CASE 4 – THE BODY SYSTEM

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- **One Too Many Hamburgers**

10-year-old Ronnie McDonald has developed abdominal cramps, bloody diarrhea and a low grade fever. His parents take him to see the family doctor. The doctor asks about what Ronnie may have eaten in the past week and his parents recall that last weekend at a neighbor's barbecue they were concerned that the hamburgers may not have been cooked thoroughly and Ronnie had eaten two burgers. The doctor performs a physical examination noting no rebound tenderness just some mild periumbilical tenderness. He asks the parents to collect a stool sample for the Microbiology Laboratory and to take Ronnie to the local lab for some routine bloodwork.

- **The Body System Questions**

1. What are the signs (objective characteristics usually detected by a healthcare professional) and symptoms (characteristics experienced by the patient, which may be subjective).
2. Which body system is affected, in what specific area and what is the normal physiological function of this area of the body (representing this diagrammatically would be helpful).
3. In what way has the normal physiological functioning of this area of the body been disturbed by the infection (without going into detail on the cause of this disturbance as this will be dealt with in questions 3 and/or 4).
4. Are there any secondary sites of infection and, if so, what enables the bacteria to (a) travel to; and (b) affect these areas of the body.
5. What tests are performed in 'routine' blood work?

QUESTION 1

What are the signs (objective characteristics usually detected by a healthcare professional) and symptoms (characteristics experienced by the patient, which may be subjective)

Signs & Symptoms

https://edc2.healthtap.com/ht-staging/user_answer/avatars/1184119/large/open-uri20130614-553-tvo2aa.jpeg?1386647766

Based on signs and symptoms, Ronnie is likely to be experiencing gastrointestinal infection.

- Signs: objective medical observations made by a healthcare professional
- Symptoms: observations experienced by the patient themselves

Signs	Symptoms
Mild periumbilical tenderness	Abdominal cramps
Low grade fever	Low grade fever
No rebound tenderness	Bloody diarrhea

Bloody diarrhea may not be a sign if the doctor was not able to see it

Stool and blood samples were taken to isolate the root pathogen and to see whether or not a system infection is occurring

QUESTION 2

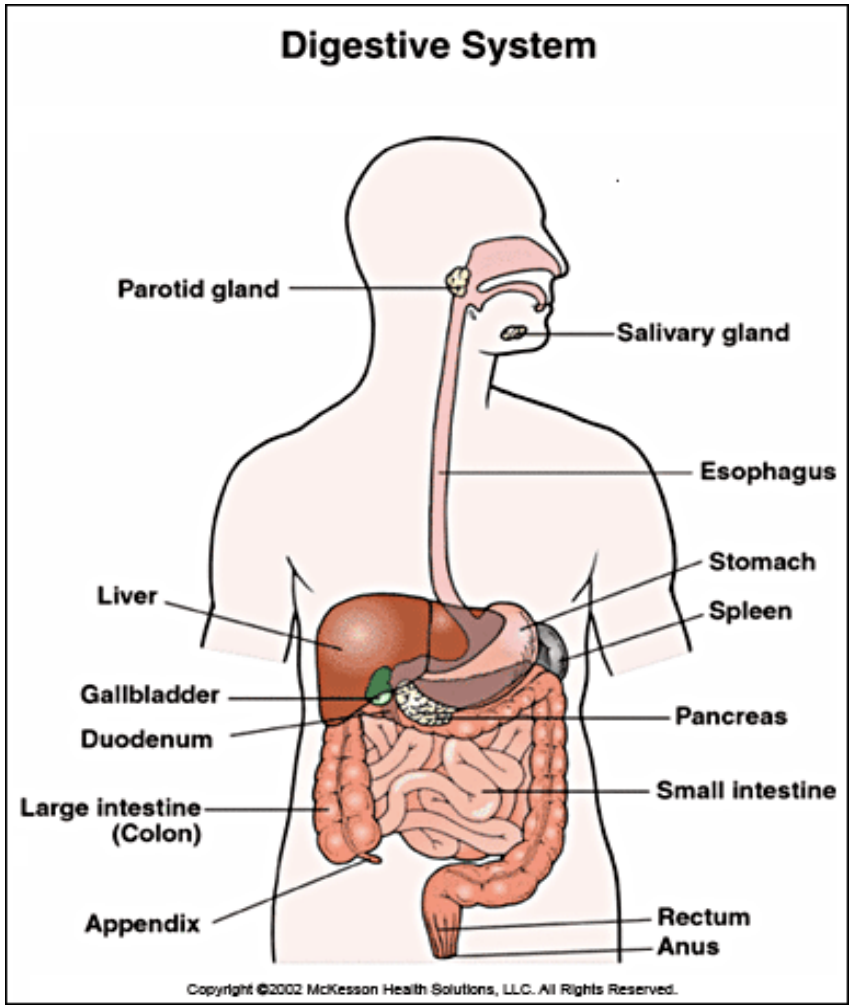
Which body system is affected, in what specific area and what is the normal physiological function of this area of the body (representing this diagrammatically would be helpful)

Gastrointestinal (GI) system

GI system = GI tract + accessory exocrine glands

GI tract	Major accessory exocrine glands
• *Mouth* • *Esophagus* • *Stomach* • *Small intestine* • *Large intestine*	• salivary glands • liver • gall bladder • pancreas

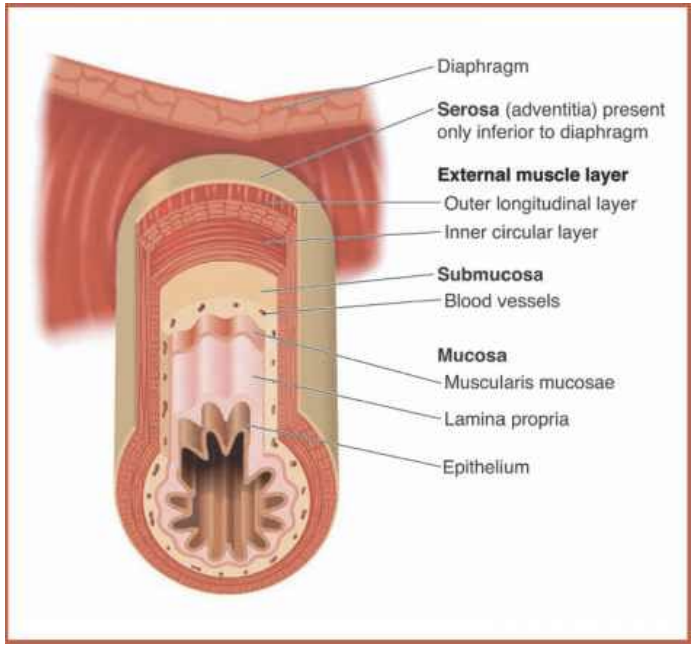
Main function of GI system:
For assimilation of nutrients and excretion of waste products via the biliary system



http://cephalicvein.com/wp-content/uploads/2016/08/gi-tract-steven-solik-md-gastroenterologist-office-consultations-in-durham-nc.gif

