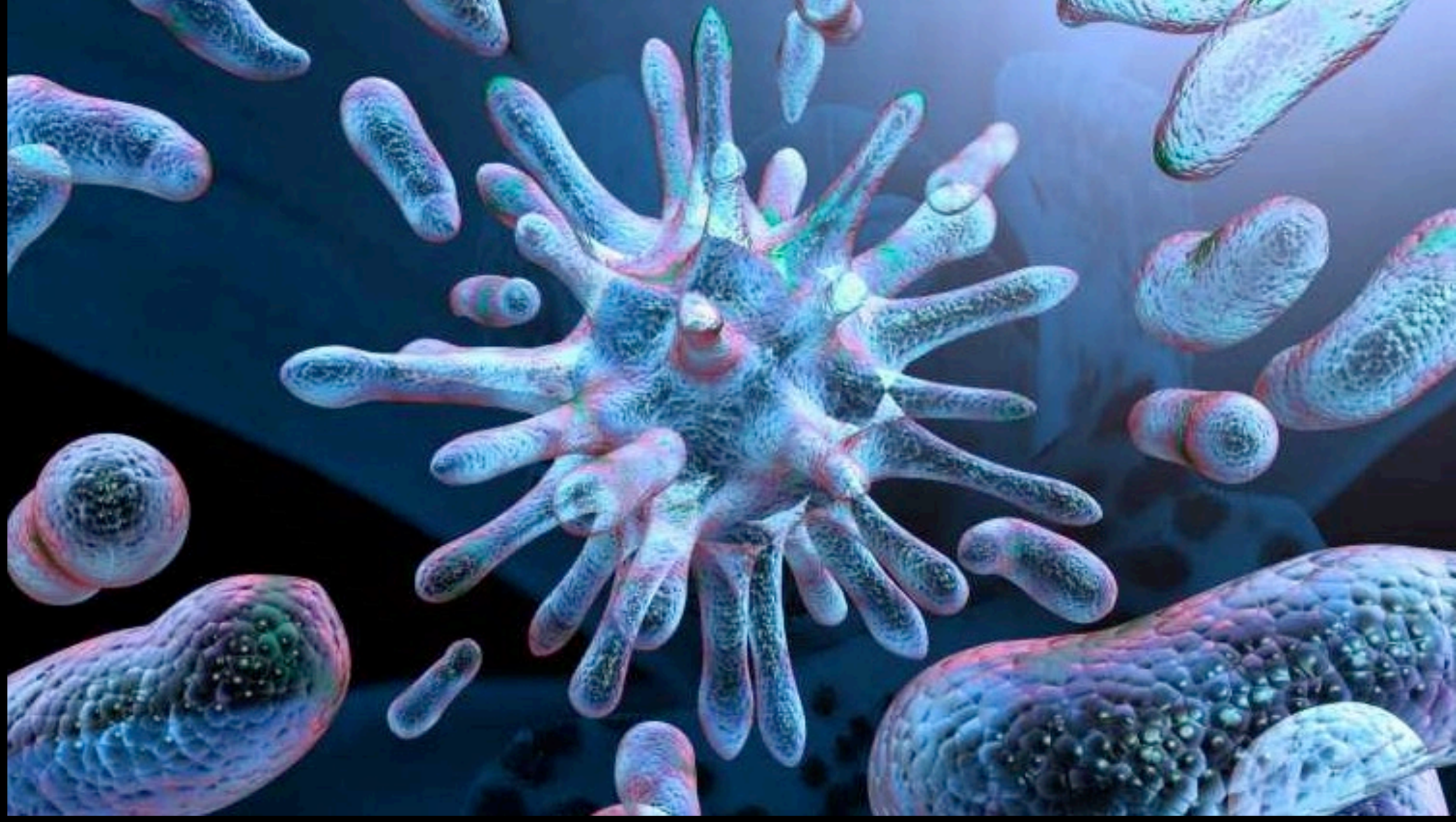


PATH 417 - CASE 1

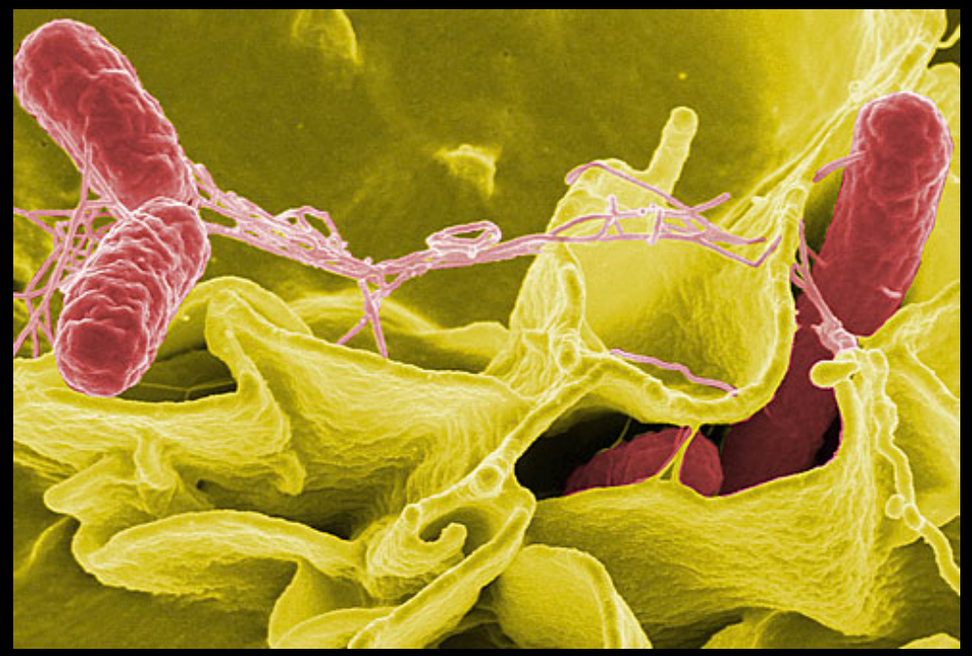
BACTERIAL PATHOGENESIS

Amanda Chao

ENCOUNTER - WHAT, WHERE, HOW?

