

1. Damage to Host

Damage to Host

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2. Mechanisms of Damage

Mechanisms of Damage

bug mediated

intoxication

growth outside
normal niche

overgrowth in
normal niche

collaborative

growth inside host cells

lytic enzymes

toxin mediated
cytokine release

host mediated

inflammation

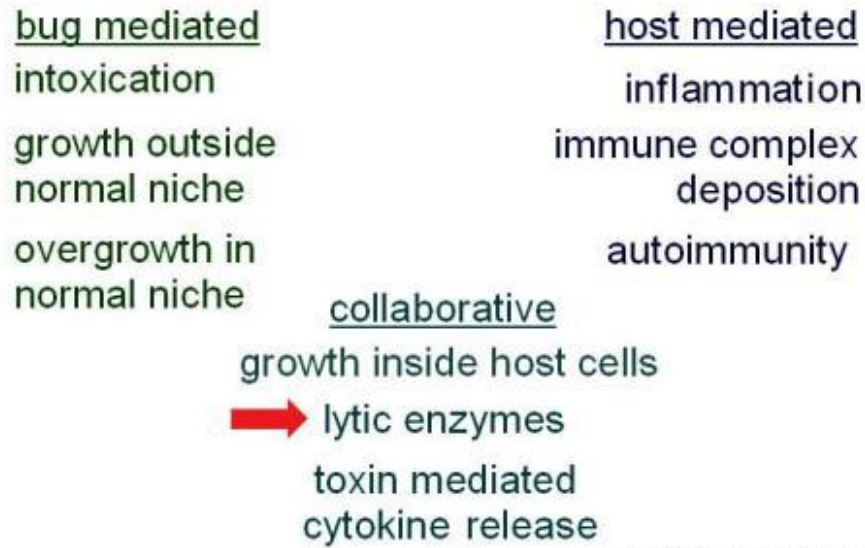
immune complex
deposition

autoimmunity

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3. Mechanisms of Damage (cont.)

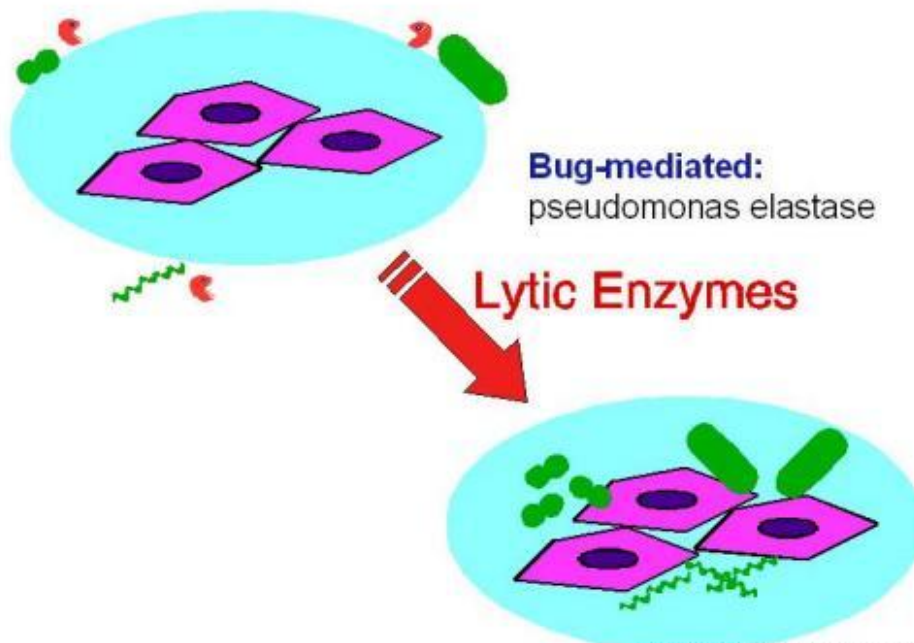
Mechanisms of Damage



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4. Non-Toxin-Mediated Damage