GI tract 4 main layers

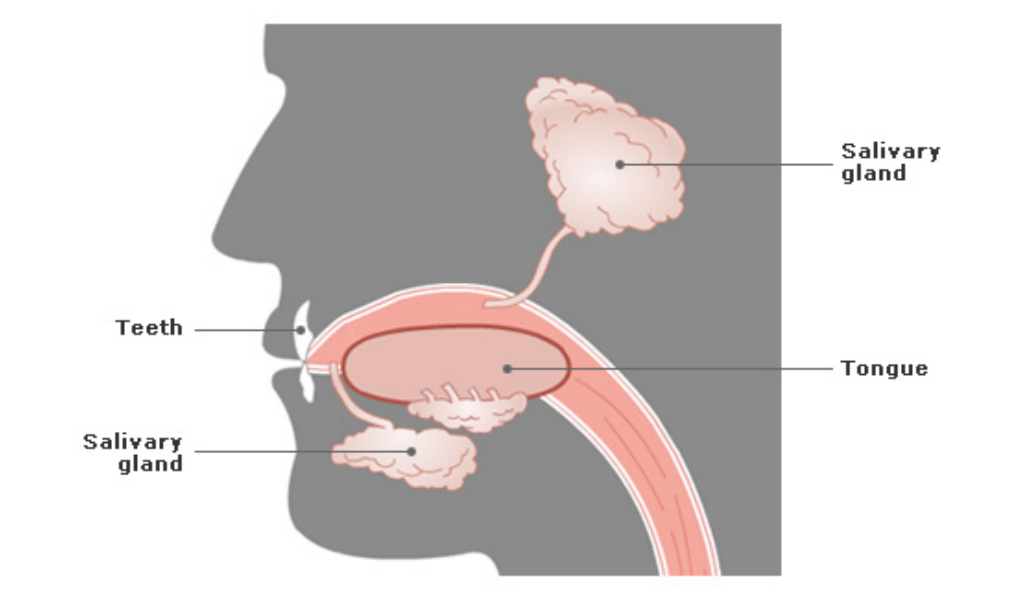
- GI tract is a muscular tube surrounded by mucous membrane
- Contains four layers:



https://www.karelsavry.us/biology/images/283_20_6-wall-structure-digestive-tract.jpg

Mucosa	1. Epithelium 2. Lamina propria • Loose supporting tissue • Plasma cells and lymphocytes dispersed throughout 3. Muscularis mucosae • Several layers of smooth muscle fibers 4 types of mucosa: 1. Squamous mucosa 2. Gastric type secretory mucosa 3. Intestinal type absorptive mucosa 4. Colorectal type
Submucosa	o collagenous connective tissue supporting mucosa o has blood vessels, nerves, lymphatics
Muscularis propria	o Smooth muscle with circular and longitudinal layers o peristalsis
Adventitia	o loose supporting tissue o blood vessels, nerves, adipose tissue

Mouth & Salivary Glands



http://www.passmyexams.co.uk/GCSE/biology/images/salivary_glands.jpg

- **Mouth**
  - To chew and reduce particle size and make bolus for swallowing
  - To taste
- **Salivary Glands**

Saliva is secreted to produce a composite juice that is mildly alkaline

- Lubrication

Moisten mouth, food, faciliatate mouth and tongue movements for speech

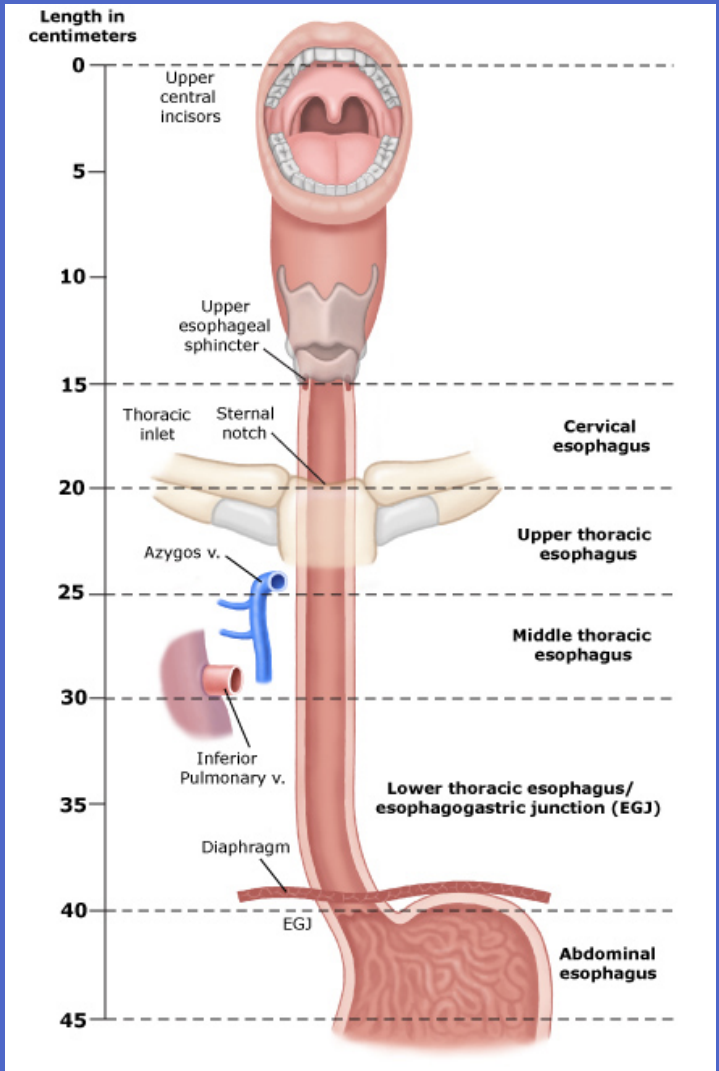
- Protection

Lysozymes, lactoferrin, and Ig-A binding proteins reduce bacterial growth and neutralize acids produced by bacteria