What: *Salmonella* Enteritidis

- Facultative intracellular pathogen that live both intracellularly and extracellularly
- Has somatic antigens, making them heat stable and alcohol resistant
- Optimal temperature for growth = 35 to 43 degrees Celsius
- Have osmoprotectants that help them to preserve water



http://www.webmd.com/food-recipes/food-poisoning/ss/slideshow-salmonella

ENCOUNTER - WHAT, WHERE, HOW?

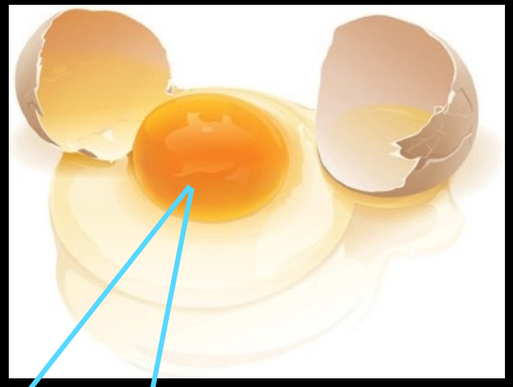
Where:

- Water-abundant places, soil, plants
- Can also survive in dry, cold environments within a wide pH range (3.8 to 9.5)
- Also found in the intestinal tract of humans (optimal pH and temperature for growth)

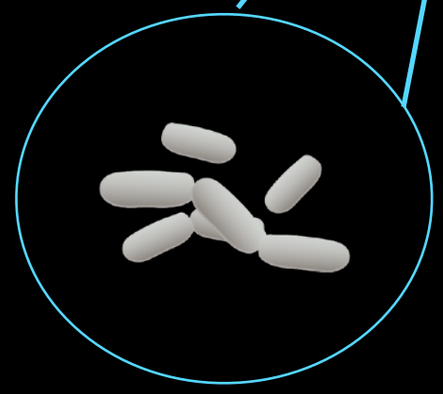
ENCOUNTER - WHAT, WHERE, HOW?

How:

- *Salmonella* Enteritidis can infect the ovaries of hens, contaminating their eggs before shell formation



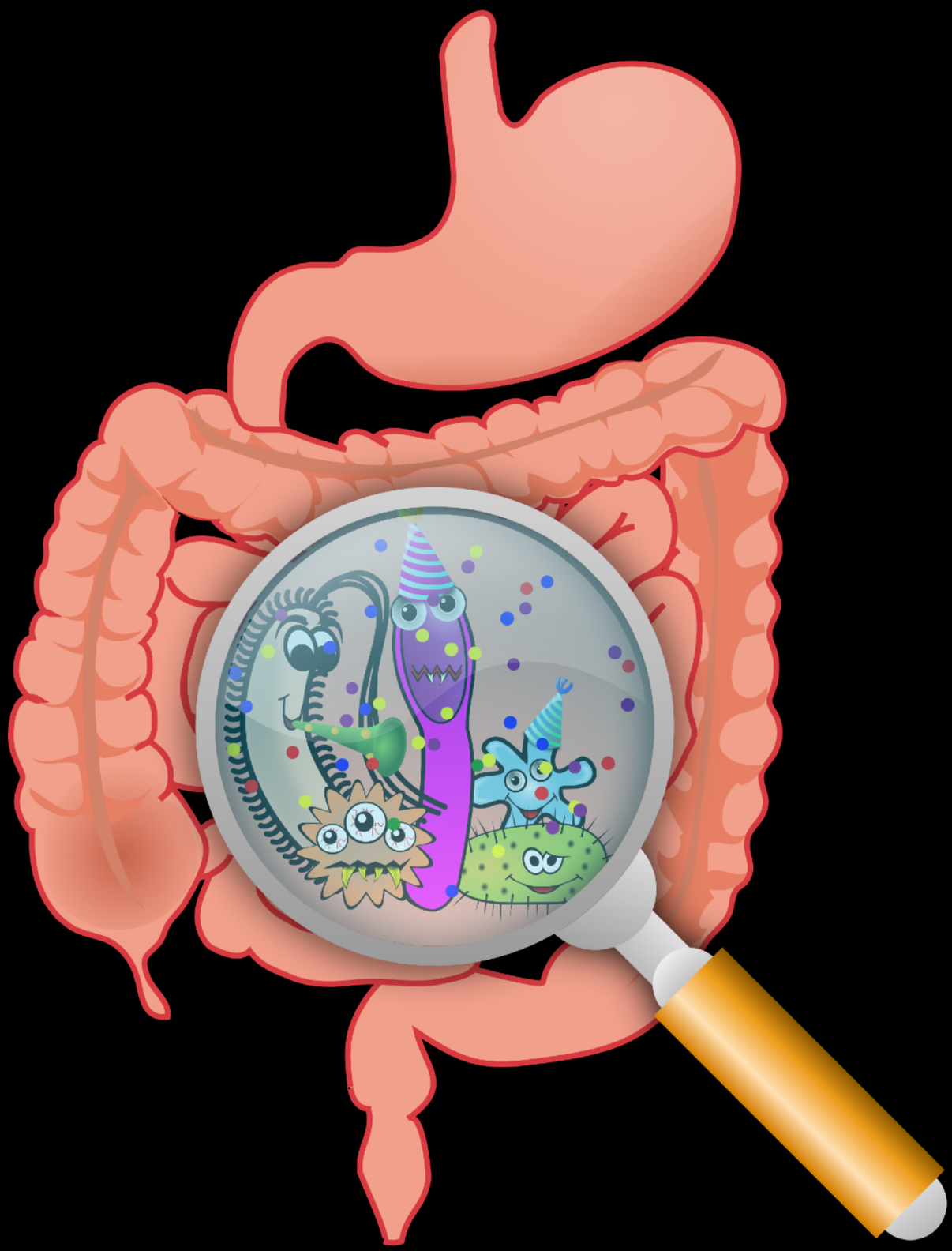
- Ingesting raw eggs (higher chance of contamination) containing these bacteria can cause illness, such as in Johnny's case



