1. Damage to Host

Damage to Host

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2. Mechanisms of Damage

Mechanisms of Damage

<u>bug mediated</u>

intoxication

growth outside normal niche

overgrowth in normal niche

<u>host mediated</u>

inflammation

immune complex deposition

autoimmunity

<u>collaborative</u>

growth inside host cells

lytic enzymes

toxin mediated cytokine release

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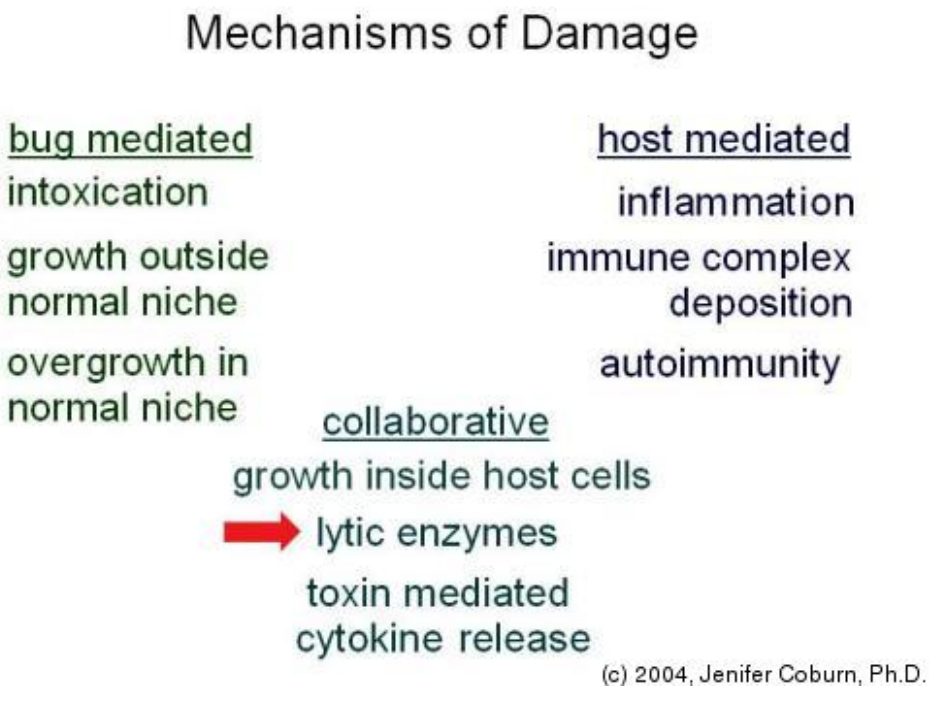
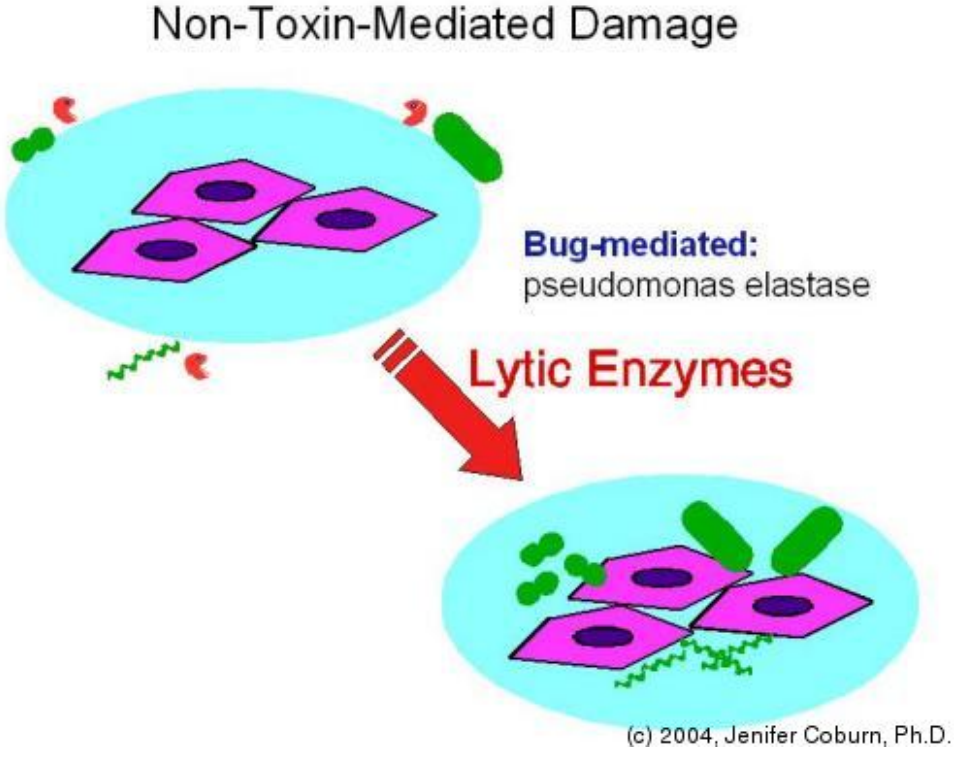
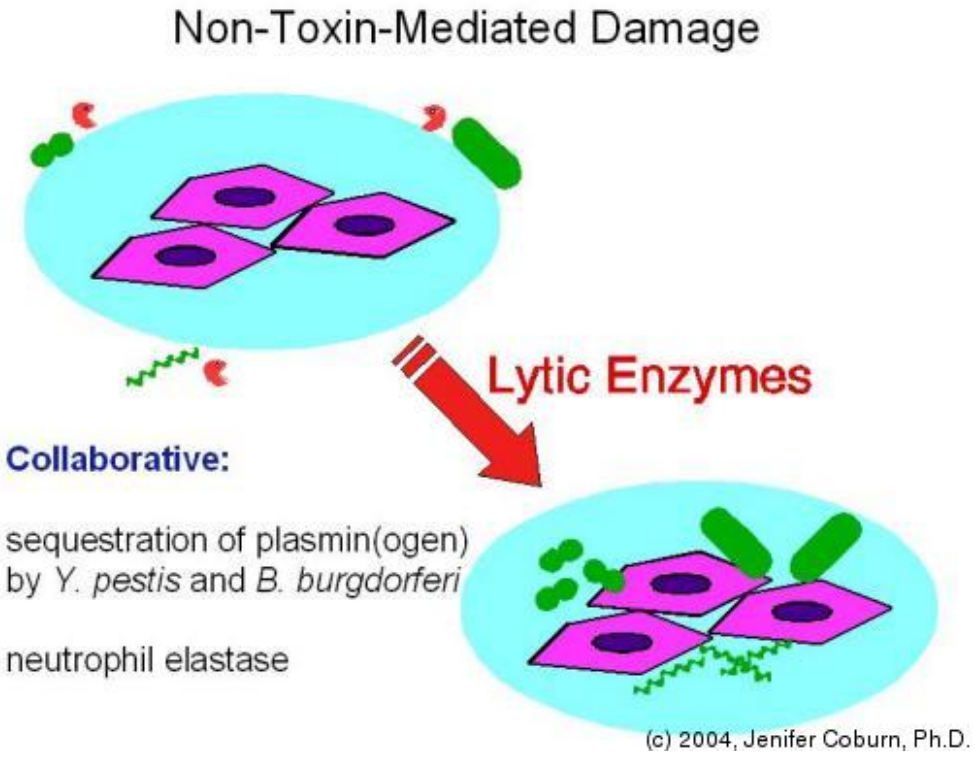
3. Mechanisms of Damage (cont.)