- Digestion

Enzymes α-amylase and lingual lipase breakdown carbohydrates and fats

Esophagus



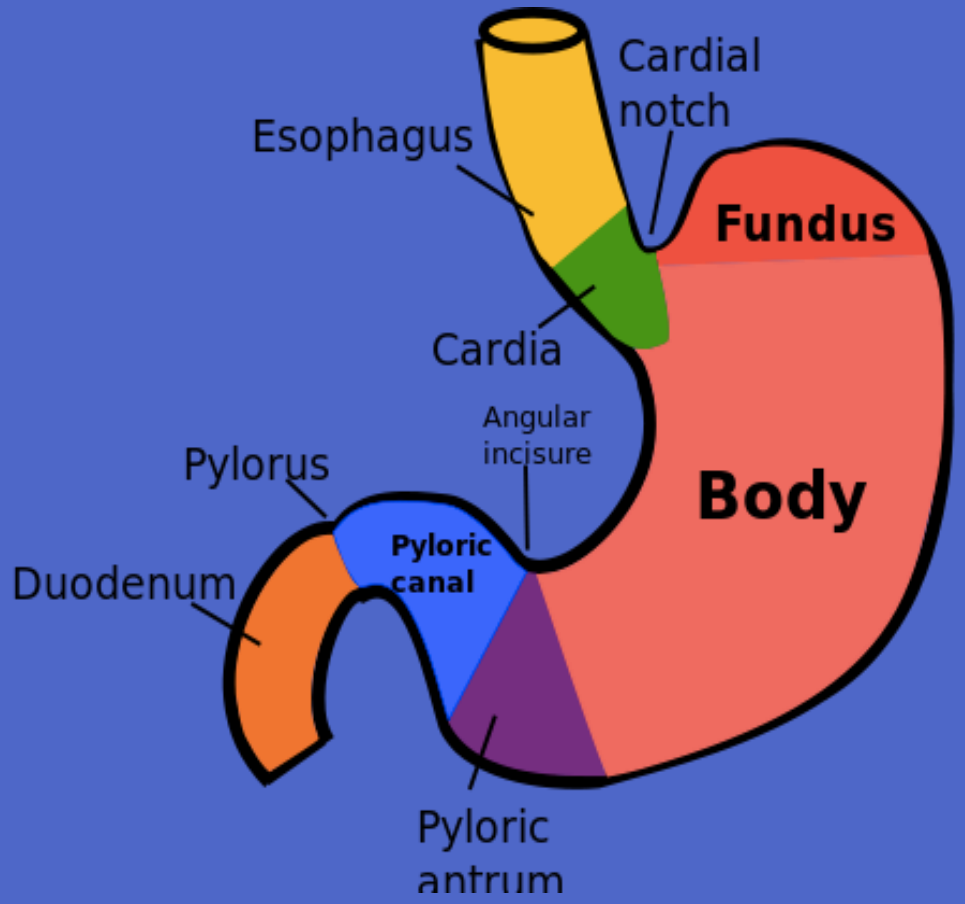
http://www.quasargroupconsulting.com/Encyclopedia/anatomy/Esophagus01.jpg

- 25cm muscular tube
- lined with moist stratified epithelium
- Main function: move food bolus and liquid to the stomach
- **3 functional zones**:
  - *Upper zone (striated muscle)*
  - *Middle zone (smooth muscle)*
  - *Lower zone (smooth muscle*
- Areas between the upper and lower esophageal sphincters remain quiescent until it's needed to transport gas, fluids, or solids

Esophagus

- Swallowing induces primary peristalsis; if this is insufficient, then secondary peristalsis is induced
- Peristalsis repeated until the bolus moves to stomach
- **Vomiting reflex**: peristalsis is reversed to allow toxic or pathogen-laden food to be removed from esophagus
- **Resting esophagus**:
  - Upper and lower sphincters exibit high pressures (maintain closure)
  - Above diaphragm, pressure is subatmospheric because the esophagus passes through the intrathoracic space
- **Upon swallowing:**
  - The upper esophageal sphincter briefly relaxes to allow food bolus to pass through
  - Peristaltic wave sweeps down the esophagus
  - The lower esophageal sphincter and the proximal stomach relax to allow bolus entry into stomach

Stomach



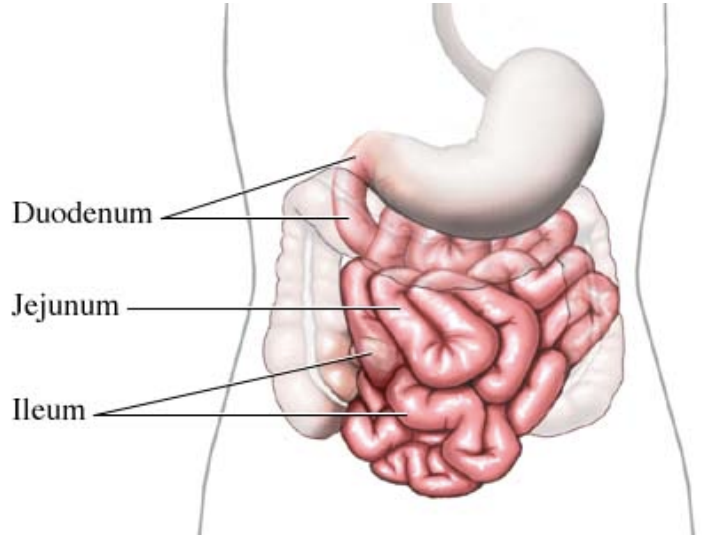
http://www.healthhype.com/wp-content/uploads/stomach.png

- Main function: to triturate and mix food contents with pepsin and acid
- Gastric acid sterilizes the upper gut
- The proximal stomach stores and accommodate food
- The distal stomach induce phasic contractions to propel food residues against the pylorus
- Repeated propelling of food allow further mixing and digesting before entering duodenum (small intestine)
- Intrinsic factor released in stomach for vit B12 absorption

Stomach

Anatomical Areas	Location	Function
Fundus	The rounded area above the cardiac region	Secretory cells contributing to gastric juice acid and pepsins
Cardia	Where the esophagus enters the stomach	Secrete mucus and bicarbonate to protect stomach surface from acidic gastric juice
Body	Below the cardiac region	Secretory cells contributing to gastric juice acid and pepsins
Pyloric antrum (gastric antrum)	Most distal part of the stomach	Extensive motility for mixing gastric contents and grinding/sieving contents
Pyloric sphincter	Guards the exit of the stomach connected to the small intestine	Relaxes for chyme to enter small intestine

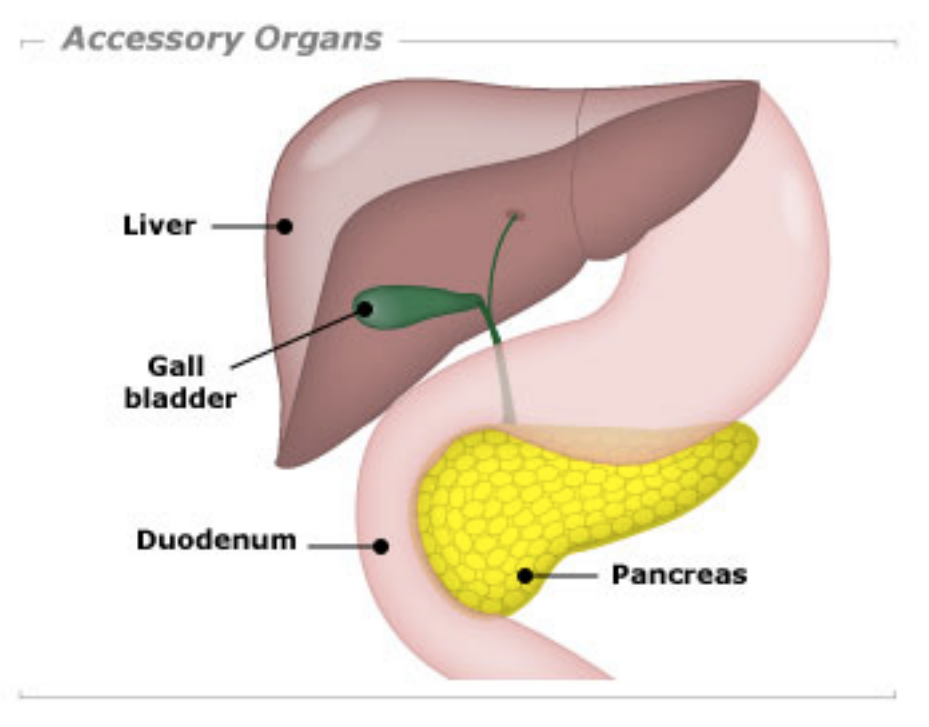
Small Intestine (S.I)



http://gastropatienteducation.com/Gatro_Pat/Pat_Ed_web_pages/images/small_intestine.jpeg