- Infection more common in developed countries due to large-scale of commercially prepared food

ENTRY

- Bacteria are ingested and need to make it past the acidic stomach environment
- Colonize the apical surface of the epithelial cells in the intestine (facilitated by flagella)
- Infection Dose (ID) = 10^6 (without food, less with food/liquid)
    - Food has increased pH on surface—>less acidic in stomach
    - Liquids may decrease gastric emptying time



ENTRY

The Main Players:

- Salmonella Pathogenicity Islands (**SPIs**)
- Type 3 Secretion Systems (**T3SS**) - **trigger mechanism**
  - Made up of needle complex + export apparatus + translocon
  - Secreted proteins: **sipA, sipB, sipC, sipD, sopE, sopE2**
- **Rck - zipper mechanism**

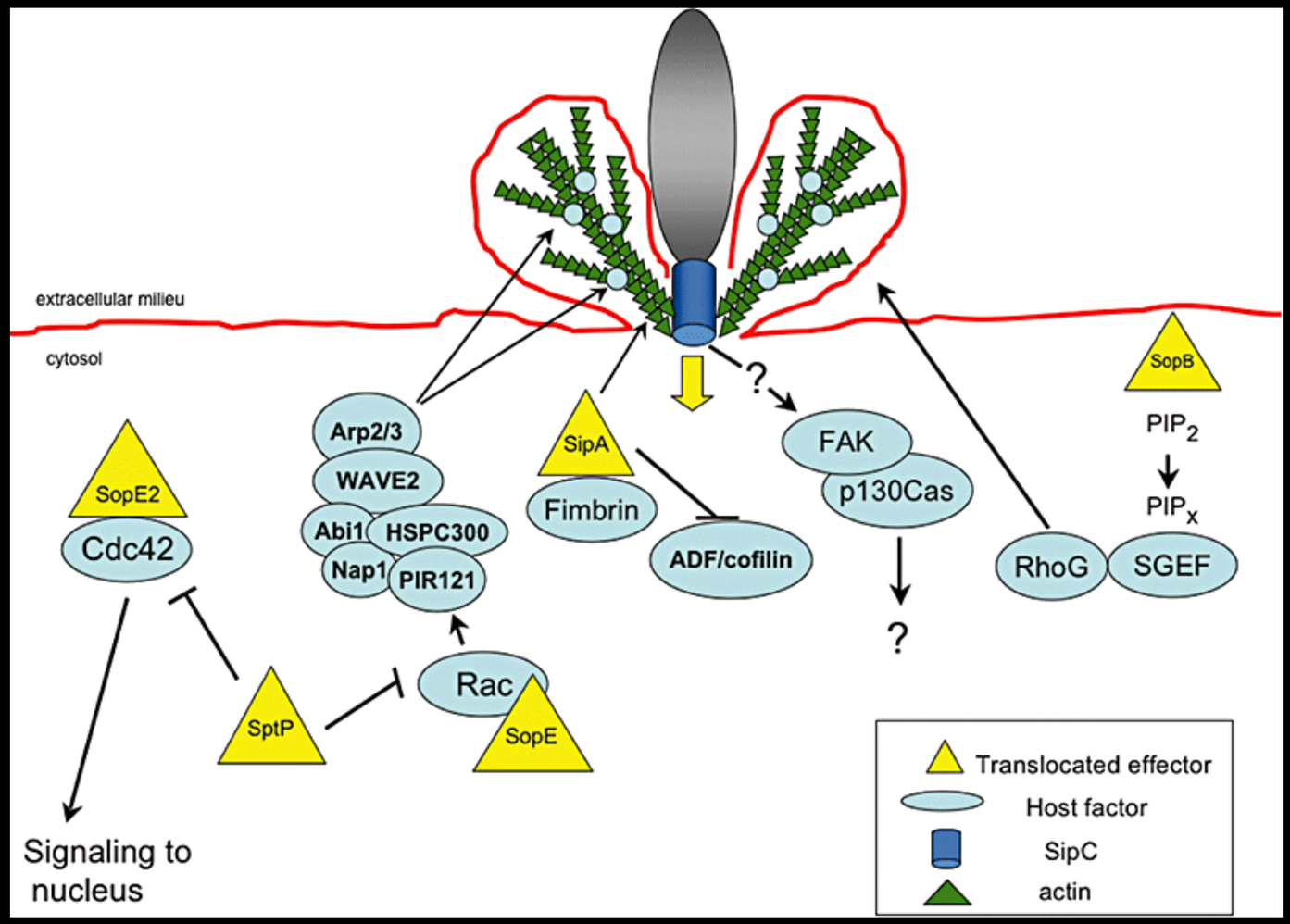
ENTRY INITIATED FROM INSIDE OF CELL VIA T3SS

TRIGGER MECHANISM

ENTRY - TRIGGER MECHANISM I

1. SPIs (genes) express T3SS, which adheres to the host epithelial cell's membrane and activates the translocon (of the T3SS)