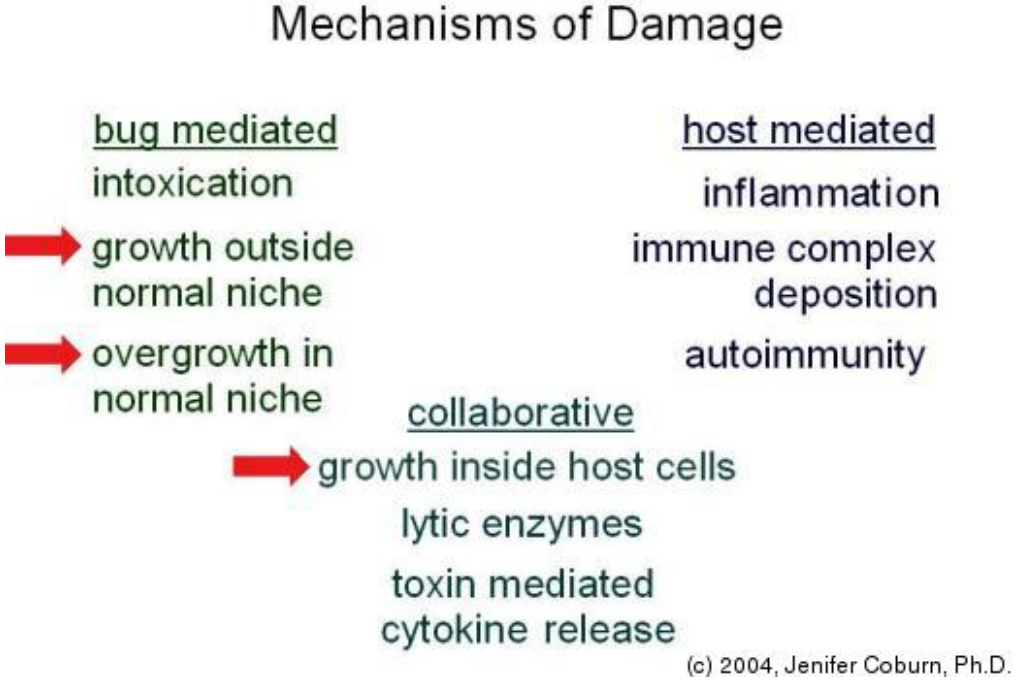
4. Non-Toxin-Mediated Damage



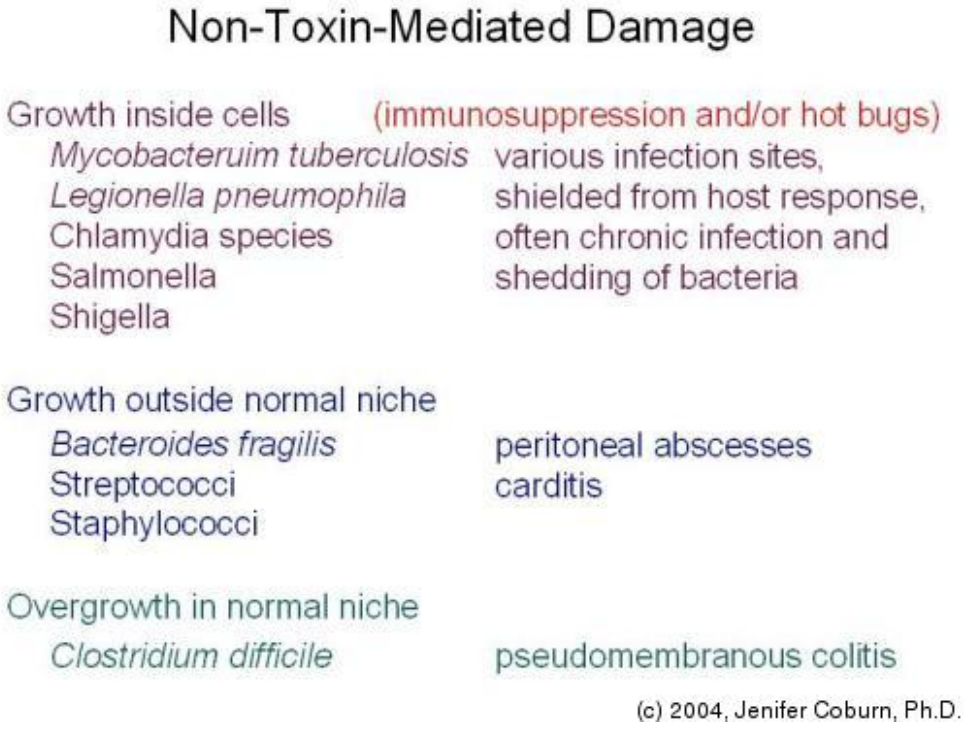
5. Non-Toxin-Mediated Damage (cont.)



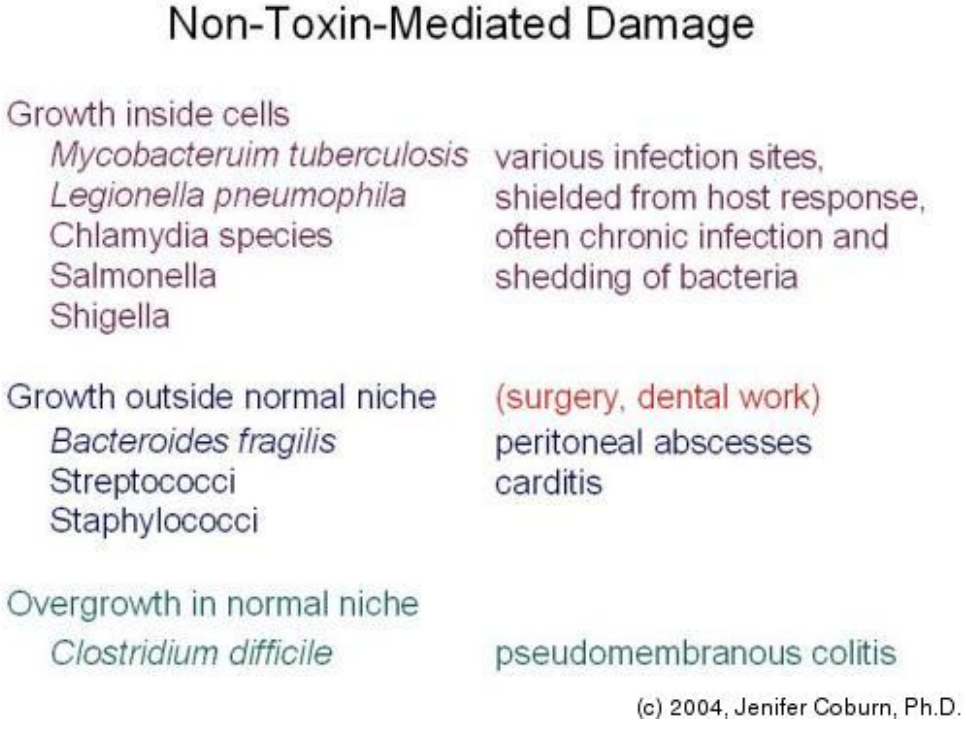
6. Mechanisms of Damage (cont.)



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



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



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

Non-Toxin-Mediated Damage

Growth inside cells	
Mycobacteruim 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	(antibiotic therapy)
Clostridium difficile	pseudomembranous colitis

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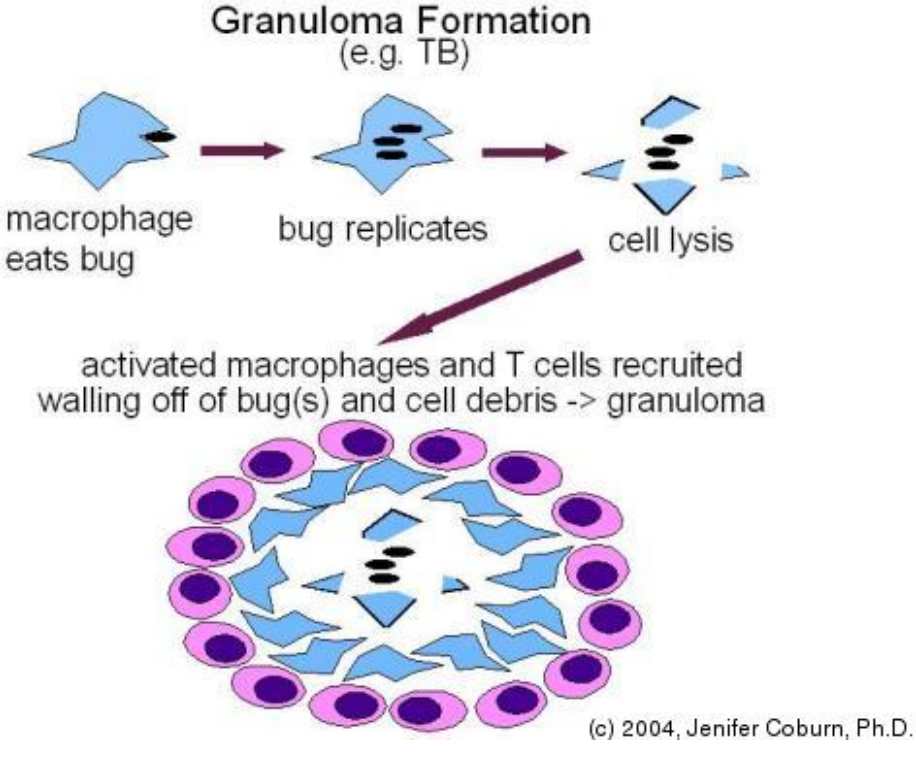
10. Granuloma Formation