- Duodenum
  - *First 12 inch of s.i*
  - *4 parts: superior, descending, horizontal, and ascending duodenum*
  - *Critical regulator of digestion and absorption (with exocrine gland secretions – next slide)*
  - *Endocrine cells, chemo- and mechanosensitive nerve endings monitor luminal contents to signal distant regions of GI tract for preparation or stomach to retard the content flow*
- Jejunum
  - *Also the site of absorption of majority of nutrients*
- Ileum
  - *Less absorption activity except for specific solutes (ex. Conjuaged bile acids)*
  - *If jejunal absorption is impaired, ileum can be called on for absorption*
  - *Important for vit B12 absorption*
- Ileocecal sphincter
  - *Prevents reflux and maintains s.i sterility*

S.I & Accessory exocrine glands

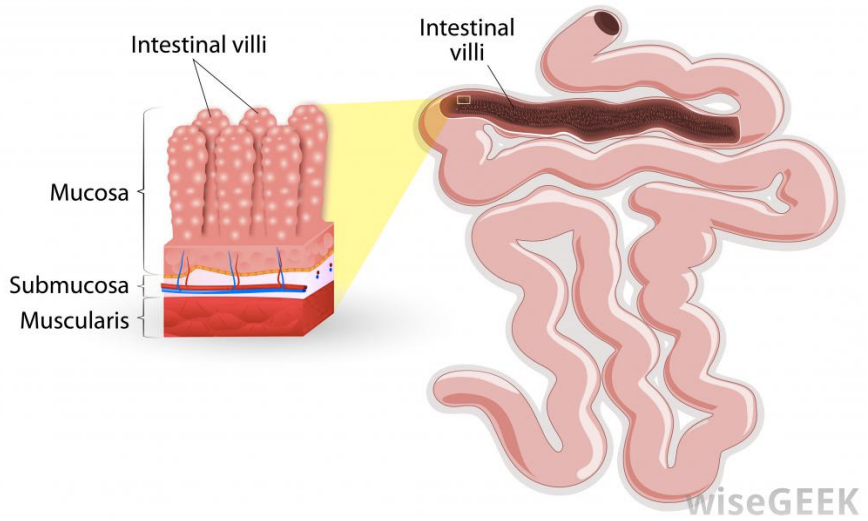


https://online.science.psu.edu/sites/default/files/bisc004/content/accessory_organs.jpg

- Triturated chyme from the stomach mixes with pancreatic juice and bile in the duodenum to facilitate digestion
- Pancreatic juice:
  - *contains enzymes for carb, fat, protein digeston*
  - *Contains bicarbonate to neutralize pH to protect s.i from gastric acid and activate enzymes*
- Bile:
  - *secreted by liver, which can be stored in the gall bladder*
  - *Bile assist lipid digestion*

SMALL INTESTINE

Small Intestine



http://images.wisegeek.com/small-intestine-diagram-with-villi.jpg

- Large apical surface area with villi and microvilli
- Digestion
- Absorption
  - *Nutrient absorption*
  - *Water absorption (~90%)*
- Waste elimination
  - *Bile contains byproducts of erythrocyte degradation, toxins, metabolized/un-metabolized medications, cholesterol*
  - *Indigestible food residue + waste + sloughed-off enterocytes => delivered to colon*

Small Intestine – Cell Types

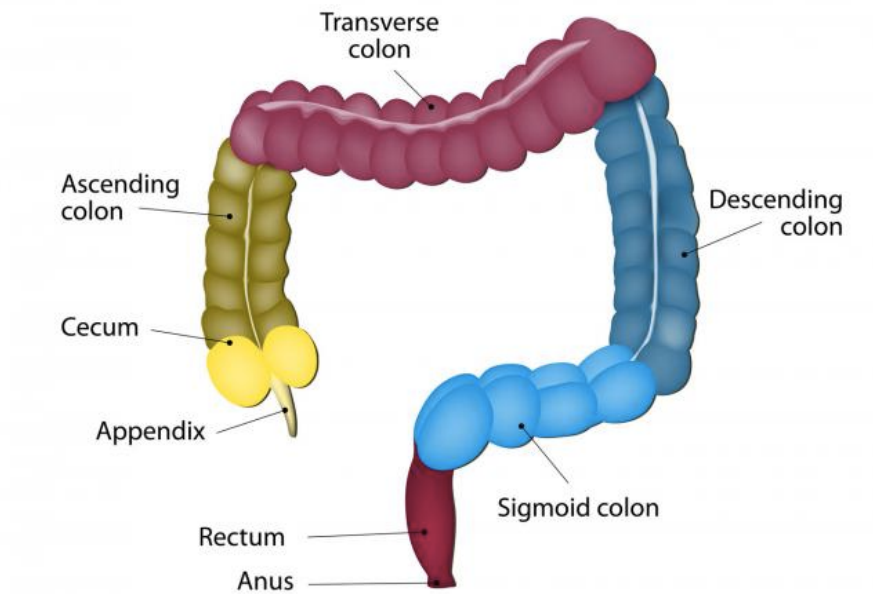
Cell Types	Function
Enterocytes	Main absorptive cells that digest and absorb food
Goblet cells	Mucin production
Paneth cells	Lysozyme secretion and phagocytosis
G cells	Gastrin secretion
I cells	Cholecytokinin (CCK) secretion that stimulates pancreatic juice and bile release
K cells	Motilin secretion that induces gastric emptying, peristalsis, and pepsin production
S cells	Secretin secretion

Large Intestine (Colon)

http://www.naturalhealth365.com/wp-content/uploads/2017/01/colon.jpg

- Reservoir for the storage of wastes and indigestible materials prior to their elimination by defecation
- Goblet cells
  - Mucous secretion to protect colon
- Enterocytes
  - Absorb water, salts, vitamins
- Dehydration to decrease daily fecal volumes from 1-1.5L to 100-200mL
  - Facilitated by slow fecal desiccation

Large Intestine (colon)



http://www.medicalnewstoday.com/content/images/articles/150/150496/diagram-of-the-large-intestine.jpg

- 4 sections with varied functions:
  - *Ascending colon*
  - *Transverse colon*
  - *Descending colon*
  - *Sigmoid colon*

Ascending and transverse colon are responsible for fluid absorption and salvage of other dietary byproducts (ex. Abosrption of short chain fatty acids produced by the bacterial fermentation of carbohydrates like dietary fiber)

Distal colon is responsible to propel fecal material through peristaltic contractions to expel the stool through anus.