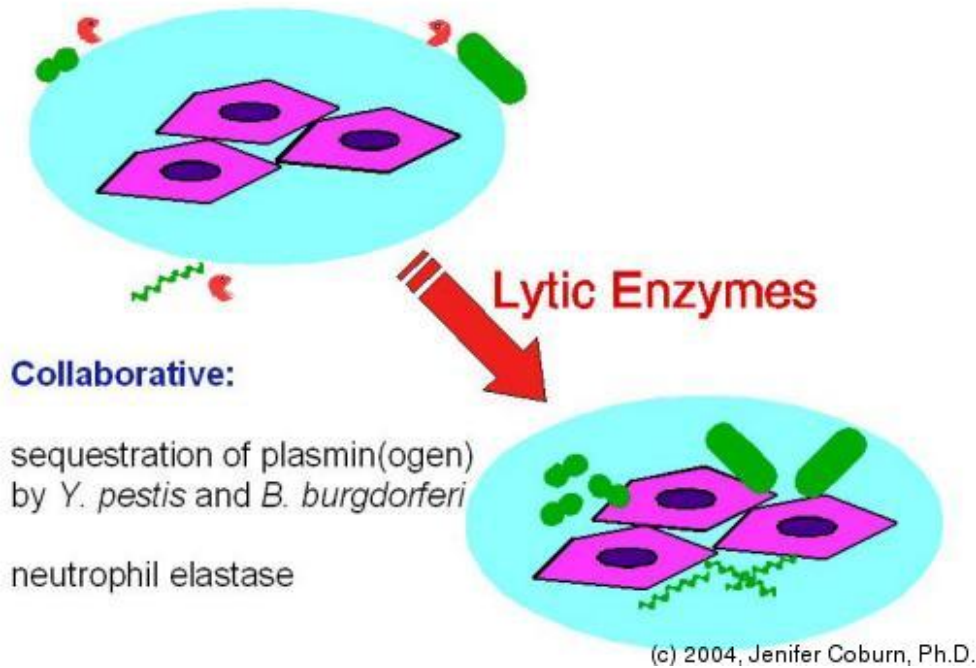
Non-Toxin-Mediated Damage



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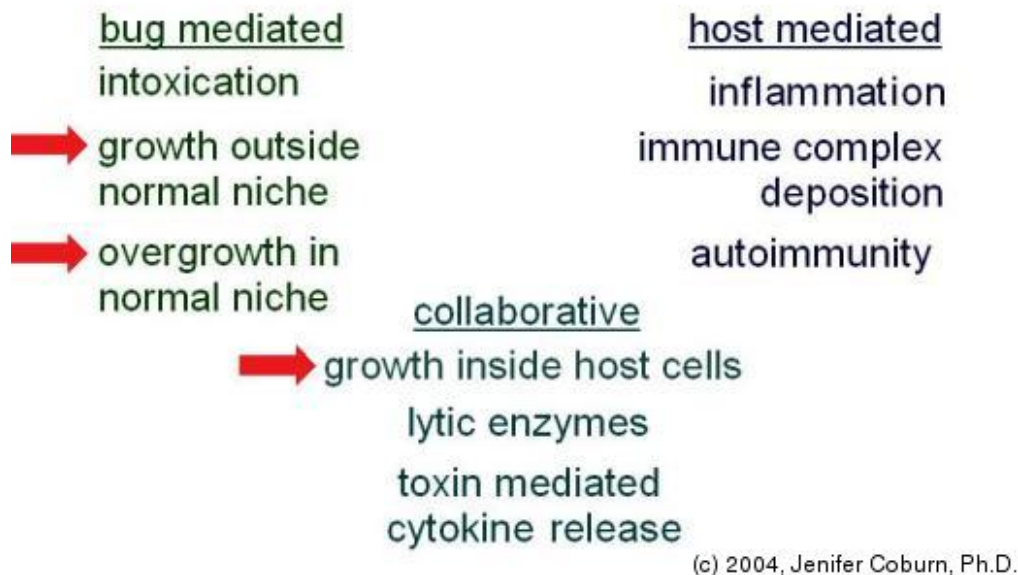
5. Non-Toxin-Mediated Damage (cont.)

Non-Toxin-Mediated Damage



6. Mechanisms of Damage (cont.)

Mechanisms of Damage



7. Non-Toxin-Mediated Damage (cont.)

Non-Toxin-Mediated Damage

Growth inside cells (immunosuppression and/or hot bugs)
Mycobacterium tuberculosis various infection sites,
Legionella pneumophila shielded from host response,
Chlamydia species often chronic infection and
Salmonella shedding of bacteria
Shigella

Growth outside normal niche
Bacteroides fragilis peritoneal abscesses
Streptococci carditis
Staphylococci

Overgrowth in normal niche
Clostridium difficile pseudomembranous colitis

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8. Non-Toxin-Mediated Damage (cont.)

Non-Toxin-Mediated Damage

Growth inside cells
Mycobacterium tuberculosis various infection sites,
Legionella pneumophila shielded from host response,
Chlamydia species often chronic infection and
Salmonella shedding of bacteria
Shigella

Growth outside normal niche (surgery, dental work)
Bacteroides fragilis peritoneal abscesses
Streptococci carditis
Staphylococci

Overgrowth in normal niche
Clostridium difficile pseudomembranous colitis

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9. Non-Toxin-Mediated Damage (cont.)

Non-Toxin-Mediated Damage

Growth inside cells

<i>Mycobacterium tuberculosis</i>	various infection sites, shielded from host response, often chronic infection and shedding of bacteria
<i>Legionella pneumophila</i>	
Chlamydia species	
Salmonella	
Shigella	

Growth outside normal niche

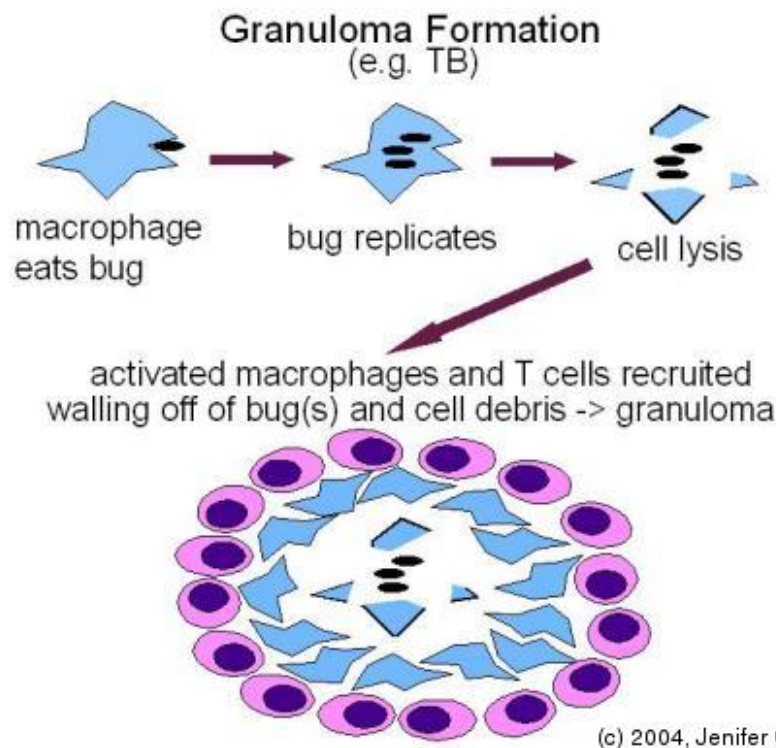
<i>Bacteroides fragilis</i>	peritoneal abscesses
Streptococci	carditis
Staphylococci	

