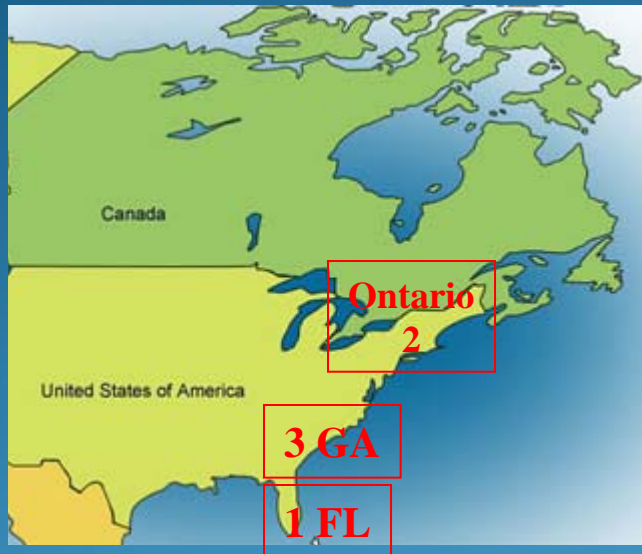
Hughes *Infections of CNS* 1994

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 intraperitoneal
LD₅₀
Patient *₂ - * 100,000 MIPLD₅₀ 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

24 M

29 M*

33 M

18 wks M*

45 M*

Prodrome

looked pale 10 pm

7:30 am found dead

nausea midday

dry mouth

found dead in bed

3 d abd pain

1 d – thirsty, dry mouth

found dead 9:30 a.m.

SIDS

cough, loss appetite

found dead 3:40 am

Pathology

Hemorrhagic

edema

Congested brain

Interstitial Pneumonia

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
44% - if within 3 days
23% - if within 4 days

0.03 nanograms

Some culture/toxin-
neg cases may be due
to not screening for
non-botulinum species



JAMA 2001; 285:1059-70

Antitoxin Therapy



<u>Product</u>	<u>FDA approved?</u>	<u>Availability</u>
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 $\frac{1}{2}$ 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
– aggravate 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

Differential Diagnosis - Botulism

Guillian Barre Syndrome:

Ascending Paralysis

Sensory Abnormalities/Paresthesias Common

Loss of DTRs; No altered pupillary activity

90% autoantibodies (GQ1b)

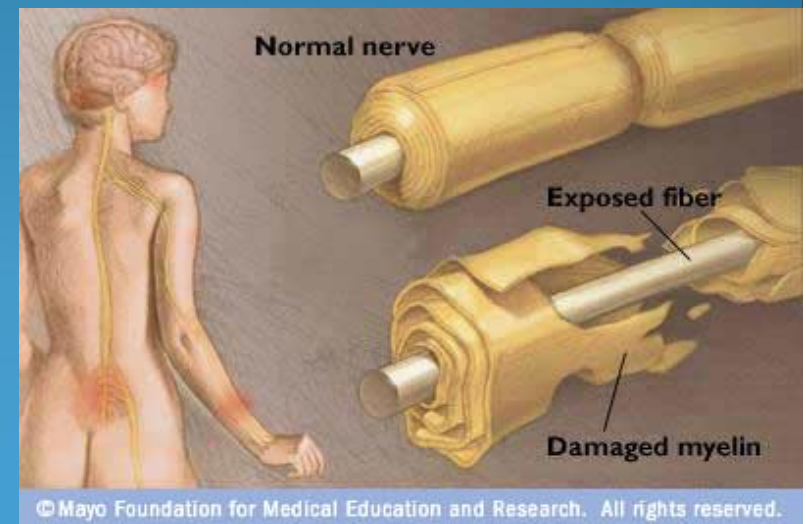
Elevated CSF protein

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



Myasthenia Gravis/Eton Lambert

Fluctuating, fatiguable weakness

MG

Dramatic (<60 sec) response to Edrophonium Chloride
Autoantibodies (Acetylcholine receptor AB – 80-90%)

EMG differentiates

5% pernicious anemia, RA, SLE

1% thyroid disease

No myalgia. No autonomic features

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

1 mg test dose

Wait 1 min

2-3 mg bolus

Repeat in 1 min if no response



Seminars in Neurol;

2001; 21:425-440



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

Tick Paralysis

Symmetric *ascending* paralysis – over 1-2 days

Tendency to fall

Truncal Instability

Parathesias common, fatigue, myalgias

Cranial nerves – usually normal

Dilated pupil – U.S. – no; Australia - yes

Find the tick!