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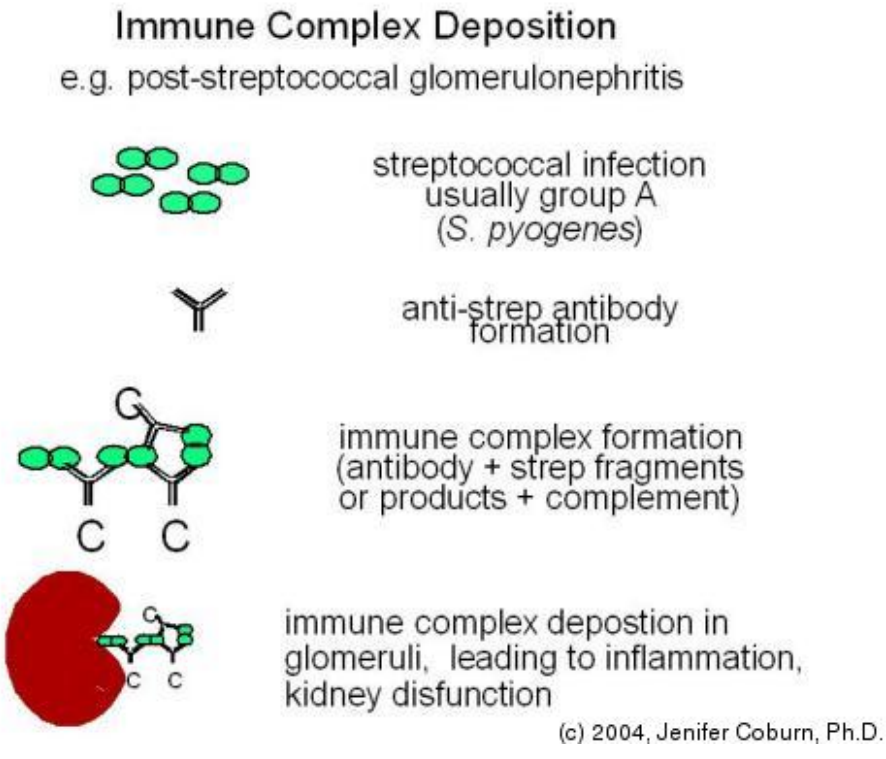
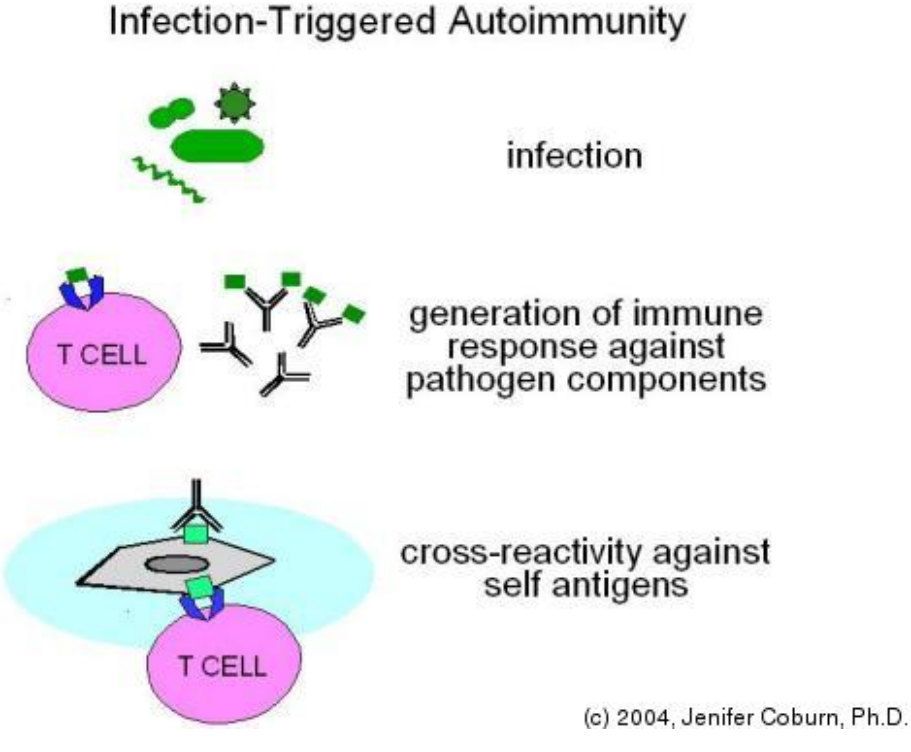
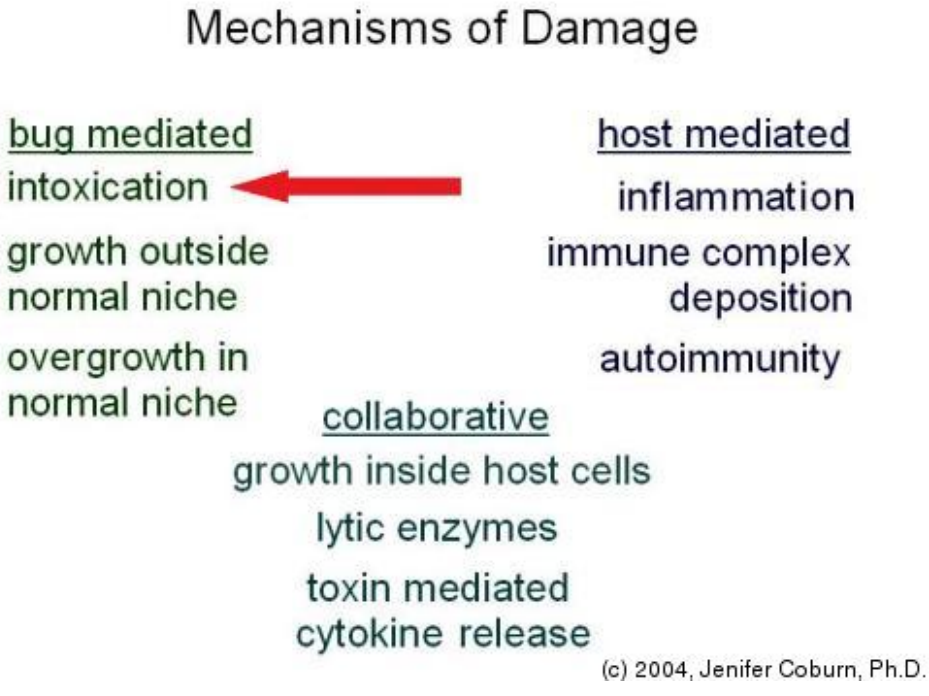
11. Immune Complex Deposition