Overgrowth in normal niche

<i>Clostridium difficile</i>	(antibiotic therapy) pseudomembranous colitis
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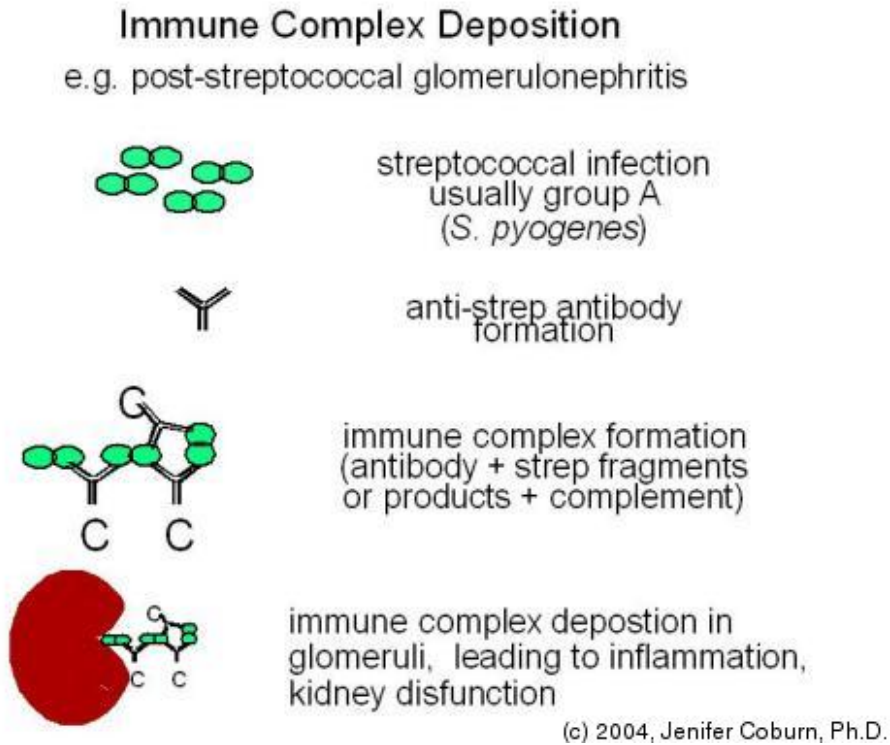
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10. Granuloma Formation

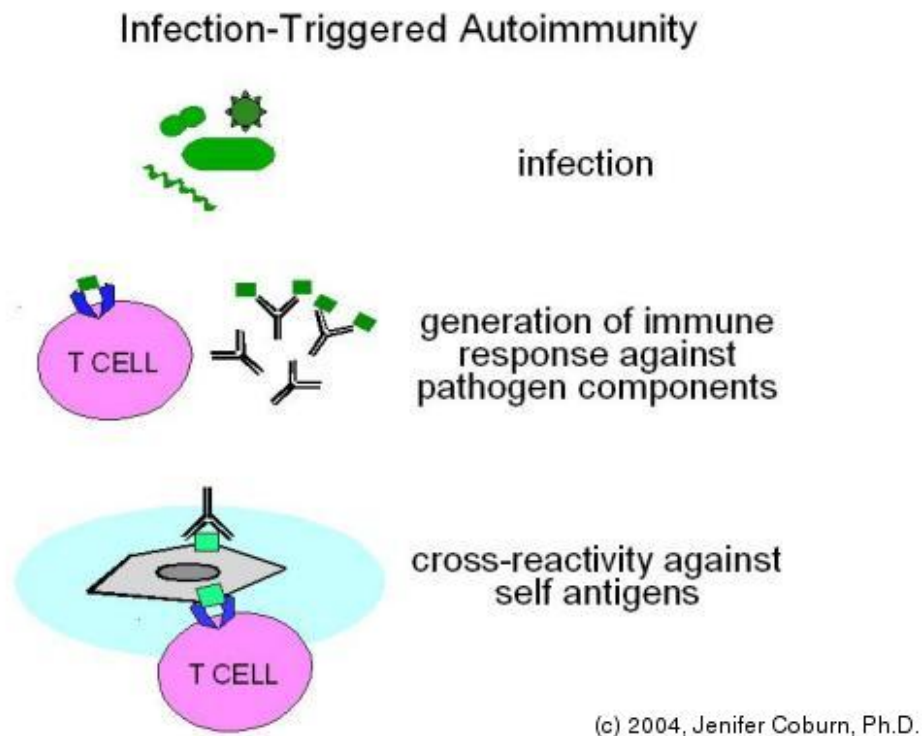


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11. Immune Complex Deposition

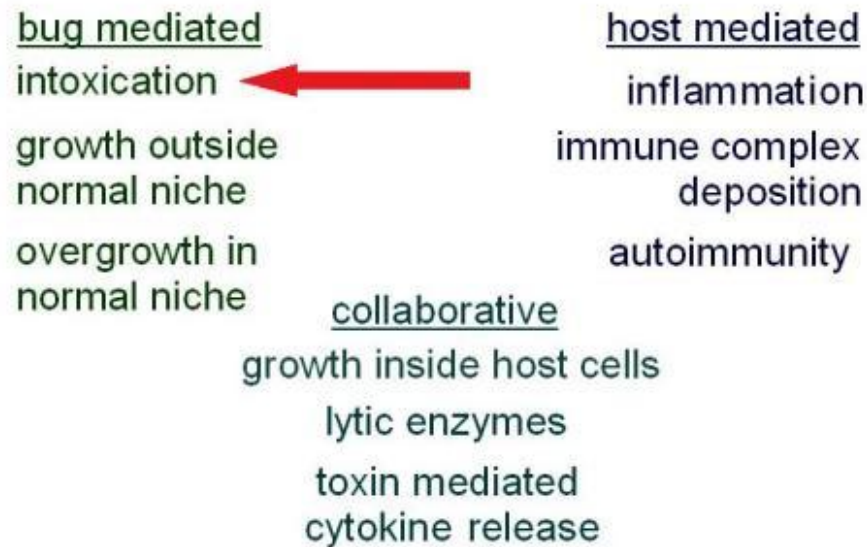


12. Infection-Triggered Autoimmunity



13. Mechanisms of Damage (cont.)

Mechanisms of Damage



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14. Toxin Definitions

TOXIN DEFINITIONS

TOXIN: a *protein* that kills or alters the function of a host cell

EXOTOXIN: a toxin that is secreted into the extracellular milieu by the bacteria

ENTEROTOXIN: a toxin that works in or is produced in the GI tract

ENDOTOXIN: the lipopolysaccharide component of the gram-negative outer membrane; **NOT a true toxin**

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15. Toxin-Mediated Damage

Toxin-Mediated Damage

Site of action- cell surface vs. intracellular
Mode of delivery

Specificity- host species or cell type
Help from host
Mechanism

Role in disease

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16. Toxin Examples

Toxin Examples

	kill cells	disrupt function
act at cell surface	streptolysin O	toxic shock syndrome toxin
act inside cells	diphtheria toxin	cholera toxin

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17.