Anus has involuntary and voluntary sphincters to permit retention of the stool before the release in a socially convenient setting

Large Intestine (colon)

Commensal Ecosystem – Bacterial Colonization

- Primarily composed of anaerobic bacteria in a healthy individual
- Bacteria in colon are important contributors to whole-body nutritional status
  - ferment undigested carb and SCFA
  - Modify luminal solutes like bile acids and bilirubin
- Immune System
  - TLR-MyD88 signaling pathway can sense microbiota and trigger responses critical for maintaining host-microbial homeostasis
  - Individual microbiota can influence the makeup of lamina propria T lymphocyte subsets with distinct effector functions
  - Commensal bacteria compete with pathogenic bacterial species for nutrients/space and give protection
  - However, upon reduction in host's immune system, they can become opportunitstic pathogens and enter the body, resulting in infection and inflammation upon disruption of intestinal epithelial integrity

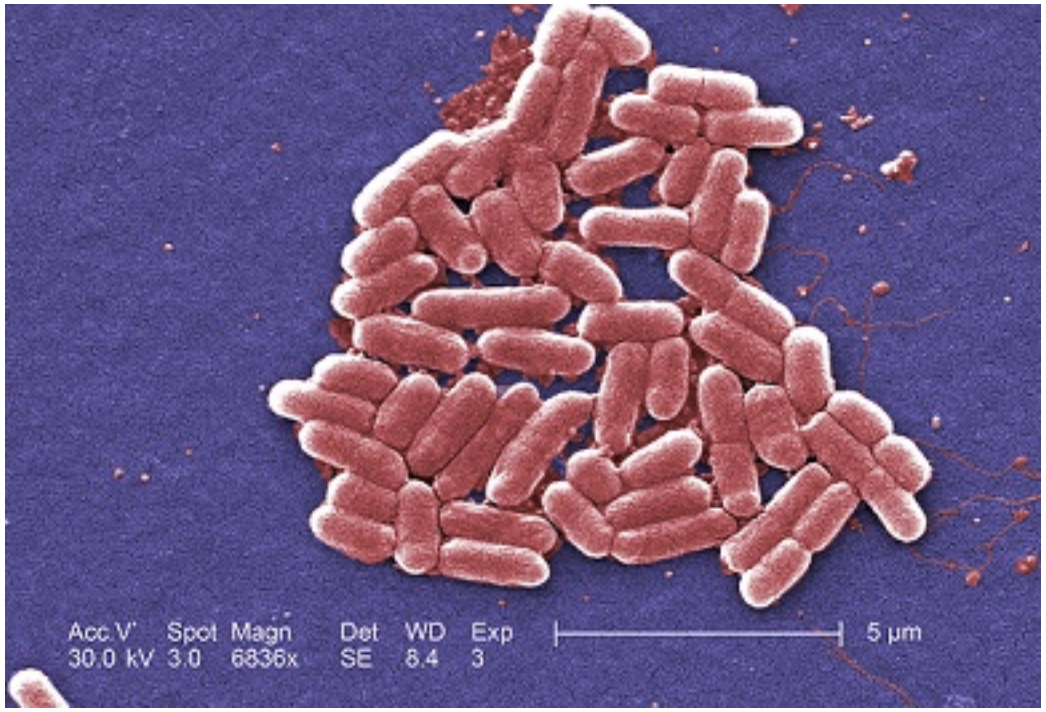
RONNIE'S CASE

Based on his symptoms and signs, it is predicted that the mainly affected area is in the enterocytes of lower intestine.

QUESTION 3

In what way has the normal physiological functioning of this area of the body been disturbed by the infection (without going into detail on the cause of this disturbance as this will be dealt with in questions 3 and/or 4)

E.coli O157:H7



http://articles.extension.org/sites/default/files/w/8/88/Ecoli.jpg

- E.coli infection is associated with:
  - *bloody diarrhea*
  - *Hemorrhagic colitis*
- E. Coli O157:H7 is highly virulent with a low infectious dose

E.coli – Stomach acidity

- E.coli survives stomach acid (pH<3) via 3 acid resistance systems that require:

1. Alternative sigma factor RpoS and glucose repression
2. Arginine addition during exposure to acidic environments

This system includes arginine decarboxylase (adiA) and the regulator of arginine decarboxylase (cysB)

3. Glutamate for protection in low pH environments

The last system is composed of two glutamate decarboxylase isoenzymes (gadA and gadB), and a putative glutamate, γ-amino butyric acid antiporter (gadC)

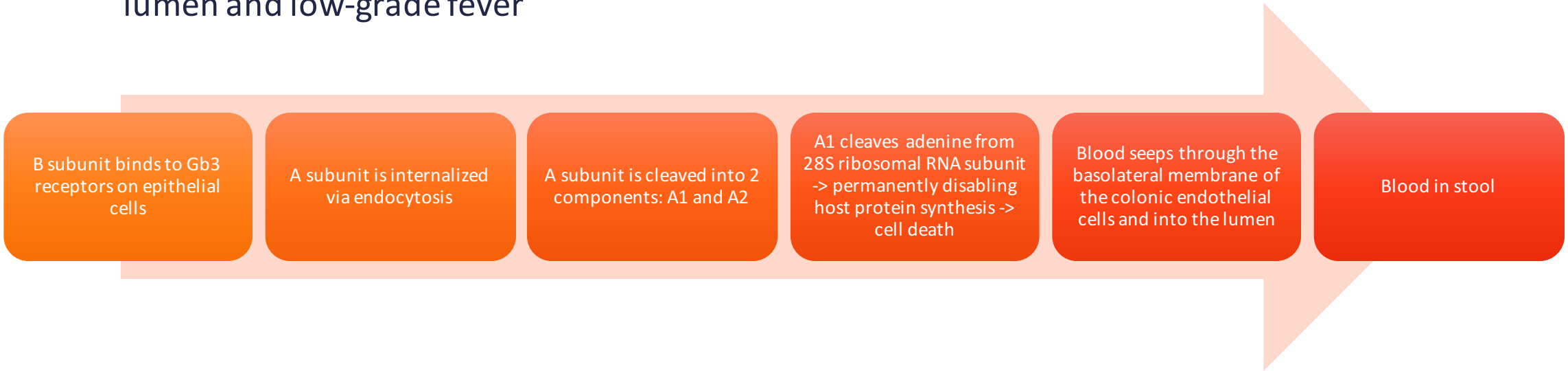
- Other than the acid resistance systems, E.coli also uses RNA polymerase-associated SspA, chaperone HdeA and DNA-binding protein Dps to protect against acidity

E.coli – Small Intestine & Large Intestine

- Adhere to the wall and release toxins to affect enterocytes
- However, rapid propulsion makes it difficult for them to adhere, resulting in entry into the colon
- Colon, with slower movement, allow E.coli colonization