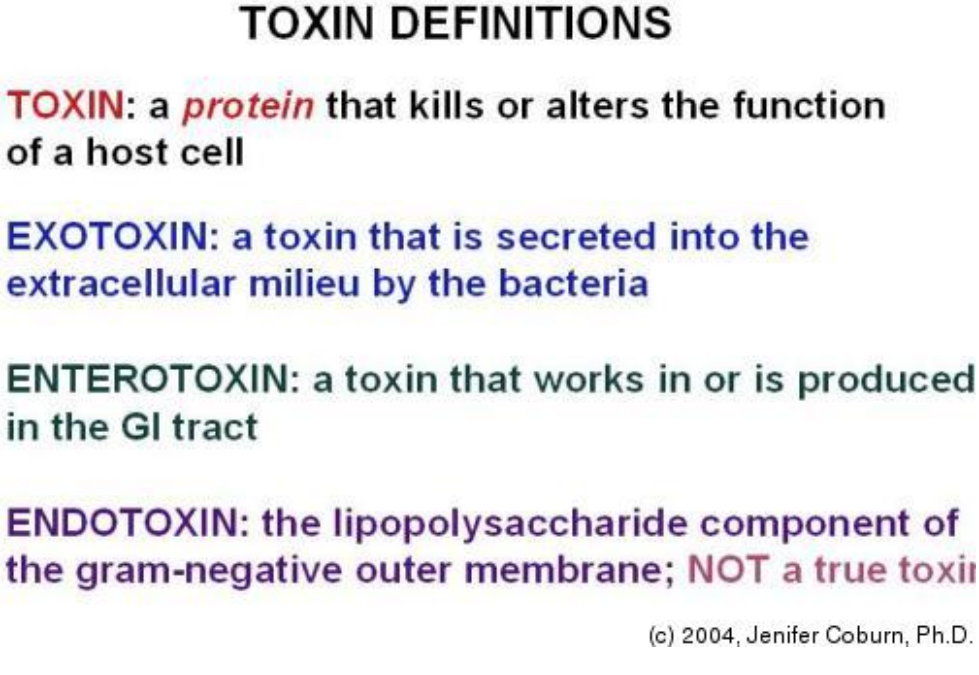
12. Infection-Triggered Autoimmunity



13. Mechanisms of Damage (cont.)



14. Toxin Definitions



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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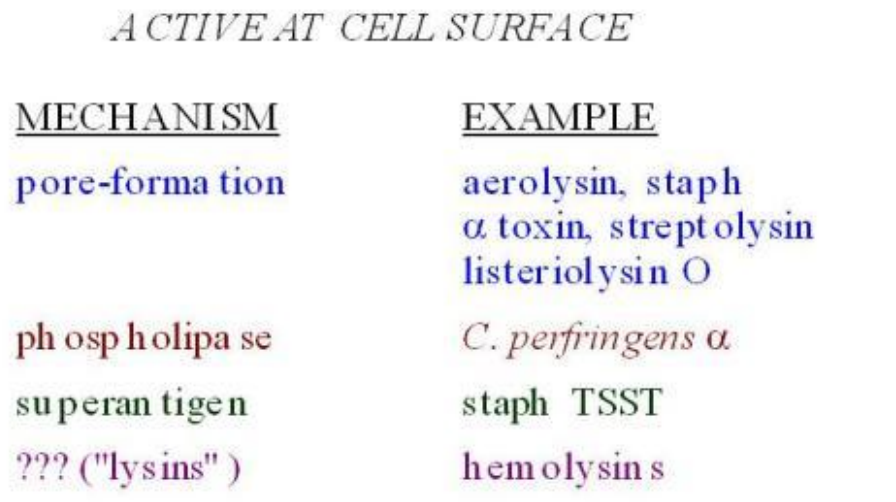
17. Active at Cell Surface



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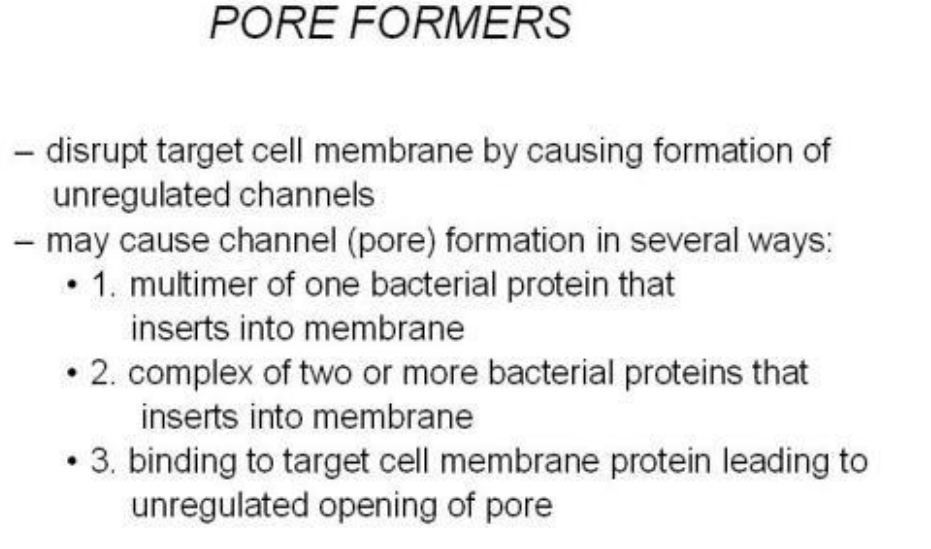
18. Pore Formers



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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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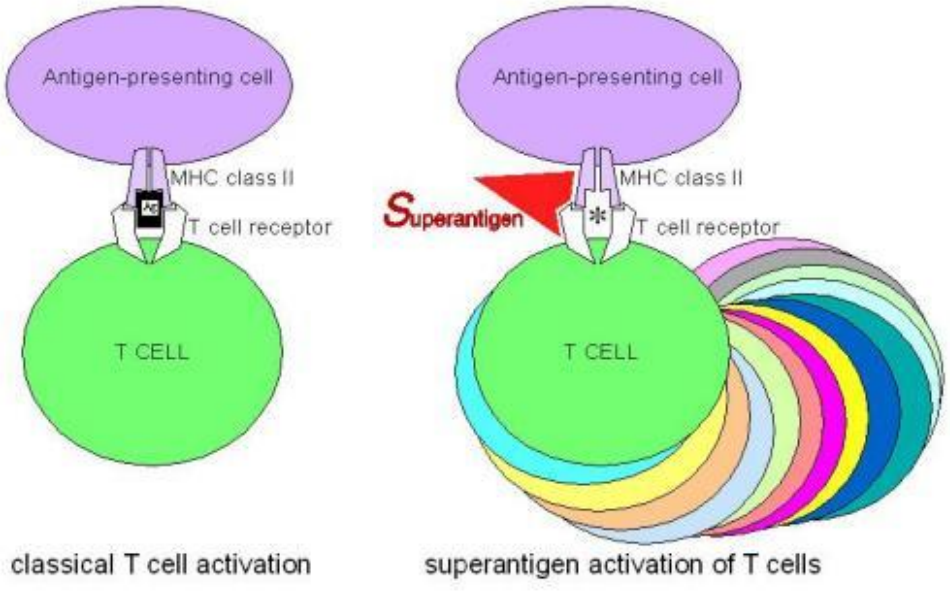
20. Classical Superantigens

Classical vs. Superantigens



classical T cell activation

superantigen activation of T cells

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21. Active in Cytoplasm (A-B Toxins)

ACTIVE IN CYTOPLASM (A-B TOXINS)

MECHANISM	EXAMPLE
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. Toxims that ADP-ribosylate Intracellular Substrates

Toxins that ADP-ribosylate Intracellular Substrates

Toxin	*Substrate*
diphtheria toxin pseudomonas exotoxin A	elongation factor 2
pertussis toxin	Giα, Goα
cholera toxin *E. Coli* heat-labile toxin	Gsα
botulinum exoenzyme C3	Rho GTPases
Pseudomonas exoenzyme S	Ras, Ral, Rab GTPases
botulinum C2 *C. Perfringens* iota toxin	actin