Active at Cell Surface

ACTIVE AT CELL SURFACE

<u>MECHANISM</u>	<u>EXAMPLE</u>
pore-formation	aerolysin, staph α toxin, streptolysin listeriolysin O
phospholipase	<i>C. perfringens</i> α
superantigen	staph TSST
?? ("lysins")	hemolysins

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18.

Pore Formers

PORE FORMERS

- disrupt target cell membrane by causing formation of unregulated channels
- may cause channel (pore) formation in several ways:
 - 1. multimer of one bacterial protein that inserts into membrane
 - 2. complex of two or more bacterial proteins that inserts into membrane
 - 3. binding to target cell membrane protein leading to unregulated opening of pore

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19. Phospholipases

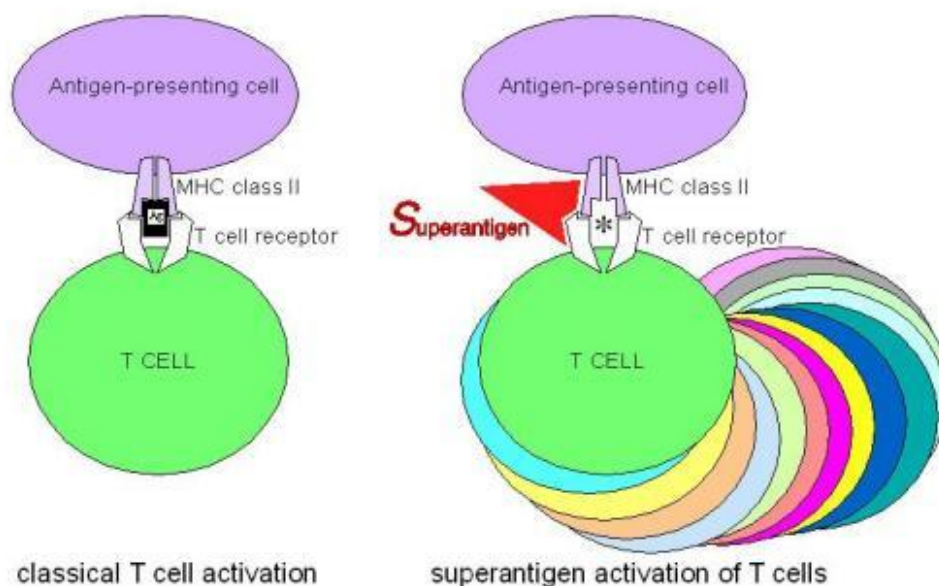
PHOSPHOLIPASES

- cleave phosphatidylcholine (lecithin) or sphingomyelin
- due to the abundance of substrate, can affect virtually all cell types
- one or more forms expressed by a large number of bacterial species
- probably facilitate bacterial dissemination and allow bacteria access to nutrients normally found only in the host cell cytoplasm

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20. Classical Superantigens

Classical vs. Superantigens



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21. Active in Cytoplasm (A-B Toxins)

ACTIVE IN CYTOPLASM (A-B TOXINS)

<u>MECHANISM</u>	<u>EXAMPLE</u>
protease	botulinum and tetanus neurotoxins anthrax lethal toxin
nuclease	shiga / shiga-like toxin
ADP-ribosyl transferase	cholera, pertussis, diphtheria toxins
adenylate cyclase	anthrax edema toxin pertussis cyclase

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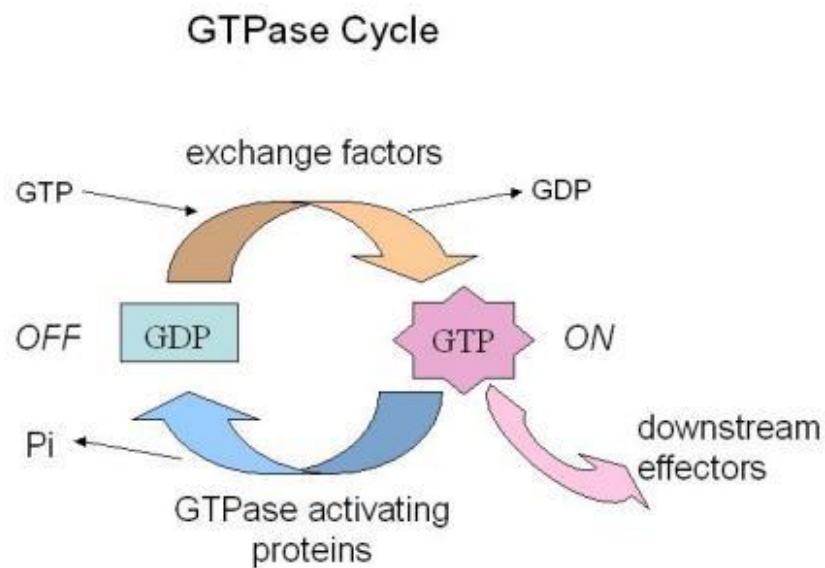
22. Toxins that ADP-ribosylate Intracellular Substrates

Toxins that ADP-ribosylate Intracellular Substrates

<i>Toxin</i>	<i>Substrate</i>
diphtheria toxin pseudomonas exotoxin A	elongation factor 2 □□□□□□
pertussis toxin	G α , G α □□□□□□s
cholera toxin <i>E. Coli</i> heat-labile toxin	Gs α □□□□□□
botulinum exoenzyme C3	Rho GTPases
Pseudomonas exoenzyme S	Ras, Ral, Rab GTPases
botulinum C2 <i>C. Perfringens</i> iota toxin	actin