No fever

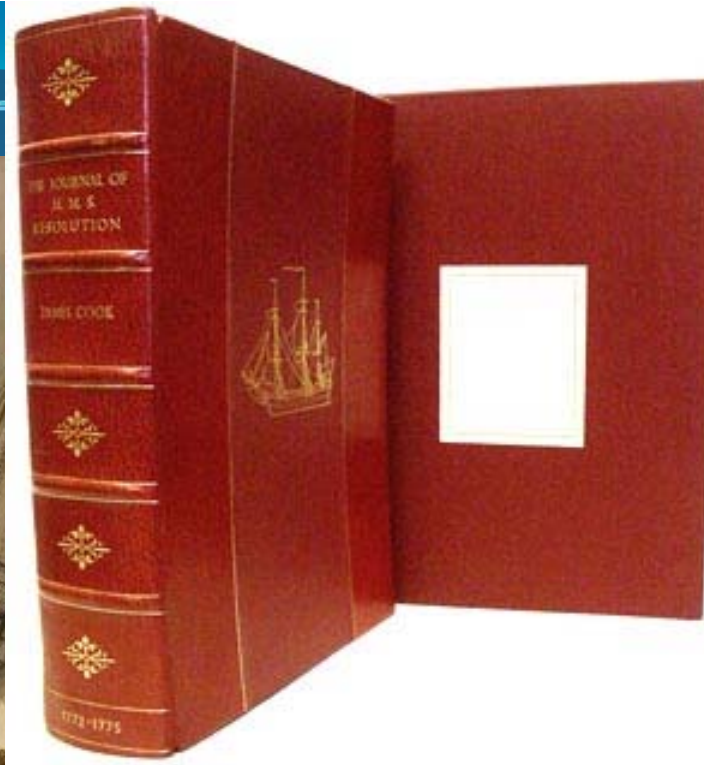
Nystagmus

DTRs – absent, diminished

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



Neurotoxin in saliva
43 tick species



“...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



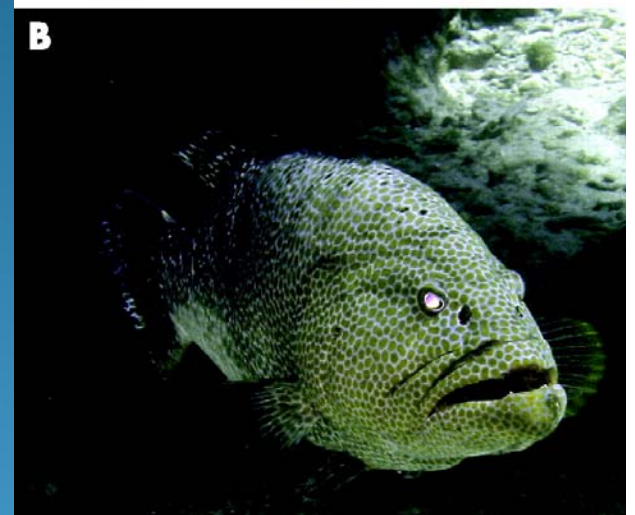
Pract Neurol 2007; 7:316-22

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?