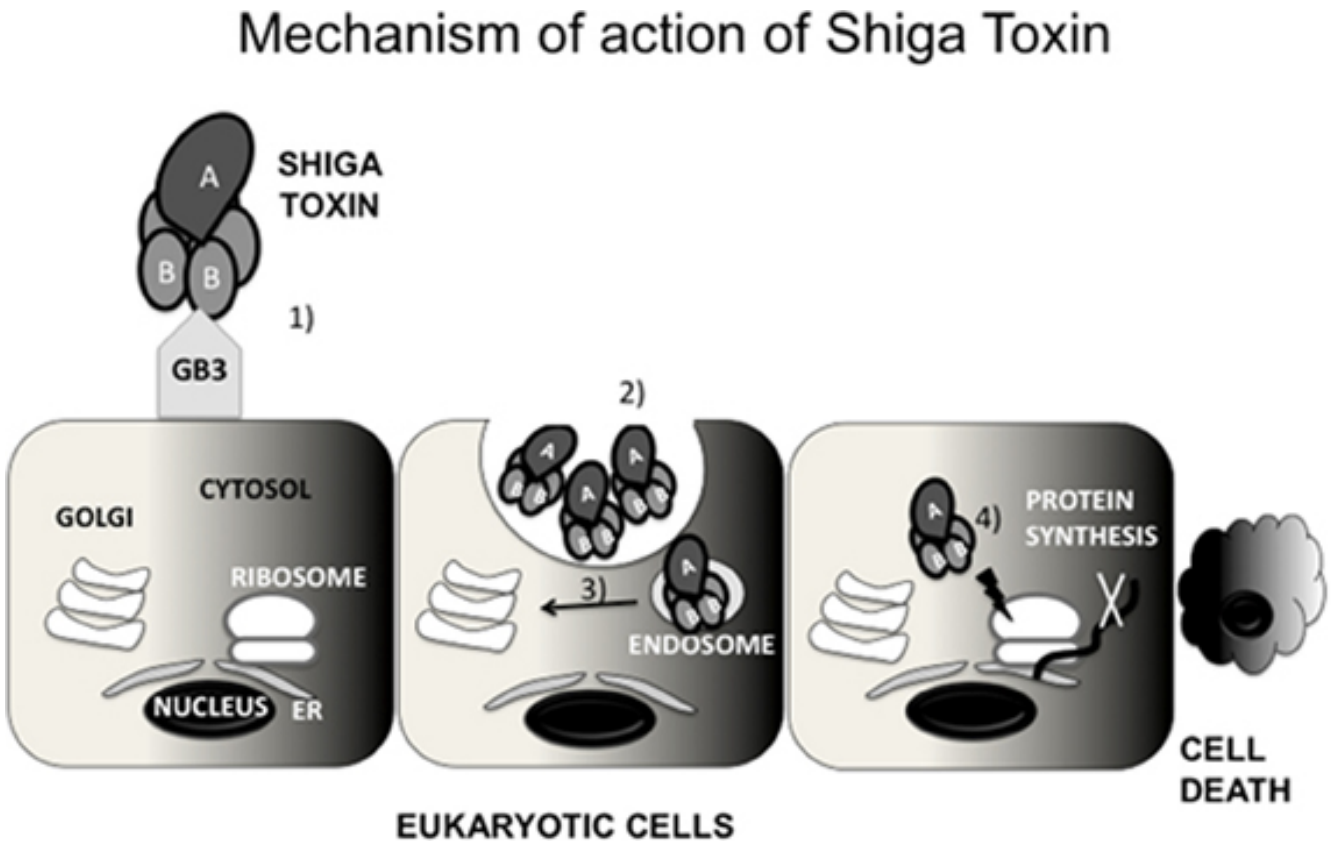
E.coli – Shiga toxins

- Shiga toxin 1(Stx1) and Shiga toxin 2 (Stx2) released after the colonization
- Stx1 and Stx2 have same functions but different antigens
- Stx is comprised of two subunits A and B
  - *A subunit: responsible for the action*
  - *B subunit: responsible for the adherence*
- Extreme inflammatory response initiated by Stx also lead to blood leakage into colon lumen and low-grade fever



E.coli – Stx and other causes

- Endothelial cell destruction decrease water reabsorption ability by colon -> diarrhea
- Stx can increase intracellular cGMP levels that decrease intestinal fluid uptake and a net secretion of fluid
- Abdominal cramping may result from all these activities of E.coli and diarrhea



http://www.frontiersin.org/files/Articles/22287/fcimb-02-00081-HTML/image_m/fcimb-02-00081-g001.jpg

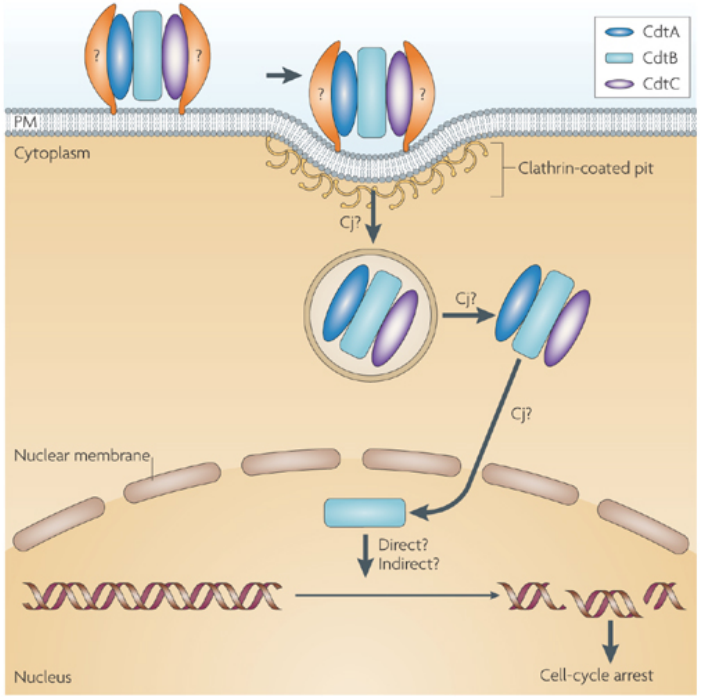
Campylobacter jejuni

http://www.bacteriainphotos.com/photo%20gallery/campylobacter%20jejuni%202.jpg

- Food-borne enteric pathogen
- Cause gastroenteritis leading to diarrhea, abdominal pain, fever, nausea, vomiting
- Primarily colonize the small and large intestines
- Ulceration and colorectal inflammation of large intestine is common

C.Jejuni adhesion and invasion

- Capsular polysaccharides (CPS) has structural variability, similarity to host antigens, and resistance to phagocytosis and complement-mediated killing
- Flagellum enables the bacteria to overcome peristalsis for entering the mucus layer
- Flagellum also undergoes N and O-linked post translational glycosylation pathways to alter flagellum gene expression to adapt to the host's immune response
- Enterotoxin production
  - Cytolethal distending toxin (CDT) cause eukaryotic cells cycle arrest at G2/M phase, inhibiting host cell mitosis and lead to cell death
  - CDT also induce pro-inflammatory host response
  - host release of IL-8 and other cytokines contributing to inflammation and immune response can cause fever, abdominal cramp, and bloody stool