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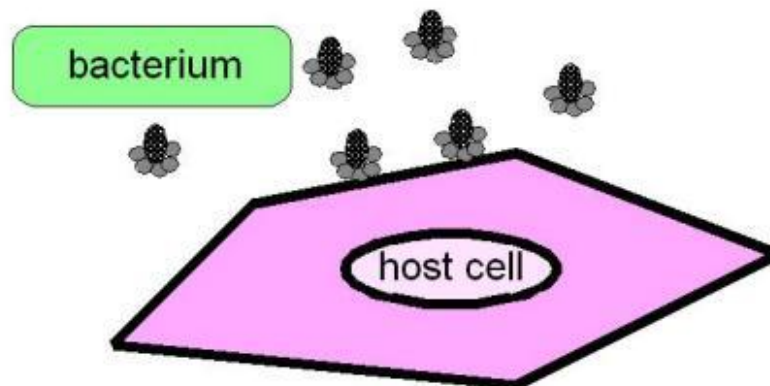
23. GTPase Cycle



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24. Classical Mechanism of Intoxication

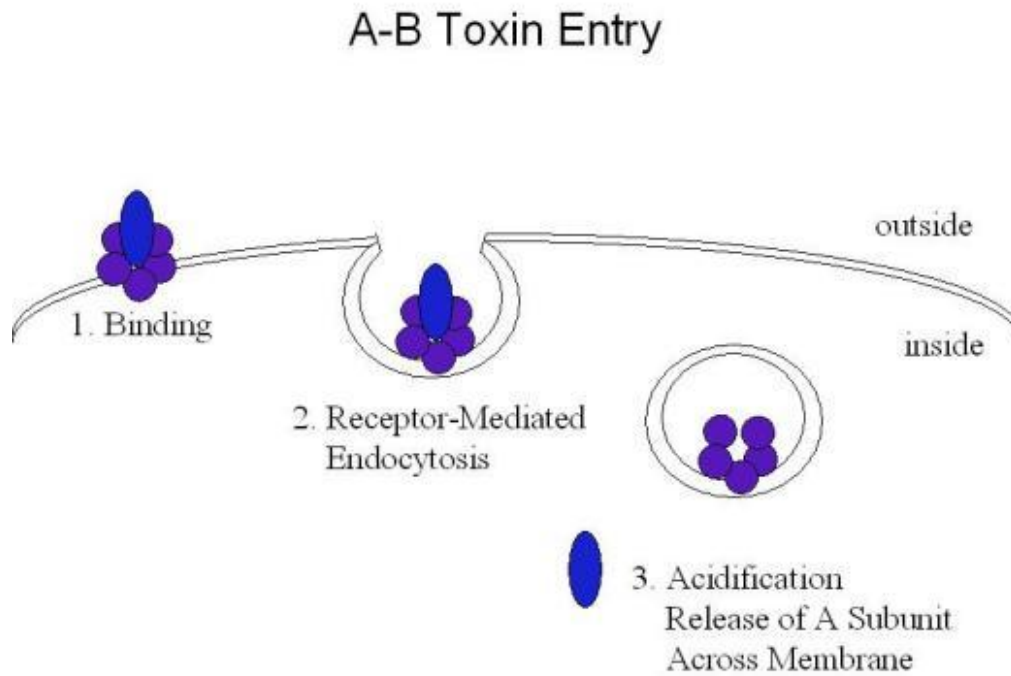
classical mechanism of intoxication:
bacteria release toxin, which then binds
to surface of host cells



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25.

A-B Toxin Entry

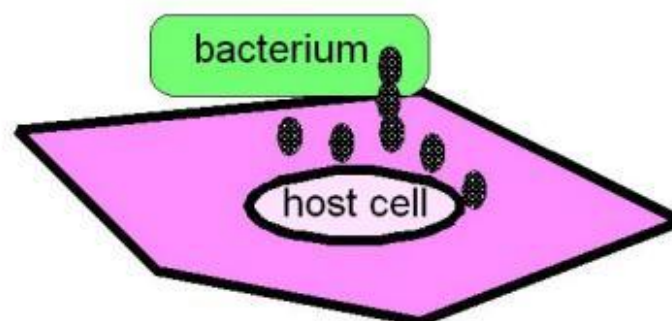


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26.

Type II Secretion System-dependent Intoxication

type III secretion system-dependent intoxication: bacteria bind to host cell, then inject toxin into cytosol



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27.

Cholera (1)

CHOLERA

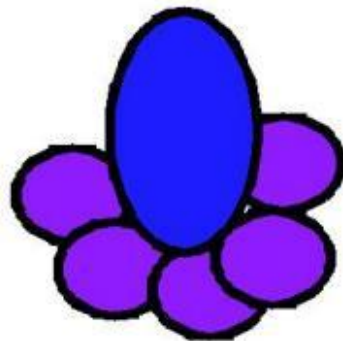
- caused by *Vibrio cholerae*, which is found in aquatic environments
- acquired by consuming contaminated water or food (e.g. uncooked shellfish)
- disease is attributable to cholera toxin action in small intestine
- disease is self-limiting if patient is kept hydrated

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28.

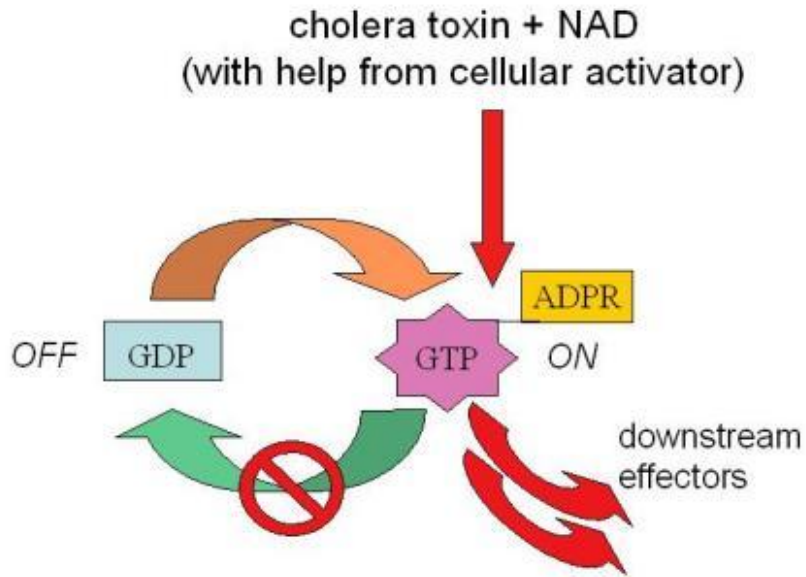
Cholera Toxin (1)