WJ Med 1995l; 163:1-5



Ciguatoxins – Polyether Toxins

Higher Concentrations in viscera, liver, head of fish

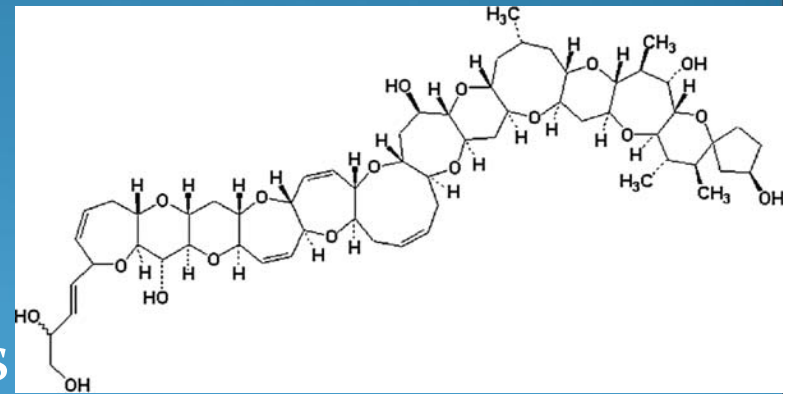
No taste or smell

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

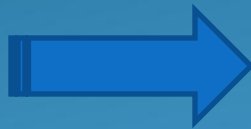


J Pub Health 2006; 28:343-6

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

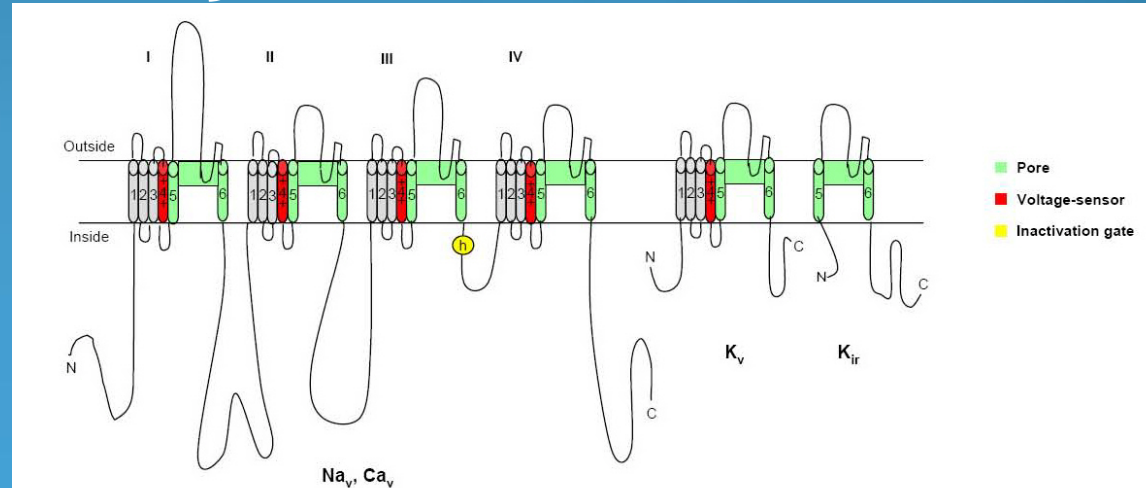
Caused by diverse specific interaction with
Ion Channels Included with
Neurotransmission

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:

4 Ds

Diplopia

Dysphagia

Dysphonia

Dysarthria

Descending paralysis

Fully alert

Ascending Paralysis:

GBS

Tick paralysis

If weakness/Paralysis + sensory
findings:

Ciguatera

Marine toxins

GBS

Disorders Mimicking Botulism

Fever

NO

Botulism
Tick paralysis
Ciguatera
Paralytic/Neurotoxic shellfish

Tick

YES

Tick
Paralysis
c
k

NO

Sensory findings

NO

Botulism
CSF
Normal Botulism
Abnormal ?GBS
Ciguatera
Marine toxins

YES

YES

Transverse Myelitis
Encephalitis
Polio
Diphtheria
?GBS

SENSORY FINDINGS

YES

GBS

Transverse
myelitis
Encephalitis

NO

Polio

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

Diphtheric Toxin

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

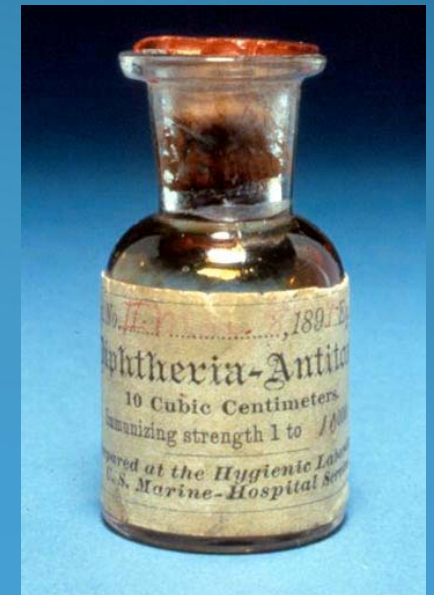
Equine antitoxin must be given
on day 1 to have effect