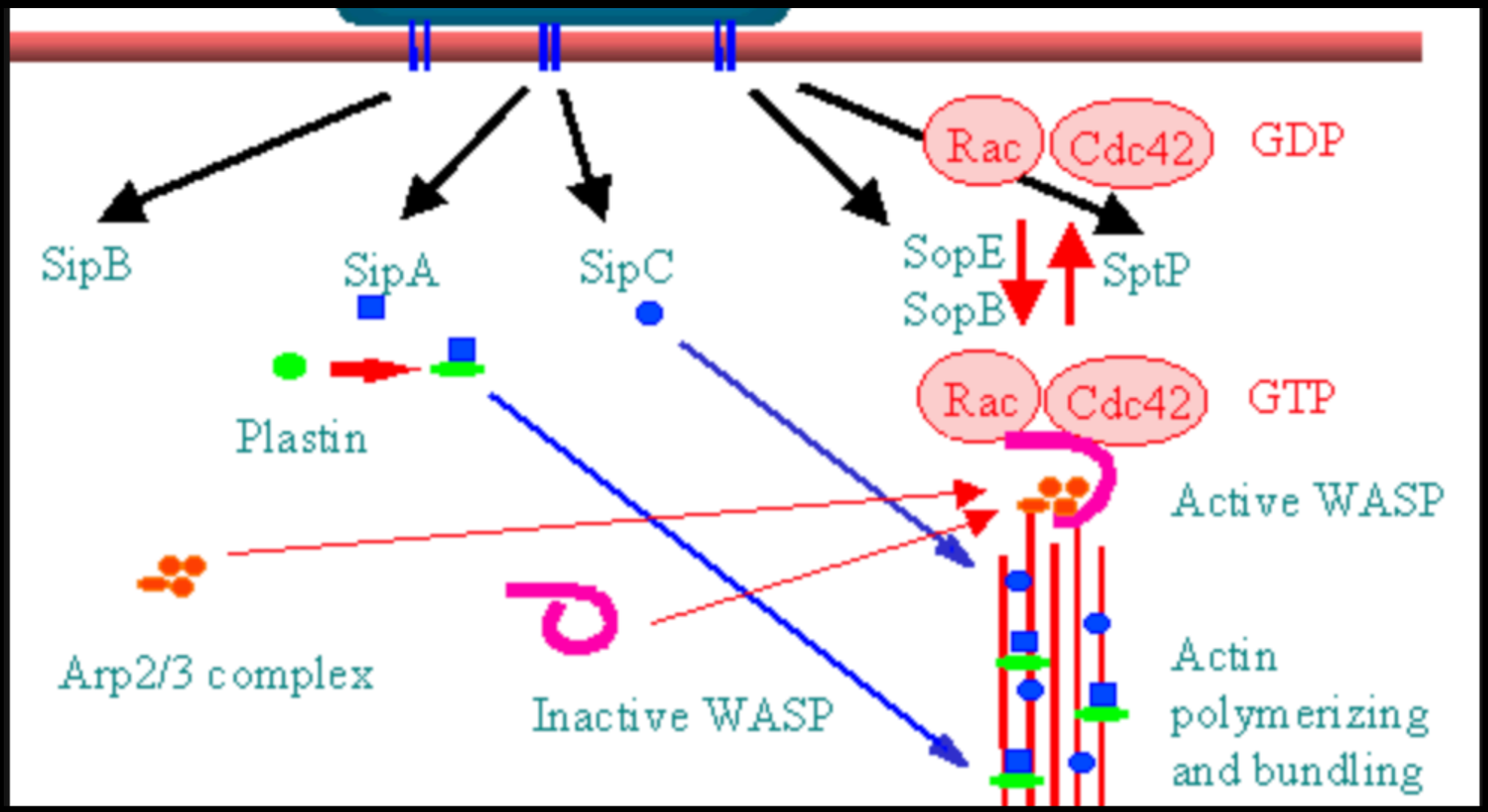
2. Adherence is followed by insertion. Once the translocon adheres, it's activated and forms a pore in the plasma membrane, allowing proteins into the host



ENTRY - TRIGGER MECHANISM II

3. Once the proteins have entered the host, an intracellular signalling cascade is triggered by effector proteins: sopE, sopE2, and sopB