Cholera Toxin :
1 **A** subunit plus 5 **B** subunits
encoded by separate genes in
the CTX phage genome



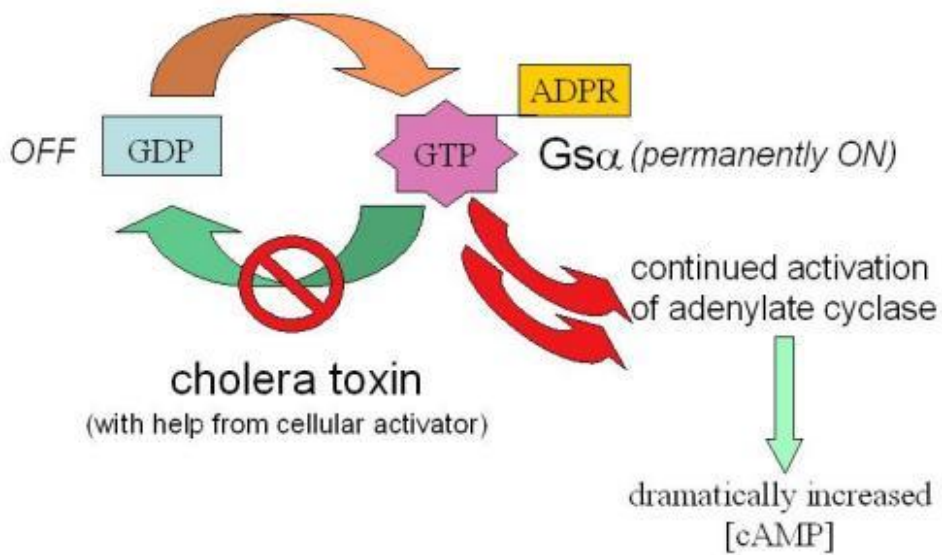
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29. Cholera Toxin + NAD



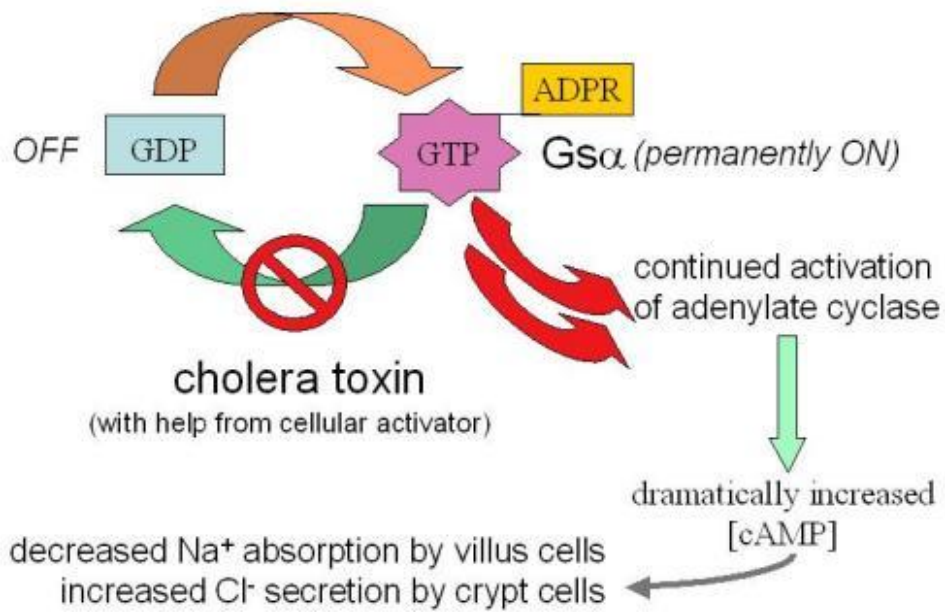
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30. Cholera Toxin (2)



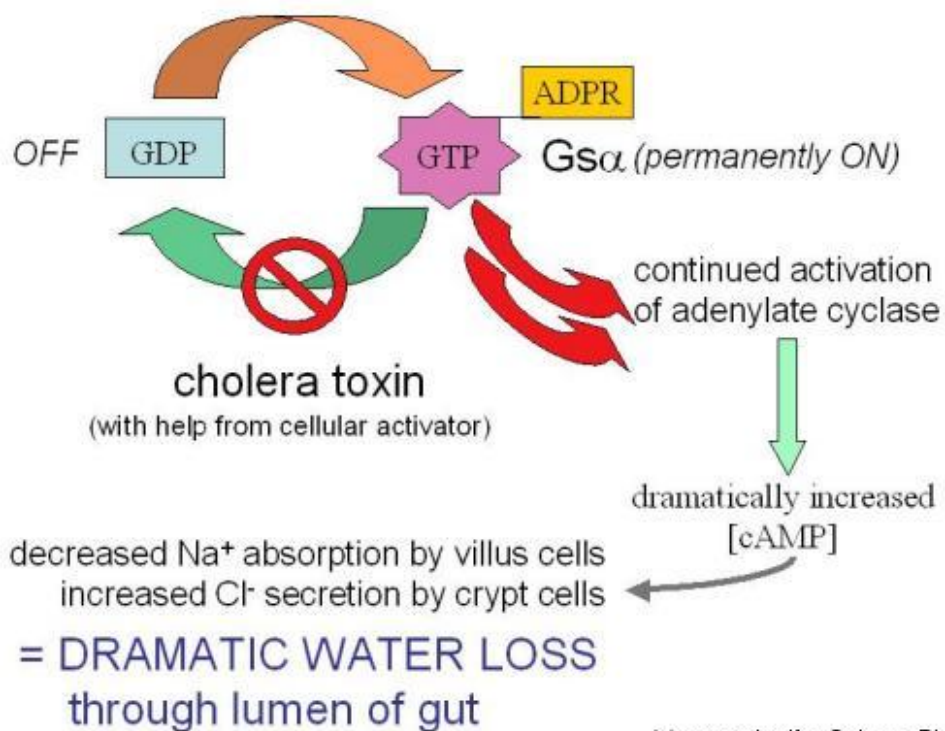
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31. Cholera Toxin (3)