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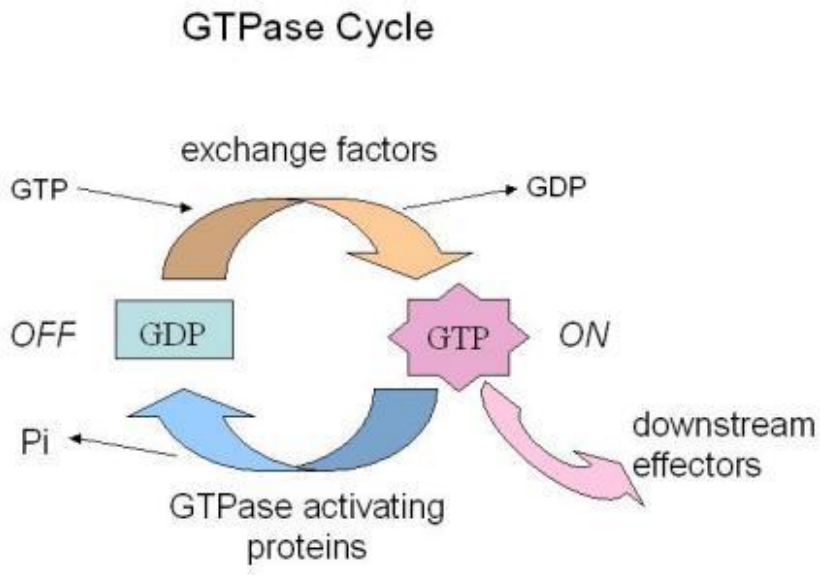
23. GTPase Cycle



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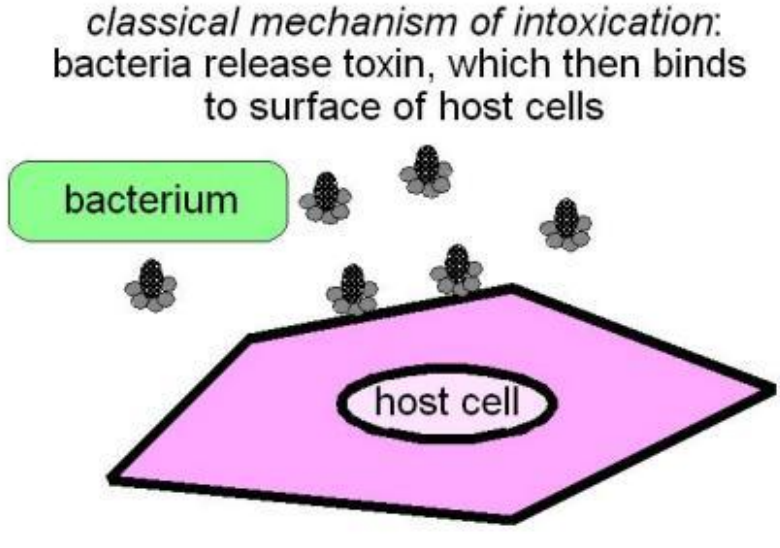
24. Classical Mechanism of Intoxication



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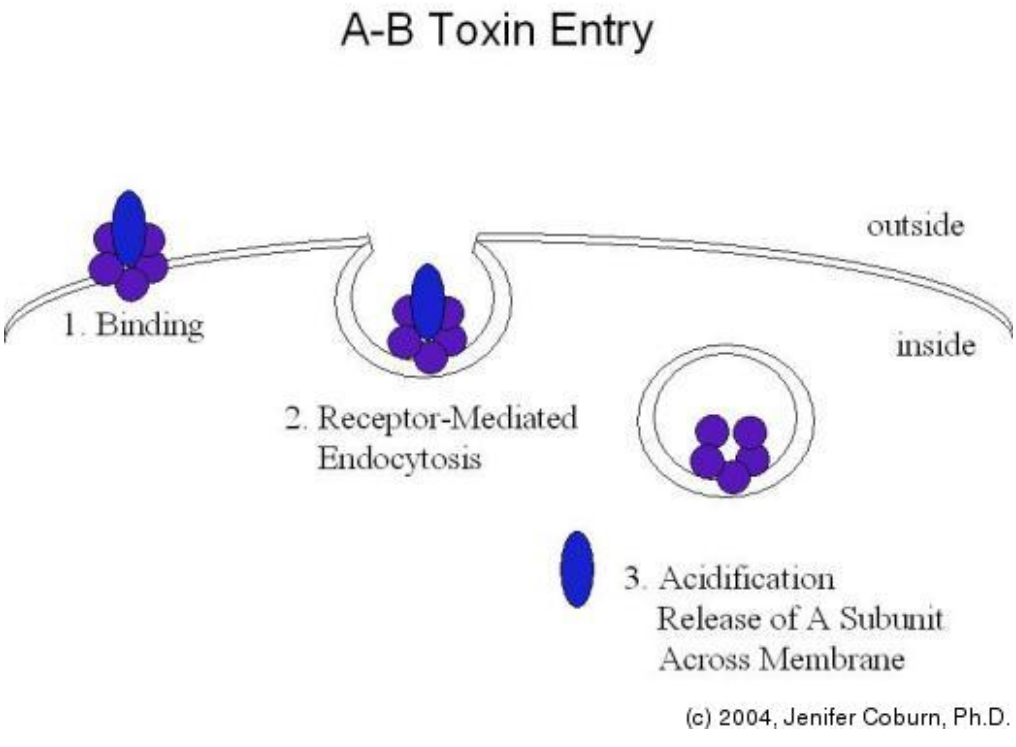
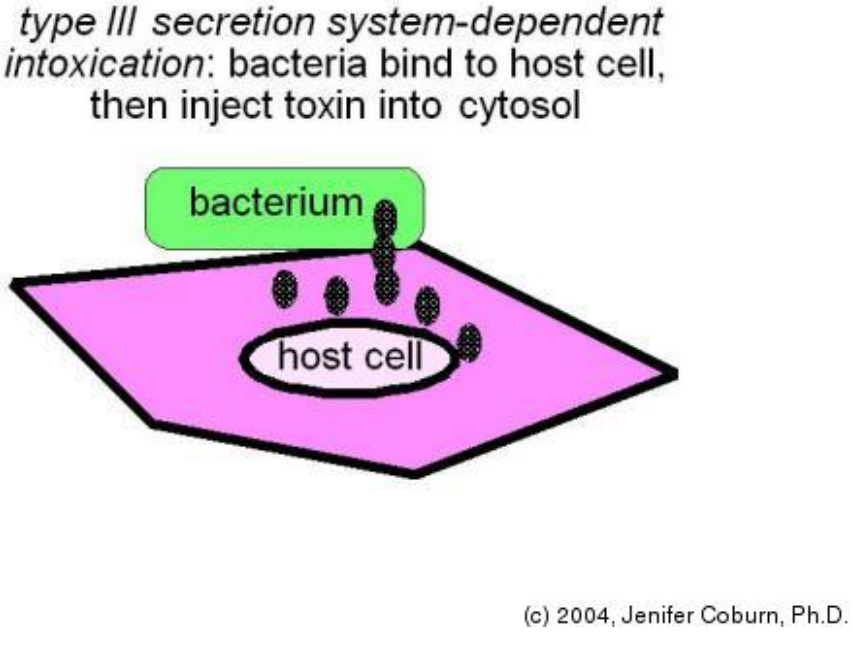
25. A-B Toxin Entry



26. Type II Secretion System-dependent Intoxication



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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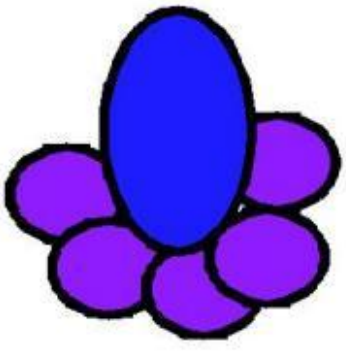
28. Cholera Toxin (1)