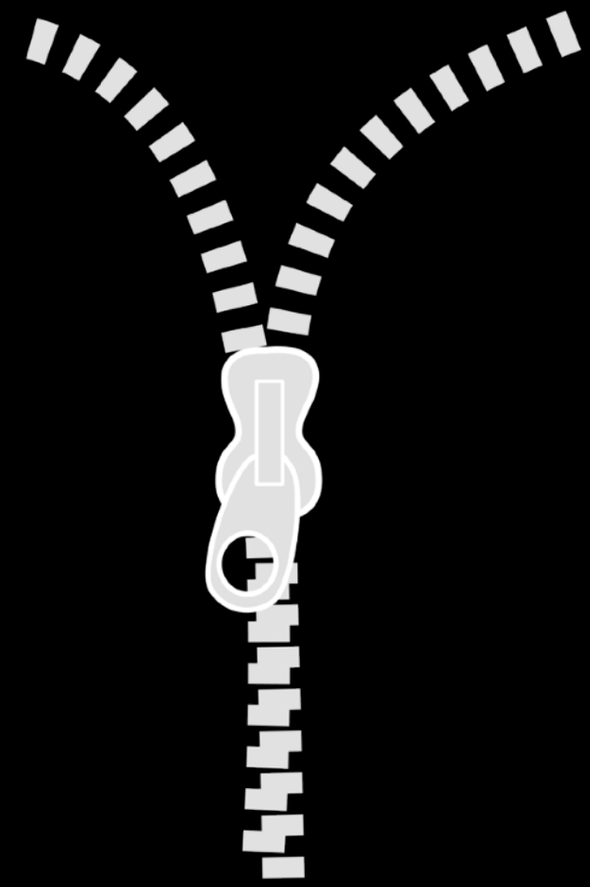
4. Effector proteins activate RhoGTPase, which activates cdc42 and Rac. Subsequently, N-WASP and ARp2 and ARp3 complexes are activated, resulting in actin rearrangement and the pinocytosis of S. enteritidis.