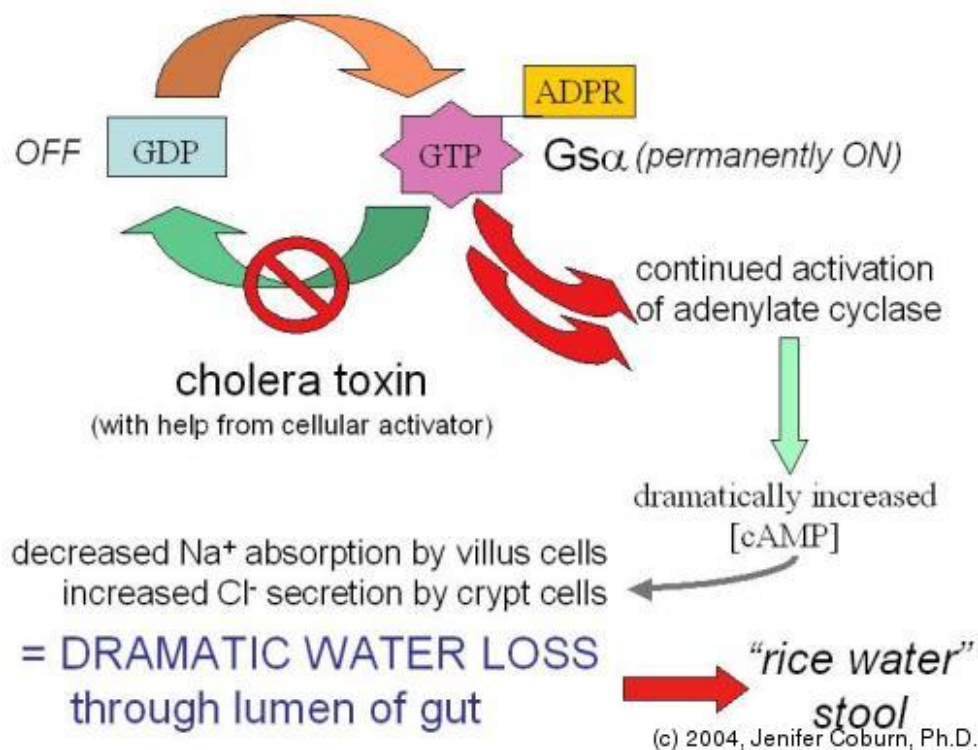
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32. Cholera Toxin (4)



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33. Cholera Toxin (5)



34. Cholera (2)

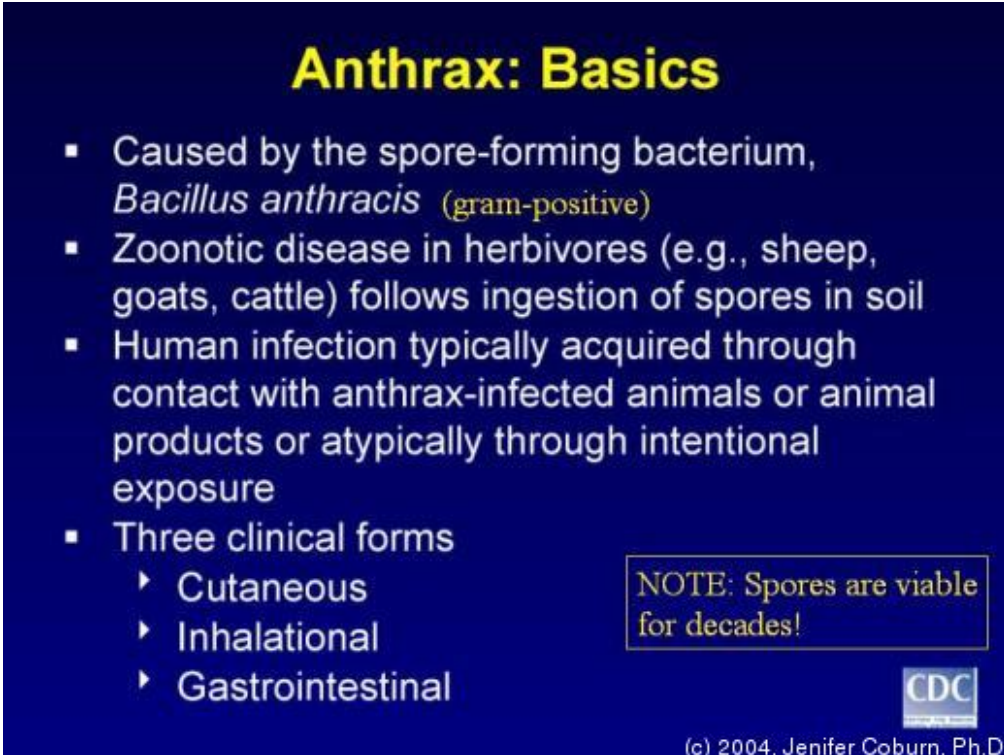
CHOLERA

- caused by *Vibrio cholerae*, which is found in aquatic environments
- acquired by consuming contaminated water or food (e.g. uncooked shellfish)
- disease is attributable to cholera toxin action in small intestine
- toxin A subunit is ADP-ribosyl transferase that alters a regulatory subunit of adenylate cyclase
- results in increased cAMP levels in cells -> decreased Na⁺ uptake and increased Cl⁻ secretion -> massive water loss and "rice-water" stool
- Na⁺/glucose symporter is not affected, allowing oral rehydration with solutions containing salts and glucose
- does not kill cells
- disease is self-limiting if patient is kept hydrated

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35.