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



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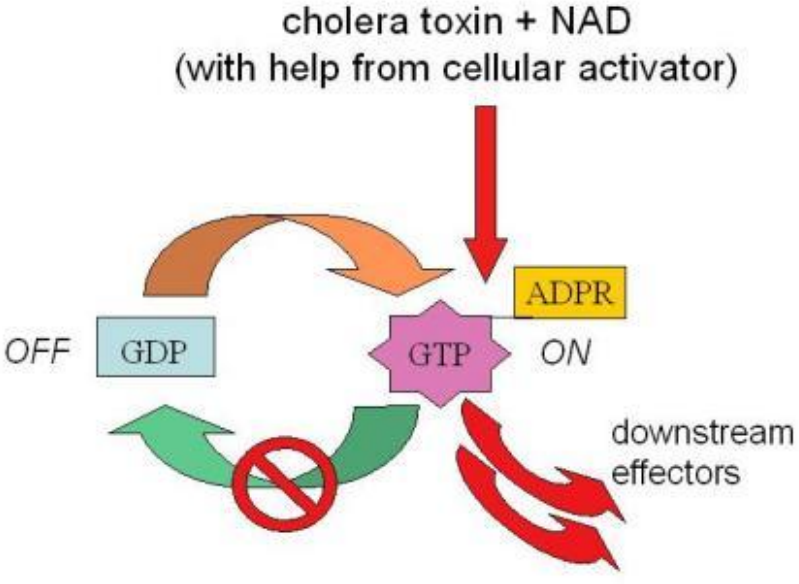
29. Cholera Toxin + NAD



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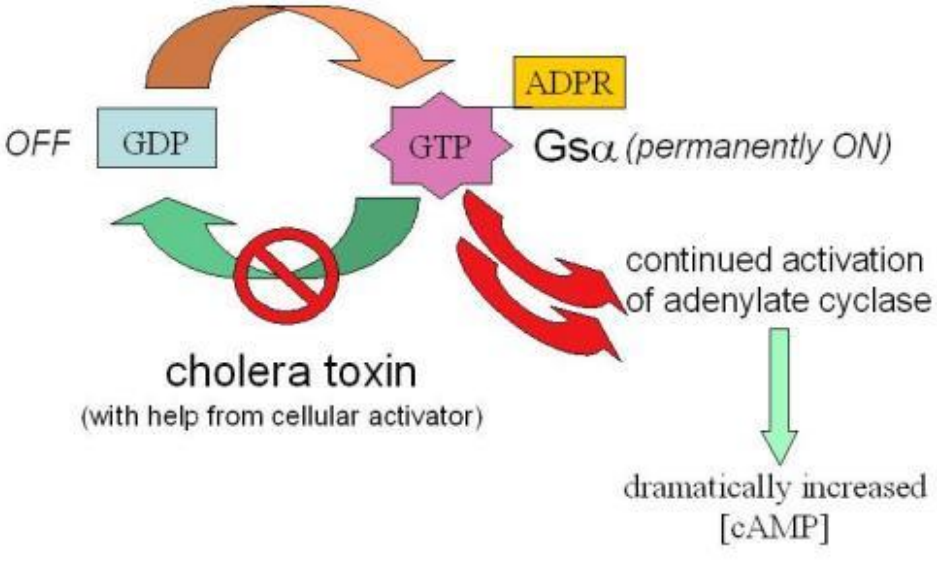
30. Cholera Toxin (2)



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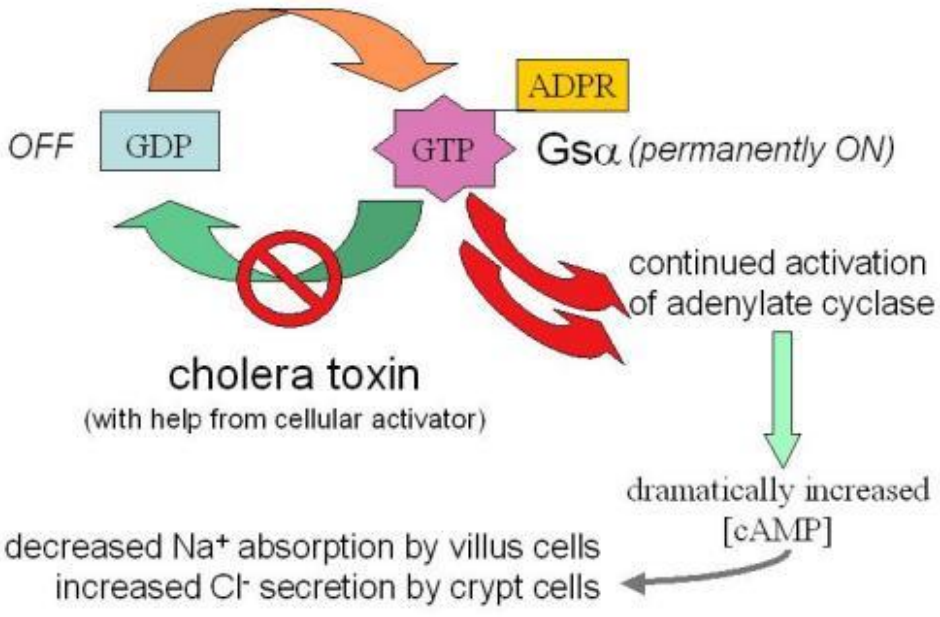
31. Cholera Toxin (3)



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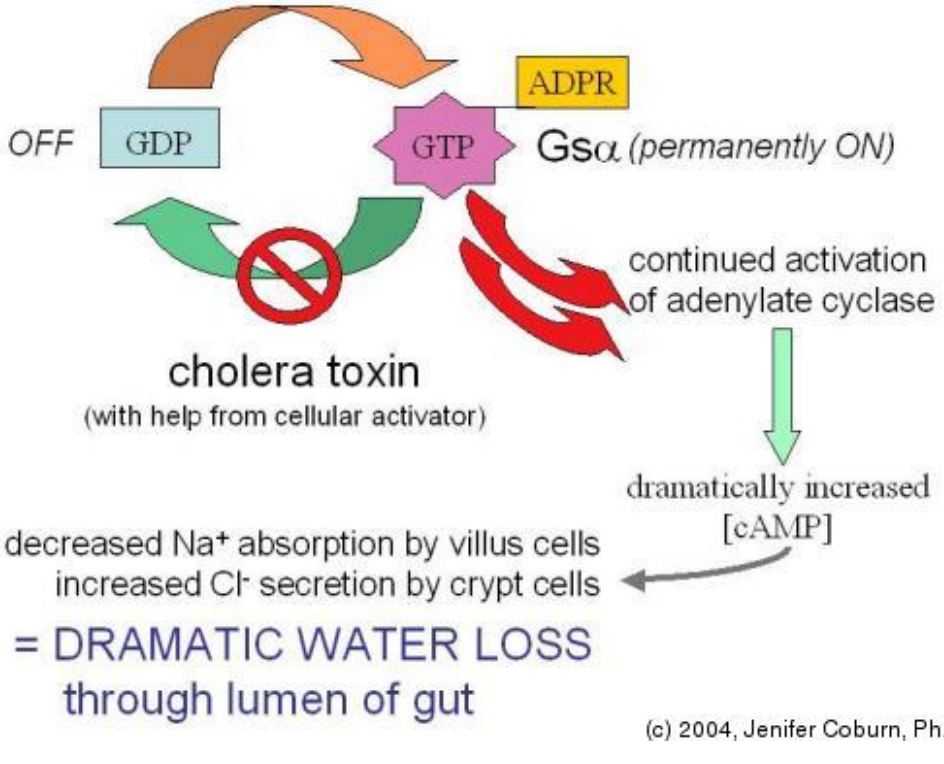
32. Cholera Toxin (4)