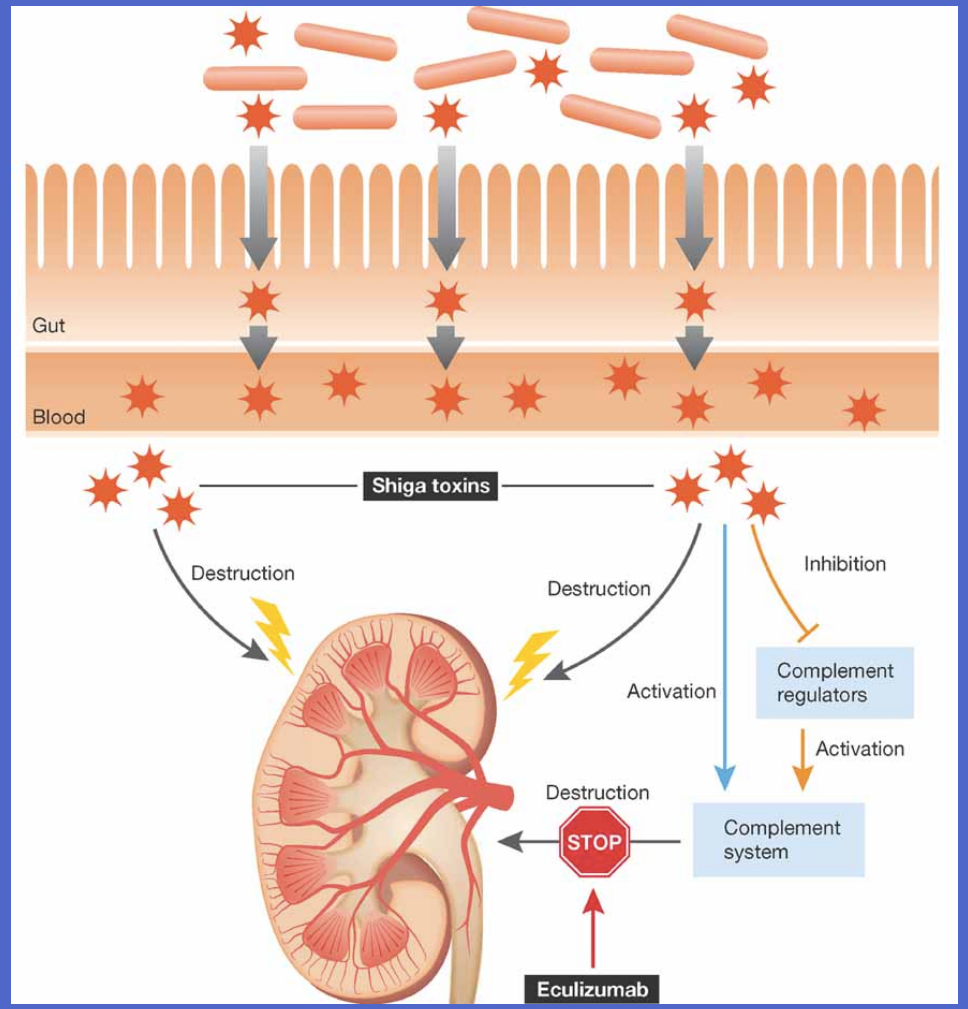
Nature Reviews | Microbiology

http://www.nature.com/nrmicro/journal/v5/n9/images/nrmicro1718-f4.jpg

QUESTION 4

Are there any secondary sites of infection and, if so, what enables the bacteria to (a) travel to; and (b) affect these areas of the body

E.coli



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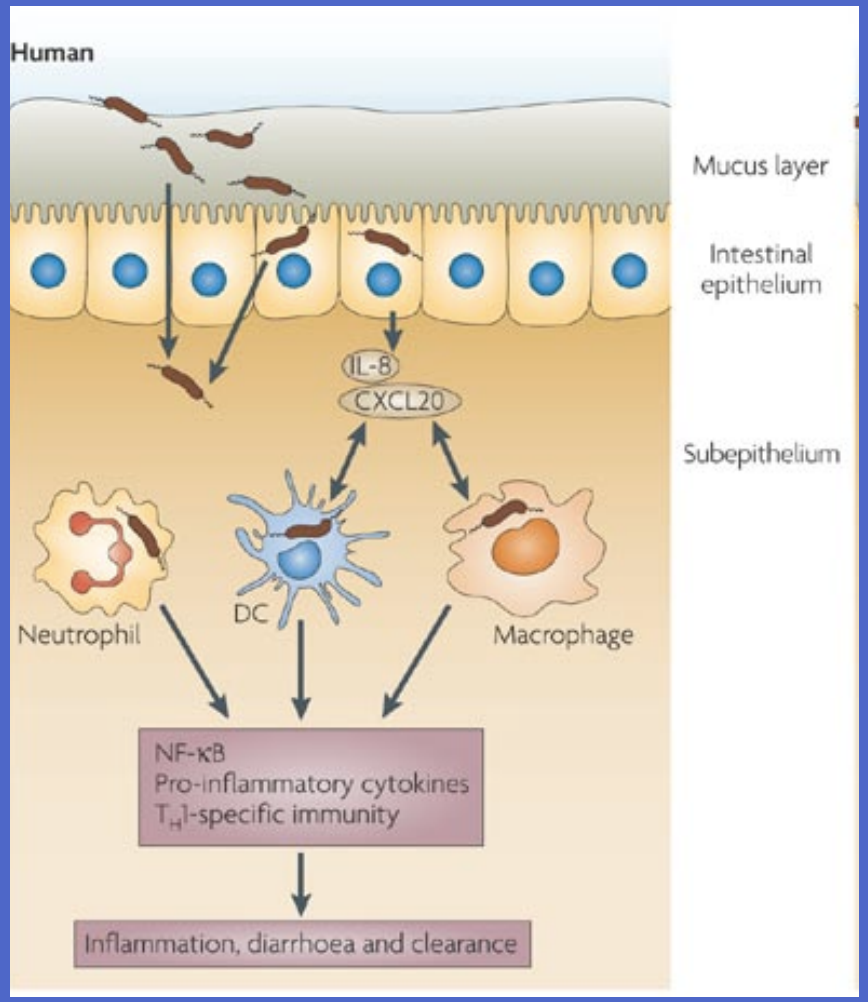
- Kidney:
  - *Upon entrance to bloodstream through infected intestinal enterocytes, Stx and LPS may travel to the kidneys, causing a condition called **hemolytic-uremic syndrome (HUS)***
  - *Stx B subunits bind to Gb3 receptors; there is an unusually high amount of Gb3 receptor in renal epithelial cells*
  - *Renal tissue necrosis leads to **renal failure***
- Endothelial cells that bind Stx can face cell death
- Red Blood Cells (RBCs)
  - *Unclear mechanism*
  - *RBCs passing by infected sites can become distorted and lyse to cause **hemolytic anemia***