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



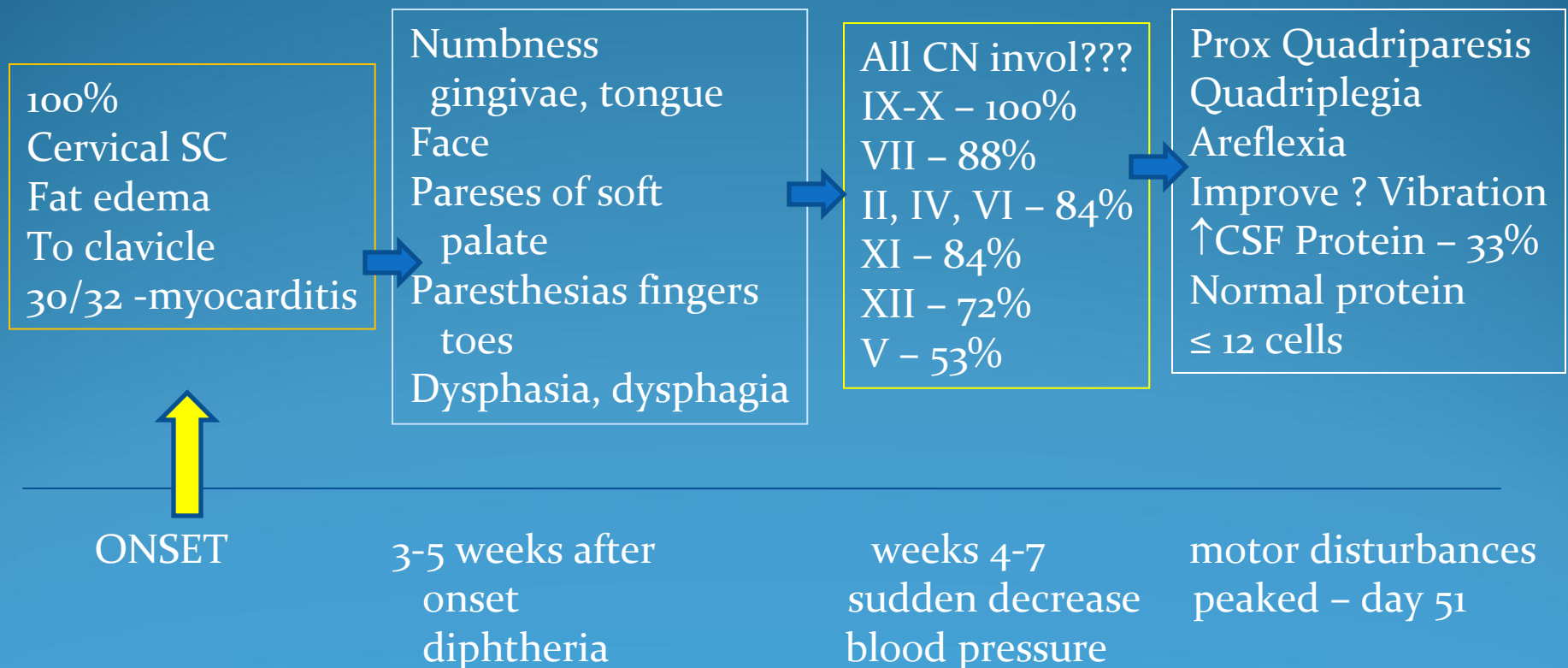
Diphtheric Polyneuropathy

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



A8 Y

SATURDAY, DECEMBER 27, 2008

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 | | 5/10(50%) neuro Δ s | | 6 survivors |
| • Vomiting | →
4 days | • paresthesias | → | had lower |
| • Dysphagia | | • painful, ascending | | limb |
| - Within hours - | | neuropathy | | spasticity |
| | | • beginning hair loss | | |

Rx: Prussian blue (ferric hexacyanoferrate)