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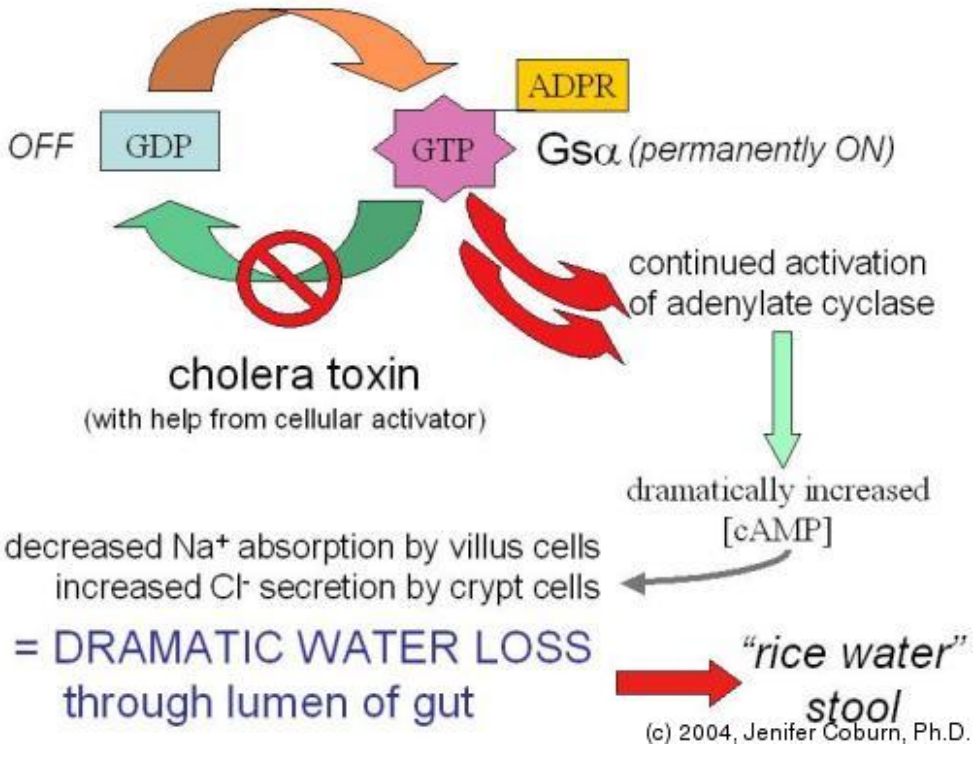
33. Cholera Toxin (5)



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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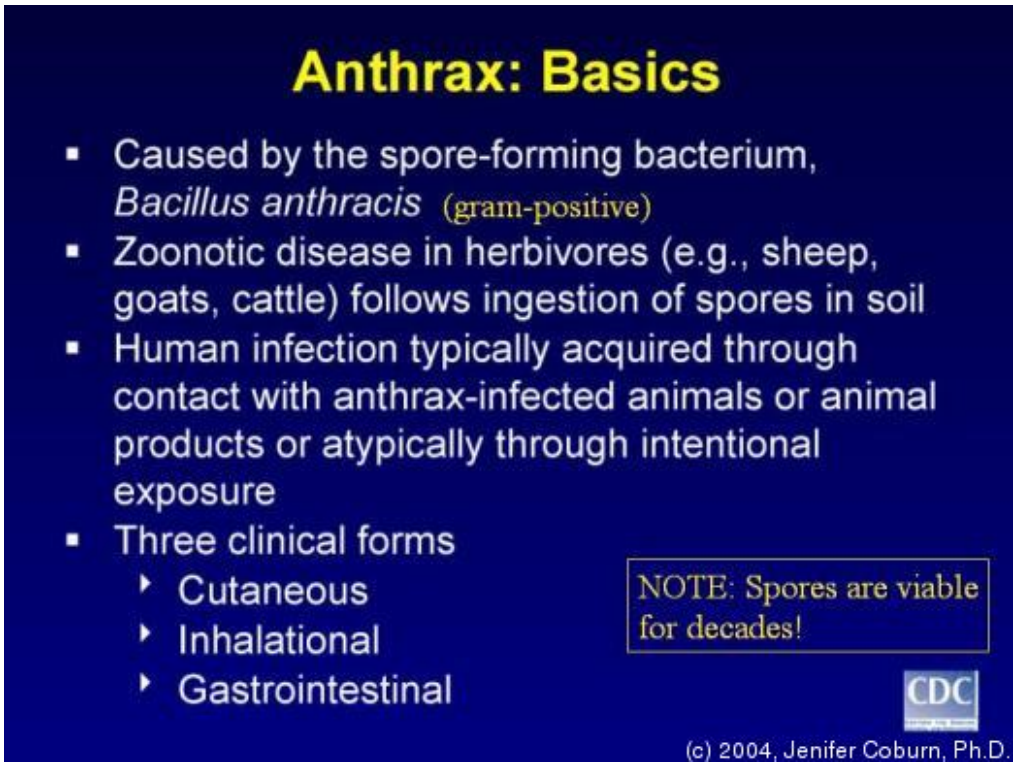
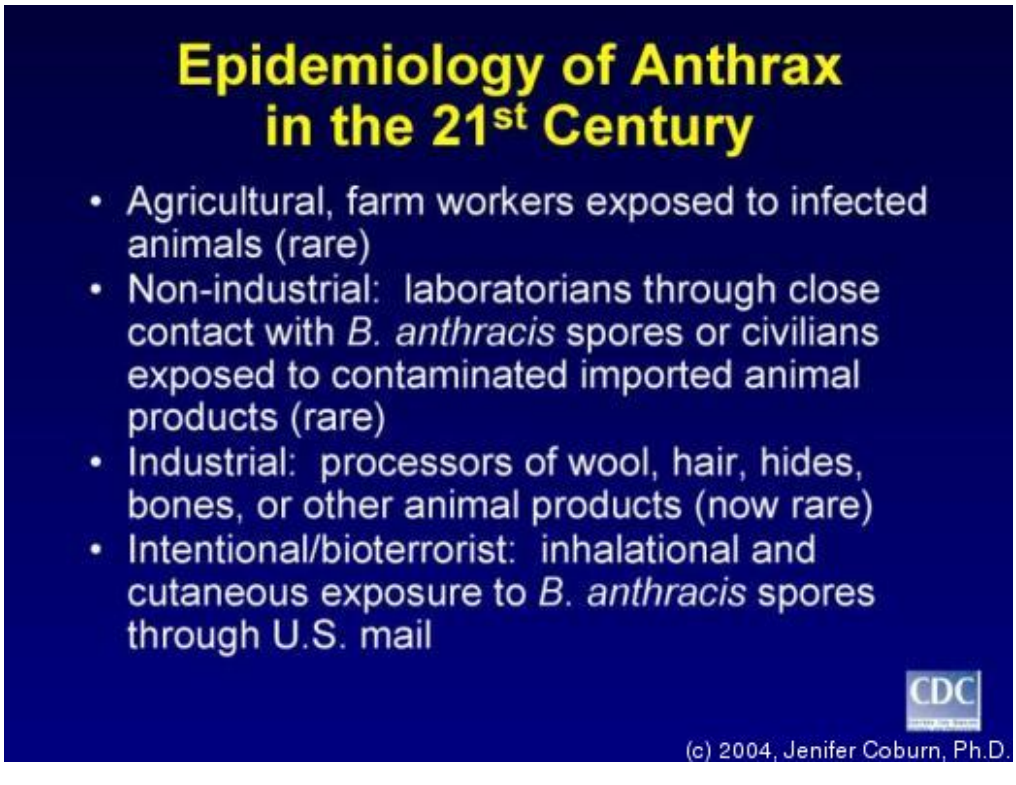
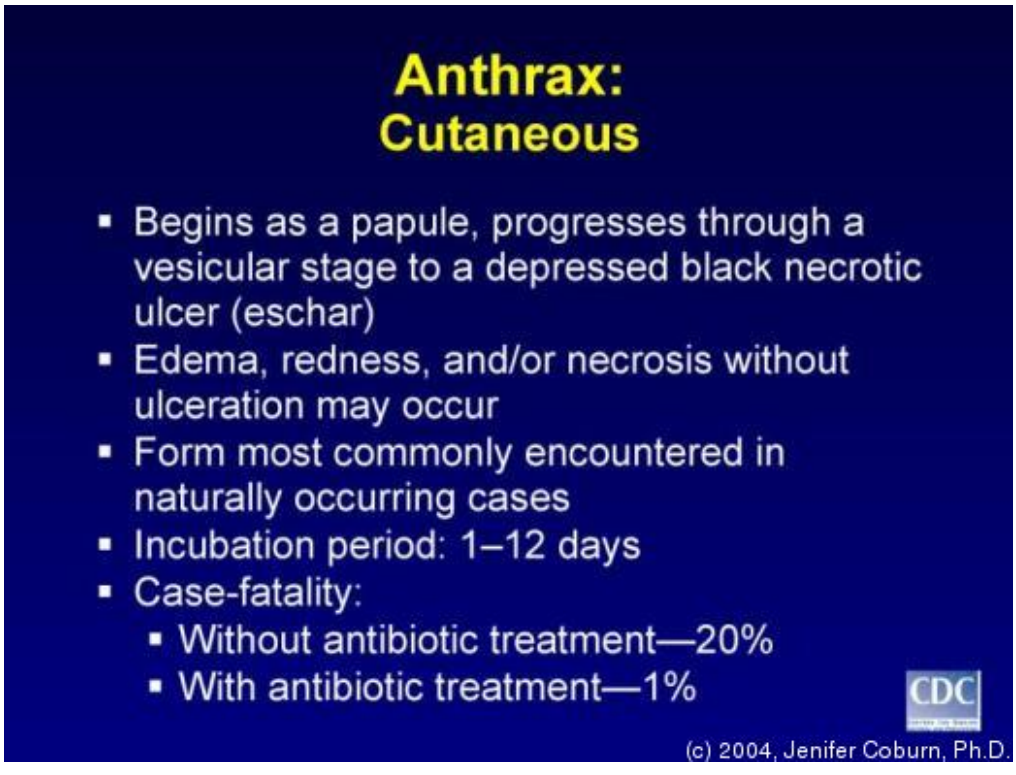
35. Anthrax: Basics