http://www.bms.ed.ac.uk/research/others/smaciver/Bacter6.gif

ENTRY INITIATED FROM OUTSIDE OF CELL VIA RCK

ZIPPER MECHANISM

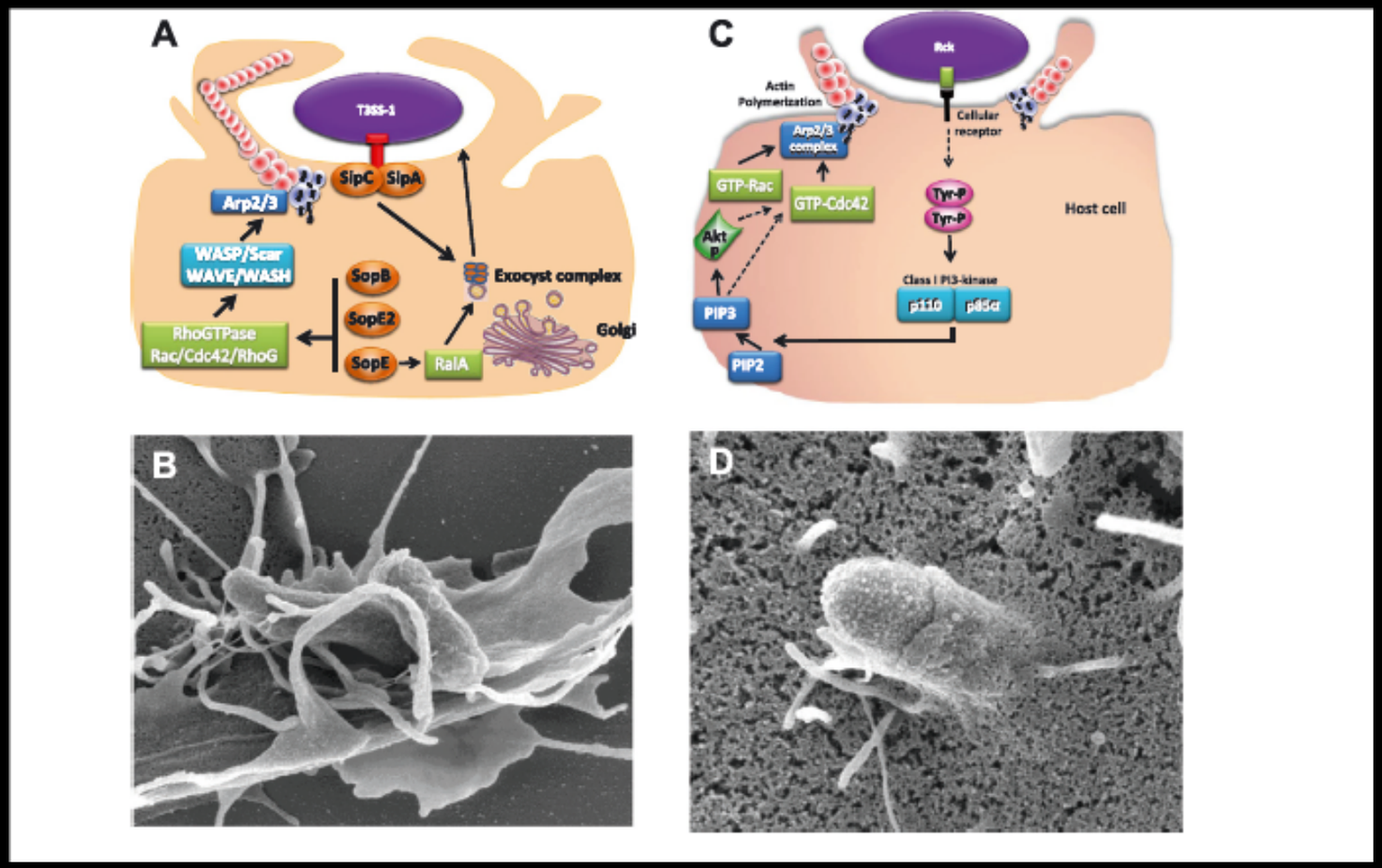


ENTRY - ZIPPER MECHANISM

1. Rck interacts with/adheres to the membrane receptor on the host cell

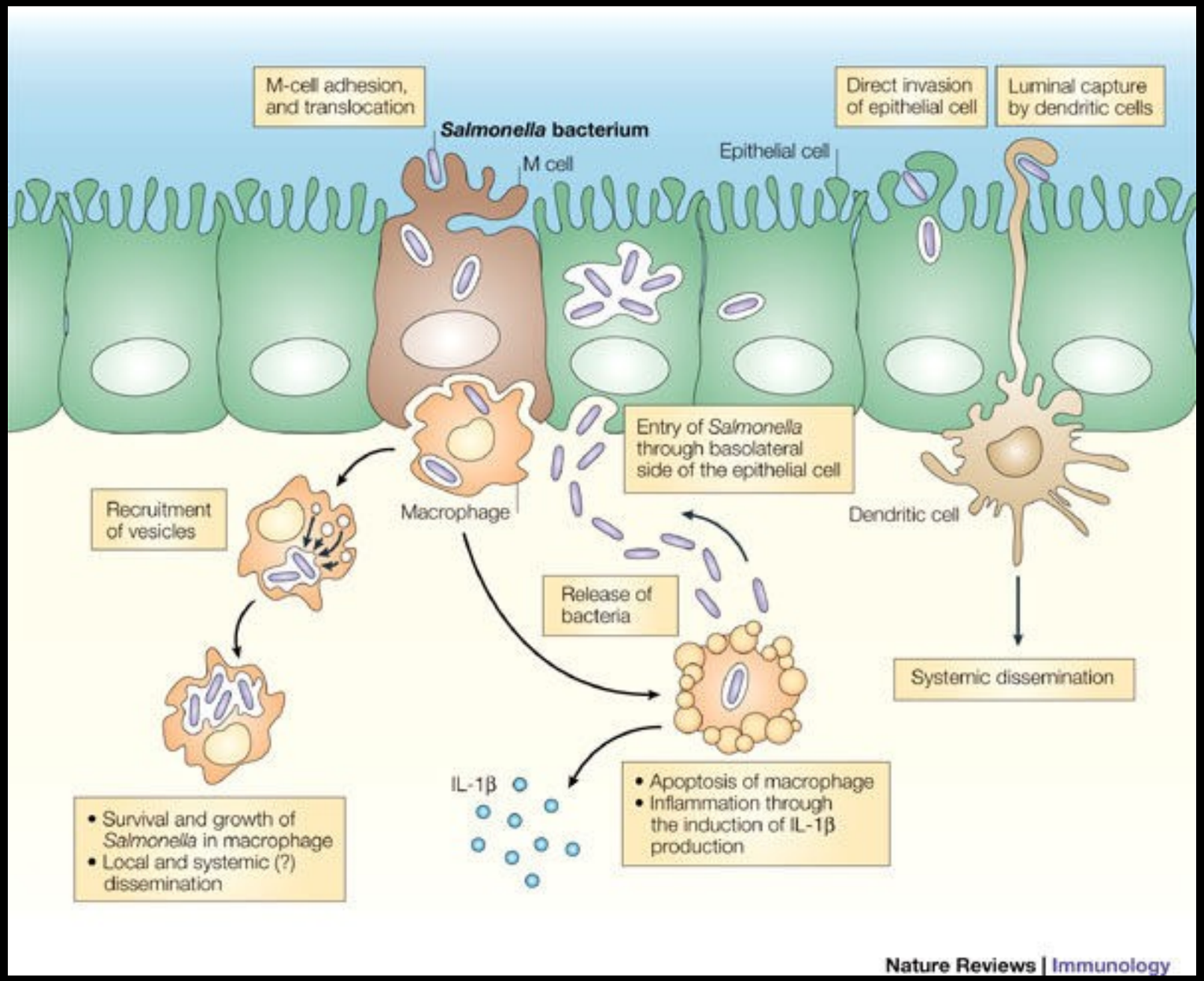
2. The adhesion of Rck to the receptor initiates intracellular cell signalling: Activates protein tyrosine kinase and class IPI3 kinase—>activates AKT + GTPase Rac1 and cdc42—>promotes Arp2/3 activation

3. Ultimately the intracellular cell signalling results in actin polymerization and membrane ruffling causing the internalization of the bacteria



Trigger vs. Zipper Mechanism

MULTIPLICATION AND SPREAD



https://images.nature.com/full/nature-assets/nri/journal/v4/n12/images/nri1499-f5.jpg

MULTIPLICATION

- Get into the gut lumen through variety of ways via the zipper and/or trigger mechanism, within phagosome (aka the Salmonella containing vacuole or SCV)

- Various effectors secreted within the SCV:

Promote replication

Modify SCV to prevent fusion with lysosomes (prevent degradation)

Allow formation of tubules allowing mature bacteria to reach edges of cell/spread