E.coli

- Fibrin and platelets
  - *Adhere to the damaged endothelial surface and cause* ***thrombocytopenia***
- **Thrombotic thrombocytopenic purpura (TTP)**
  - *Similar to HUS but added symptoms of fever and neurologic symptoms*
- Endothelial cell secretion of ADAMTS13 protease that **degrades ultralarge von Willebrand factor multimers**
  - *Some multimer residues remain anchored to endothelial cells and attract platelet formation and intravascular platelet-fibrin thombus*

C. jejuni



https://www.researchgate.net/profile/Victor_Dirita2/publication/6137015/figure/fig5/AS:272727462379528@1442034702127/Figure-5-Molecular-and-cellular-features-of-the-innate-immune-response-to-Campylobacter.png

- *C. jejuni local* spread lead to cholecystitis, pancreatitis, and peritonitis
- Live within the mucus layer or invade the epithelium
- Flagella aid its motility and adherence
- Surface proteins with host affinity:
  - CadF bind to fibronectin
  - JlpA bind to Human epithelial type 2 (HEp-2) cells
- Upon binding, its endotoxic lipid A component of LOS trigger inflammatory response (secretion of IL-8 to establish new infection)

C. jejuni

- *C. jejuni* can access bloodstream through infected enterocytes and spread to other regions of the body to cause the following but this is rare (<1%)
  - *Meningitis, endocarditis, septic arthritis, osteomyelitis, and neonatal sepsis*
  - Its vulnerability to complement-mediated lysis prevents its survival in the bloodstream
- Guillain-Barre syndrome (GBS)
  - Post-infectious autoimmune disease that may be caused by *C.jejuni*
  - Muscle weakness; life-threatening if respiratory muscles are compromised
  - Done through its lipooligosaccharide's molecular mimicry of human GM1 ganglioside
  - Host develops anti-GM1 antibodies that leads to destruction of myelin sheeth and axons => impaired nerve function and signal transductons

QUESTION 5

What tests are performed in ‘routine’ blood work?

Routine blood work

- Routine blood work is done to test whether the secondary site infection or complications have occurred
- 3 tests commonly done:

1. Complete blood count
2. Basic metabolic panel
3. C-reactive protein

After reviewing Ronnie's symptoms, there may be a chance of dehydration and post-infection causing HUS. Taking routine blood work would be useful to find out.

Complete Blood Count (CBC)

- A common lab test
  - *To provide information on blood cell production, function, and the immune system*
  - *By looking at RBC and WBC counts, cell dimensions, and hemoglobin weight*
  - *Results can indicate blood and bone marrow disorders, infection and inflammation*
  - *Blood is retrieved from the patient and analyzed*

Test Parameter	Normal Range	Description
Red blood cell count (RBC count)	4.0 to 6.2 million/µL	• # of erythrocytes/ cm3 of blood • Elevated levels: dehydration • Decreased levels: anemia
Hematocrit (Hct)	Women 35-47% Men 39-50%	• % of RBC volume to total blood volume
Hemoglobin (Hgb)	Women 12-16g/dL Men 14-18g/dL	• # of Hgb molecules (g/dL) • Hgb functions to transport CO2 and O2
RBC indices		
Mean corpuscular volume	82 to 93 µm3	• Size of the RBC by size or volume
Mean corpuscular Hgb	26 to 34 pg	• Average weight of Hgb in a RBC

Complete Blood Count (CBC)

Test Parameter	Normal Range	Description
Mean corpuscular Hgb concentration	31% to 38%	• Average concentration of Hgb in the RBC
Red blood cell distribution width (RDW)	11.5-14.5%	• Measures variation in RBC size/volume • Results are usually compared with MCV • Can help to determine if anemia is present if RDW and MCV are high
Platelet count	150,000 to 400,000 µL	• Increases in platelet count (thrombocytosis) • Not an indicator of how platelets function
White blood cell count (WBC)	4,500 to 11,000/µL	• # of WBC's (leukocytes) (in a total # and %) • Trauma, burns, infections trigger inflammation, increasing the amount of leukocytes circulating in the blood • Elevated level (>11,000µL) is referred to as leukocytosis • Can indicate issues such as infection, burns, radiation exposure, lymphoma, anxiety • Decreased counts (<4,500µL) is referred to as leukopenia • Can indicate disorders affecting production of WBCs or WBC destruction stemming from viral infections

Basic Metabolic Panel (BMP/CHEM-7)

- BMP evaluates through some key compounds and electrolytes in the body
- Results provided indicative of kidney function, liver function, and acid/base balance

Test Parameter	Normal Range	Description
Blood glucose	70-100mg/dL (3.9-5.5 mmol/L)	• Measures amount of glucose in the blood • Elevated results: pancreatitis, hyperthyroidism, glucagonoma • Decreased levels: hypothyroidism, diabetes medication overload
Blood urea nitrogen	7-20mg/dL	• Measures amount of blood nitrogen in the blood • Provides an indicator of kidney and liver function • When protein is broken down, the liver produces urea and the kidney filters it out into urine • High values may indicate kidney failure, GI bleeding, excessive protein levels in the GI tract • Lower values may indicate liver failure
Creatinine	0.8-1.4mg/dL	• Measures levels of creatinine, which is a produce of muscle metabolism • Used to evaluate kidney function as the kidney filters out creatinine from the body • High values can be indicative of kidney failure • Low values can be indicative of muscular dystrophy

Basic Metabolic Panel (BMP/CHEM-7)

Test Parameter	Normal Range	Description
Electrolytes		
Sodium	136-144 mEq/L	• High levels (hypernatremia) can be indicative of diarrhea as there is less fluid reabsorption in the body • Low levels (hyponatremia) can also be due to diarrhea or overhydration
Potassium	3.7-5.2mEq/L	• Kidney failure can prevent clearing of K+, resulting in higher levels • Low values can indicate chronic diarrhea and vomiting
Chloride	101-111mmol/L	• Increased levels (hyperchloremia) can be signs of kidney failure or dehydration • Hypochloremia can be sign of congestive heart failure and prolonged vomiting
Carbon dioxide	20-29 mmol/L	• Most of the CO2 in the body is in the form of HCO3-, so this test is a measure of blood bicarbonate level • Increased levels can indicate impaired lung function or breathing disorders • Decreased levels can indicate kidney disease or chronic diarrhea

C-reactive protein

- Indicative of inflammation, especially in the heart arteries that could lead to cardiac arrest

Test Parameter	Normal Range	Description
C-reactive protein	Lower: <1.0mg/L Average: 1.0-3.0mg/L High: >3.0mg/L	• IL-6, IL-1β, and tumor necrosis factor-α (TNF-α) stimulate production of CRP from the liver during inflammation • Can be used to detect inflammation during an infection •Higher levels can indicate an infection or a heart attack