36. Epidemiology of Anthrax in the 21st Century



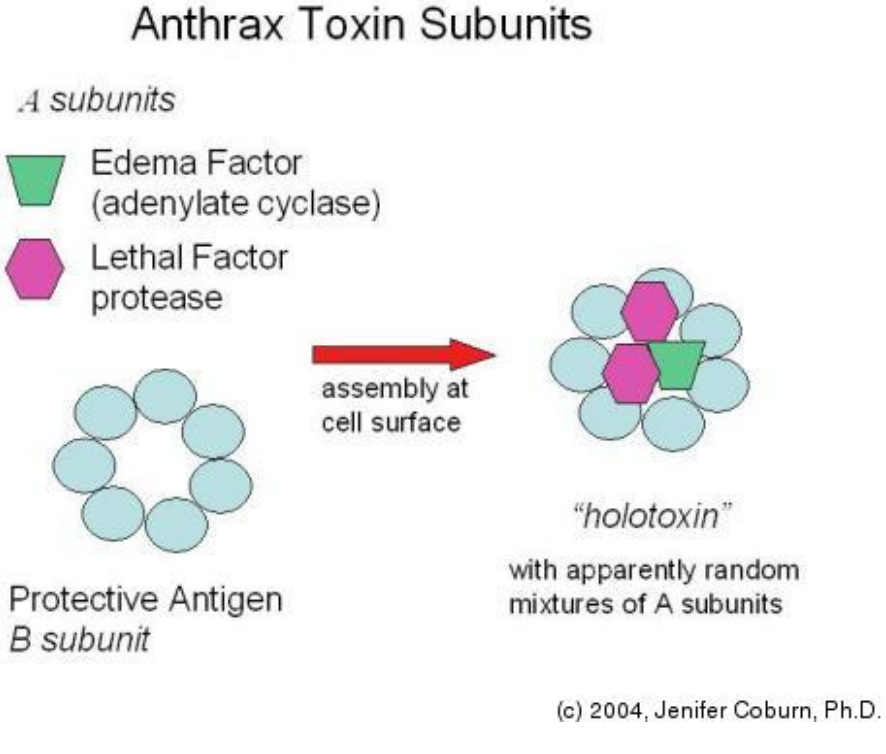
37. Anthrax: Cutaneous



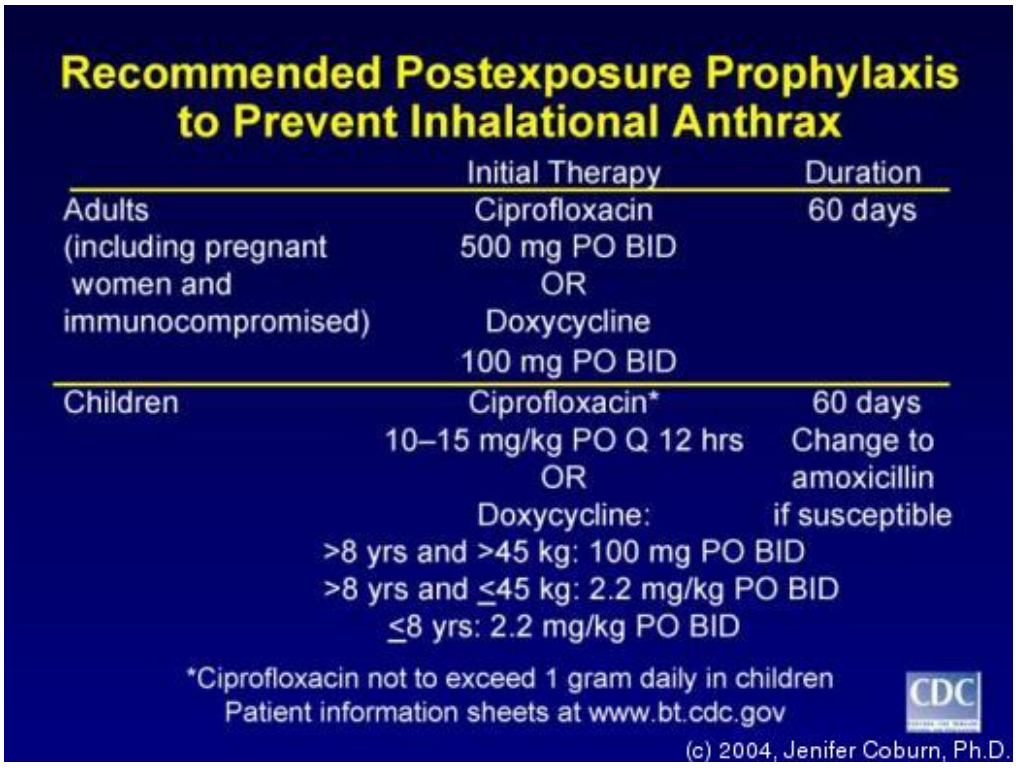
38. Anthrax: Inhalational (1)

39. Anthrax: Inhalational (2)

40. Anthrax Toxin Subunits



41. Recommended Postexposure Prophylaxis



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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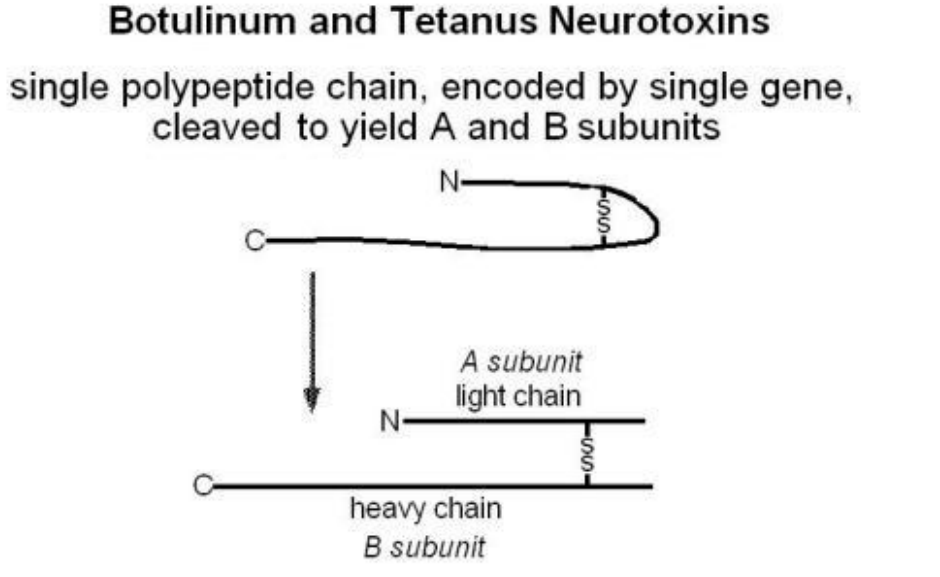
43. Botulinum and Tetanus Neurotoxins



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44. Tetanus and Botulinum Neurotoxins (cont.)

TETANUS AND BOTULINUM NEUROTOXINS

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- 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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