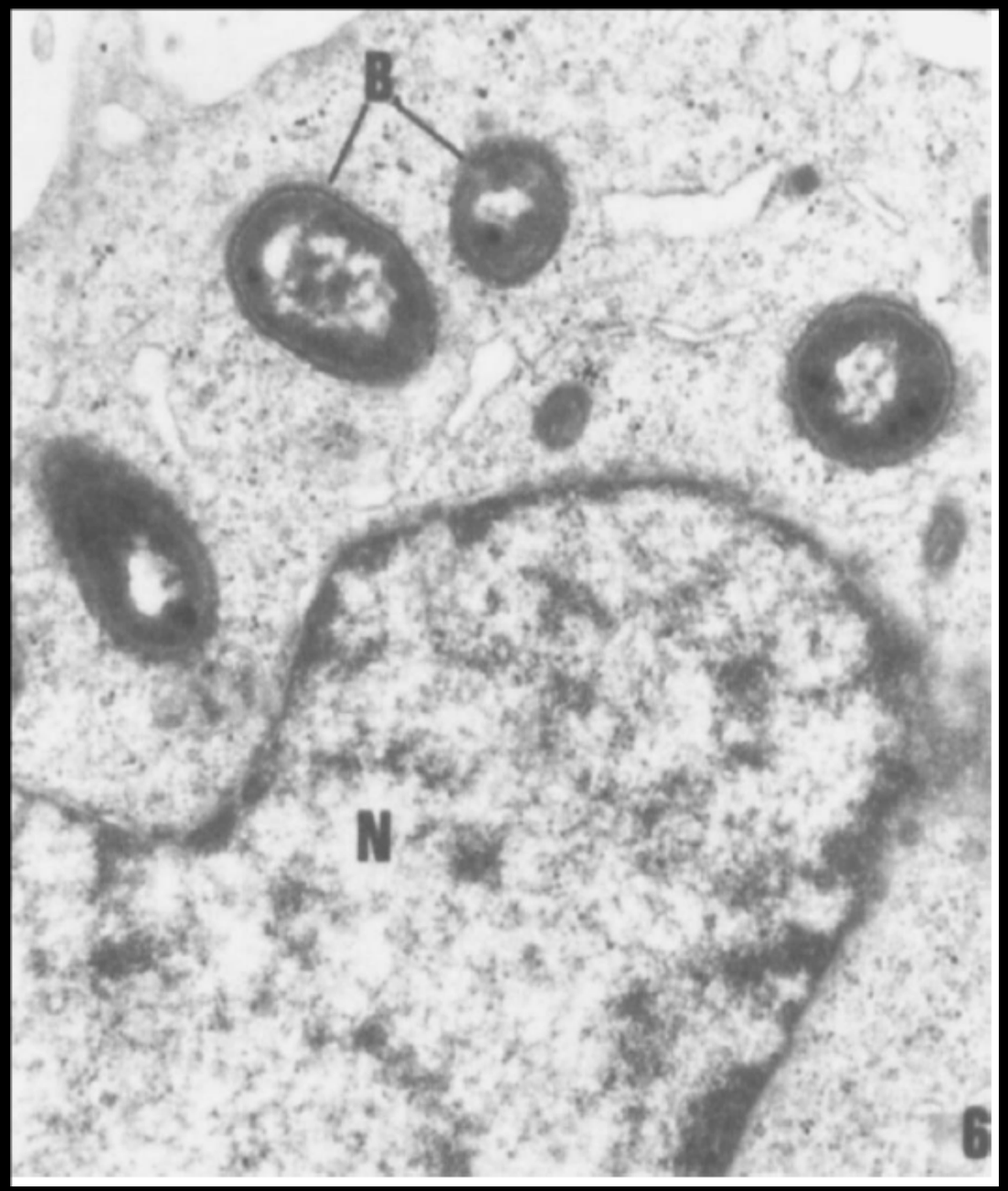
SPREADING BEYOND THE INTESTINES

- Infected intestinal epithelial cells can travel to the draining lymphatics (usually the mesenteric lymph node), where they can replicate and spread systemically

- In attempt to confine the infection, reticuloendothial cells (i.e. macrophages) in the lymph node try to engulf the bacteria in order to confine the infection

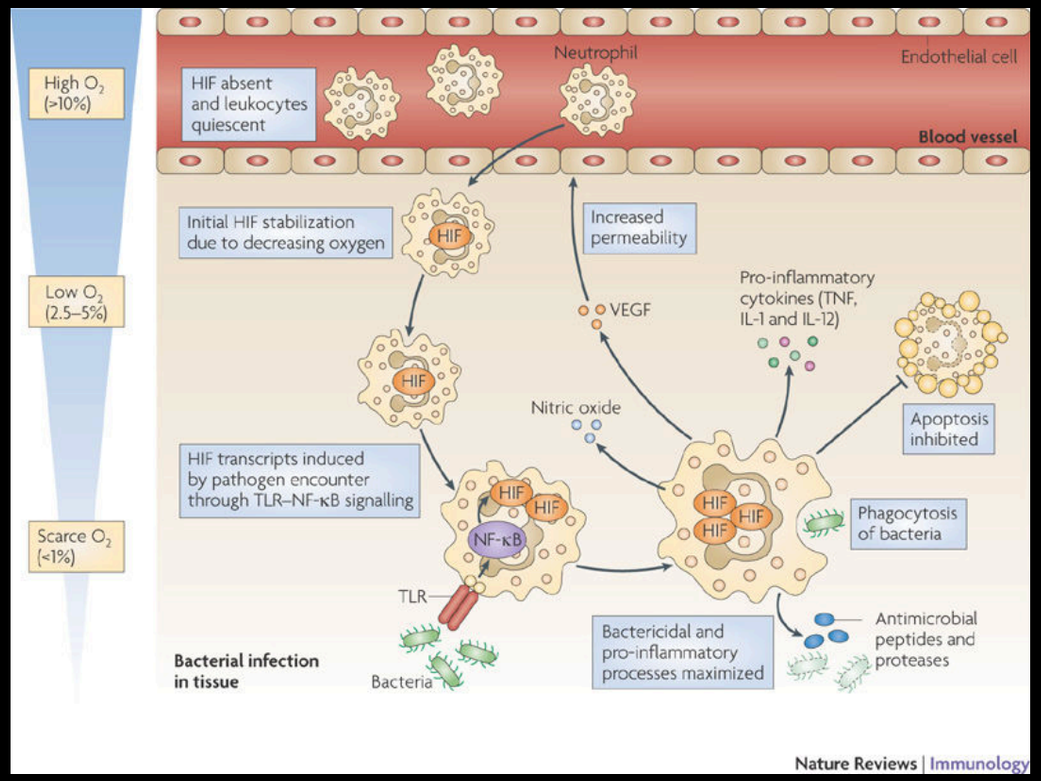
- Certain variations of bacteria (serovars) can survive these macrophages and instead use them to spread to other organs