Anthrax: Basics



Anthrax: Basics

- Caused by the spore-forming bacterium, *Bacillus anthracis* (gram-positive)
- Zoonotic disease in herbivores (e.g., sheep, goats, cattle) follows ingestion of spores in soil
- Human infection typically acquired through contact with anthrax-infected animals or animal products or atypically through intentional exposure
- Three clinical forms
 - Cutaneous
 - Inhalational
 - Gastrointestinal

NOTE: Spores are viable for decades!



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36.

Epidemiology of Anthrax in the 21st Century



Epidemiology of Anthrax in the 21st Century

- Agricultural, farm workers exposed to infected animals (rare)
- Non-industrial: laboratorians through close contact with *B. anthracis* spores or civilians exposed to contaminated imported animal products (rare)
- Industrial: processors of wool, hair, hides, bones, or other animal products (now rare)
- Intentional/bioterrorist: inhalational and cutaneous exposure to *B. anthracis* spores through U.S. mail




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37.

Anthrax: Cutaneous

**Anthrax:
Cutaneous**

- Begins as a papule, progresses through a vesicular stage to a depressed black necrotic ulcer (eschar)
- Edema, redness, and/or necrosis without ulceration may occur
- Form most commonly encountered in naturally occurring cases
- Incubation period: 1–12 days
- Case-fatality:
 - Without antibiotic treatment—20%
 - With antibiotic treatment—1%



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38.

Anthrax: Inhalational (1)

**Anthrax:
Inhalational (1)**

- A brief prodrome resembling a “viral-like” illness, characterized by myalgia, fatigue, fever, with or without respiratory symptoms, followed by hypoxia and dyspnea, often with radiographic evidence of mediastinal widening.
- Meningitis in 50% of patients
- Rhinorrhea (rare)



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39.

Anthrax: Inhalational (2)

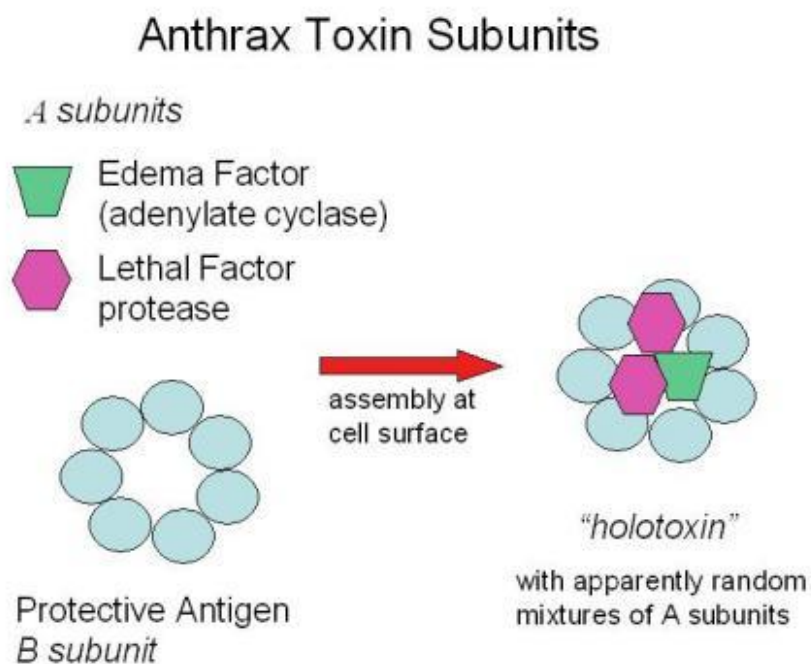
**Anthrax:
Inhalational (2)**

- Extremely rare in United States (20 reported cases in last century)
- Incubation period: 1–7 days (possibly ranging up to 42 days)
- Case fatality:
 - Without antibiotic treatment—97%
 - With antibiotic treatment—75%


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40.

Anthrax Toxin Subunits




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41. Recommended Postexposure Prophylaxis

	Initial Therapy	Duration
Adults (including pregnant women and immunocompromised)	Ciprofloxacin 500 mg PO BID OR Doxycycline 100 mg PO BID	60 days
Children	Ciprofloxacin* 10–15 mg/kg PO Q 12 hrs OR Doxycycline: >8 yrs and >45 kg: 100 mg PO BID >8 yrs and ≤45 kg: 2.2 mg/kg PO BID ≤8 yrs: 2.2 mg/kg PO BID	60 days Change to amoxicillin if susceptible

*Ciprofloxacin not to exceed 1 gram daily in children
Patient information sheets at www.bt.cdc.gov



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42. Tetanus and Botulinum Neurotoxins

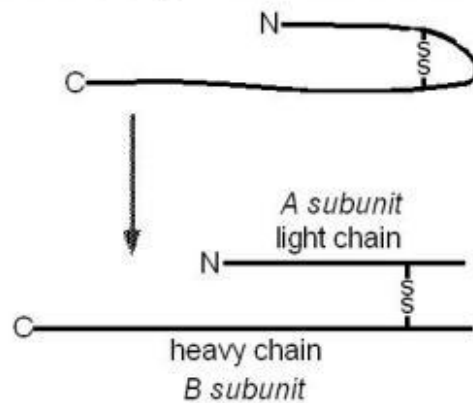
TETANUS AND BOTULINUM NEUROTOXINS

- synthesized as single polypeptide chains by *Clostridium tetani* and *Clostridium botulinum*, respectively
- A subunits cleave proteins involved in docking of synaptic vesicles to plasma membrane, leading to disruption of neurotransmission
- opposite effects on host due to selection of target neurons by B subunits:
- botulinum toxin:
 - peripheral neurons
 - blocks release of stimulatory neurotransmitters
 - flaccid paralysis
- tetanus toxin:
 - retrograde transport to CNS
 - blocks release of inhibitory neurotransmitters
 - spastic paralysis

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43. Botulinum and Tetanus Neurotoxins

Botulinum and Tetanus Neurotoxins
single polypeptide chain, encoded by single gene,
cleaved to yield A and B subunits



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44. Tetanus and Botulinum Neurotoxins (cont.)

TETANUS AND BOTULINUM NEUROTOXINS

- synthesized as single polypeptide chains by *Clostridium tetani* and *Clostridium botulinum*, respectively
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- tetanus toxin:
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