BACTERIAL DAMAGE



DIRECT DAMAGE TO HOST

- Produce cytotoxins that inhibit protein synthesis of host cells and induce low pH within SCV
- Can disintegrate cytoplasm + cause decreased calcium levels
- Endotoxins from decaying bacteria can damage adjacent cells
- Production of CO2 and hydrogen that build up intestine, making host uncomfortable



DAMAGE DUE TO HOST CELL RESPONSE

Invasion of Intestinal Mucosa

↓

Release of Proinflammatory Cytokines

↓

Acute Inflammatory State in Intestine

- Abdominal Pain
- Fever
- Chills
- Leukocytosis

WHAT CAUSES DIARRHEA?

Adherence—>Increased Adenylate Levels

↓

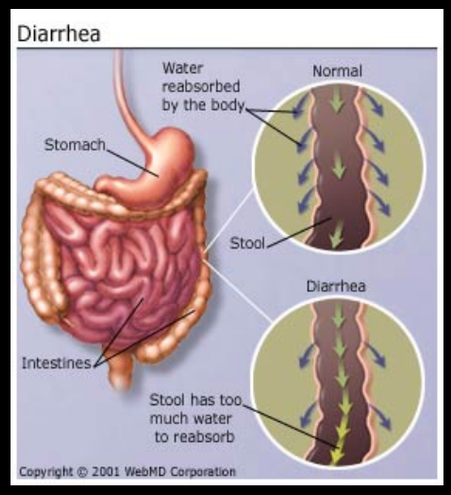
Affects cAMP production (regulator for ion/fluid channels)

↓

Increase Secretion of Channels

↓

Electrolyte Loss



http://www.webmd.com/digestive-disorders/chronic-diarrhea-16/diarrhea-causes

Tight jxns of infected intestinal wall cells compromised

↓

Lack control over water/ion flow in & out of intestine

↓

Effector Protein released by T3SS (SigD)

↓

Disrupts growth/ differentiation of cells involved in signalling pathway

↓

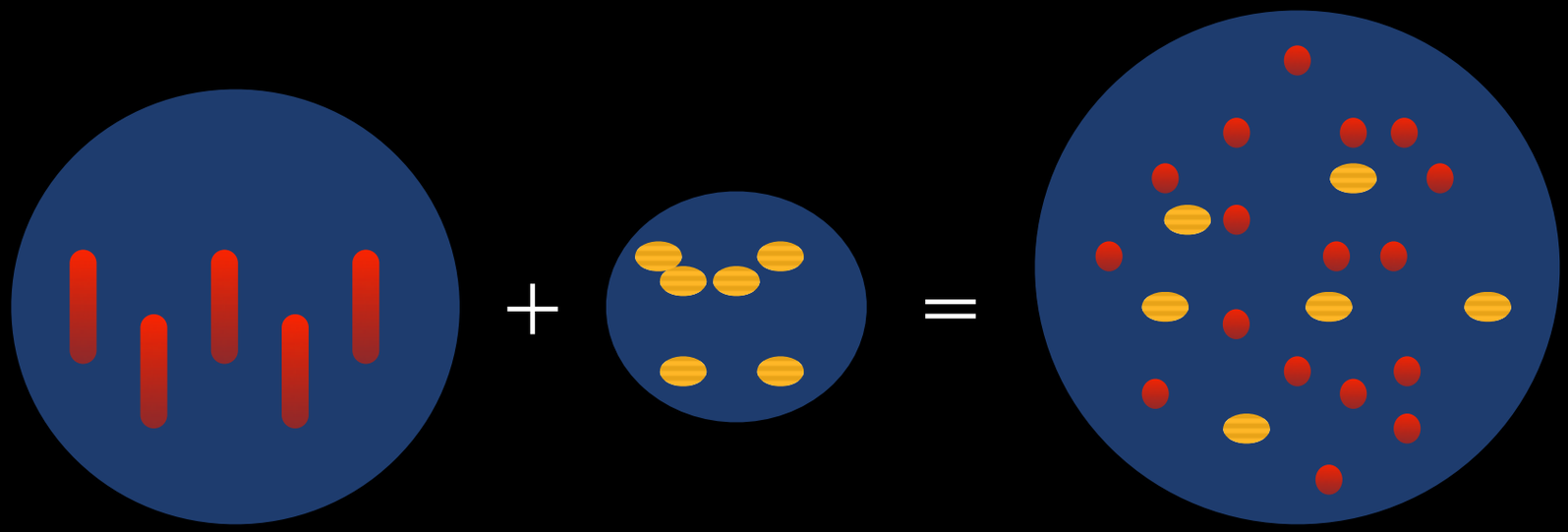
Increased chlorine secretion into lumen

↓

Lack of ion intake & Volume Depletion

→ DIARRHEA ←

WHAT CAN CAUSE ABDOMINAL TENDERNESS?



Phagosome containing Salmonella

Lysosome containing enzymes

Phagolysosome (degrades bacteria/ damages cells)

Lack cells + Weakened cells

TENDERNESS IN ABDOMINAL REGION

THE END