Hilury Ha
PATH 417A
Case 4 Q1

Case 4 – One too Many Hamburgers

Introduction

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

I. Signs and Symptoms

To better understand Ronnie's condition, it is important to distinguish between signs, and symptoms that he is experiencing. Medical signs are objective characteristics that are detected by healthcare professionals such as a physician, that may or may not be evident to the patient themselves (Niamh & Lowe, 2016). On the other hand, symptoms are subjective characteristics experienced by the patient (Niamh & Lowe, 2016).

Based on Ronnie's case, his symptoms appear to be his experienced abdominal cramps, bloody diarrhea, and presence of fever (Table 1). Conversely, signs that would be observed by his doctor include the lack of rebound tenderness, presence of mild periumbilical tenderness, and low grade fever (Table 1). When lab testing results become available, the stool sample and blood work results will also be classified as a sign of illness (Table 1). Ronnie's fever is characterized as both a sign and a symptom, first noticed by the patient, then by the physician who may record the temperature and classify it as "low grade" (Table 1).

Sign	Symptom
• No rebound tenderness • Mild periumbilical tenderness • Stool sample results • Blood work results • Low grade fever (based on temperature recorded)	• Abdominal cramps • Bloody diarrhea • Fever

Table 1. Signs and symptoms pertaining to Ronnie's case.

Many of these signs and symptoms are associated with food-borne illnesses. In this case it appears that the causative factor would be Ronnie's consumption of under-cooked hamburgers. A common disease associated with the ingestion of under-cooked meat is hemorrhagic colitis and hamburger disease, otherwise known as haemolytic uremic syndrome (HUS). Bacteria such as *Escherichida coli* (particularly *E. coli* O157:H7), various strains of *Salmonella* such as *S. enterica* and *S. typhimirium*, and *Campylobacter jejuni* are common pathogens associated with the consumption of raw meat since they all have bovine reservoirs (Bush & Perez, 2014).

Salmonella infection is least likely, although still possible, in this case because it is commonly found in raw poultry and result in vomiting and watery diarrhea, which are symptoms not exhibited by Ronnie (Vyas, 2014). *E. Coli* and *C. jejuni* are found in raw beef, often cause bloody diarrhea, and are associated with HUS and hemorrhagic colitis (Spika et al., 1986). Symptoms of hemorrhagic colitis include abdominal cramps, watery diarrhea that becomes bloody within 24 hours, and mild fever (Bush & Perez, 2014), similar to what is experienced by Ronnie. In rare cases, hemorrhagic colitis can develop into HUS, typically during the second week of illness (Bush & Perez, 2014). *E. coli* infection can occur at any age, although severe infection is more common in children such as Ronnie, and the elderly (Bush & Perez, 2014).

II. Effect on the Body

Based on Ronnie's signs and symptoms and the high likelihood that *E. Coli* and *C. jejuni* are responsible for his illness, it appears that the primary body system affected is the gastrointestinal system. The predominant area affected appears to be the small and large intestine due to Ronnie's exhibited abdominal cramps and bloody diarrhea.

The Gastrointestinal System

The gastrointestinal (GI) system is comprised of many organs and glands that physically and chemically process consumed food, and excretes waste products (Trowers, 2014). Furthermore, it is responsible for delivering nutrients, electrolytes and water throughout the body, collaborating with the liver and the circulatory system to ensure that nutritional requirements of cells distant from the GI tract are met (Barrett, 2014). Oftentimes, nutrients of the human diet are macromolecules that must be broken down by and mixed with various secreted molecules such as enzymes in order to be able to permeate across cell membranes (Barrett, 2014). The intestines are primarily responsible for absorption and reduction of the size of ingested nutrients through a process called digestion, although some digestion of starches is initiated in the oral cavity through the actions of enzymes in salivary secretions (Trowers, 2014). The nutrients are then absorbed across the intestinal lining into the circulatory system, or the lymphatic system for transfer to other locations in the body; this process is called absorption (Barrett, 2014). Non-absorbable compounds are then excreted out of the body through a process called excretion (Barrett, 2014).

Ingestion, secretion, mixing, propulsion, digestion, absorption and excretion processes are achieved through the collaborative efforts of numerous organs. The GI system consists of the alimentary canal, and associated glands located from the mouth to the anus, as well as the hormones and enzymes involved in digestion (Figure 1) (Trowers, 2014). More generally it can be divided into the upper and lower gastrointestinal tract. The upper GI tract consists of the oral cavity, pharynx, esophagus, stomach and duodenum, while the lower GI tract is made up of the remaining segments of the small intestine and the large intestine.

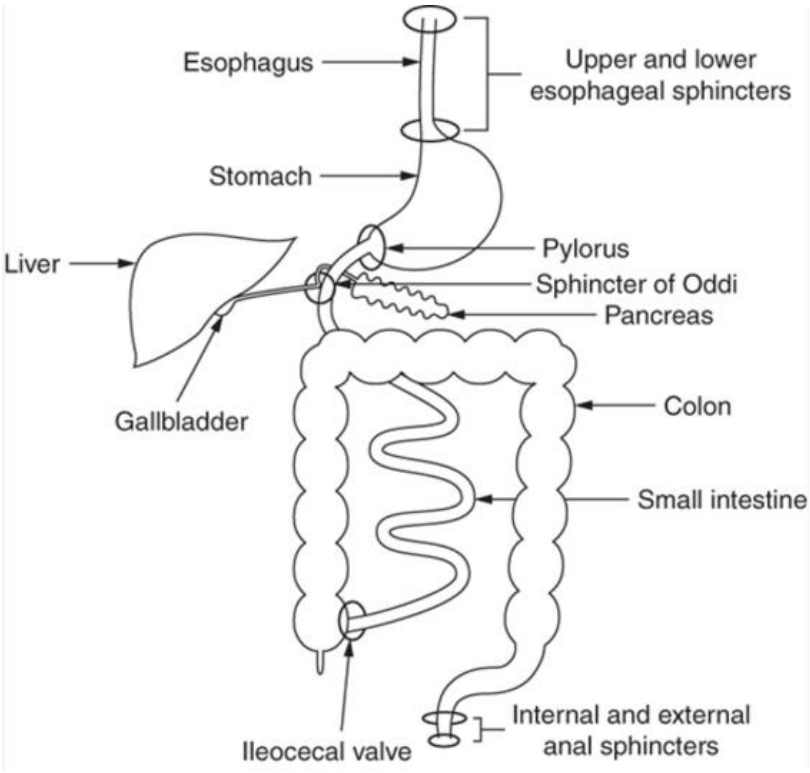

Figure 1. Overall anatomy of the gastrointestinal tract. Image reproduced from Barrett (2014).

A. The Upper Gastrointestinal Tract

i) Oral Cavity

The upper gastrointestinal tract begins with the mouth, otherwise known as the oral cavity. The oral cavity serves as the entrance to the alimentary tract and consists of the lips, gingivobuccal mucosa, superior and inferior alveolar ridges and teeth, mandible, oral tongue, and hard palate (Figure 2) (Laine & Smoker, 1995). When food enters the oral cavity, it is mechanically broken down by the teeth into smaller particles by chewing. Three pairs of salivary glands (the parotid, submandibular, and sublingual glands) drain into the oral cavity, providing various enzymes, water, ions, and proteins that are important for dental and oral mucosa health as well as aid in taste, bolus formation in preparation for swallowing, and the initial digestion of starch and lipids through the actions of amylase and lipase respectively (Pederson, Bardow, Jensen, and Nauntofte, 2002).

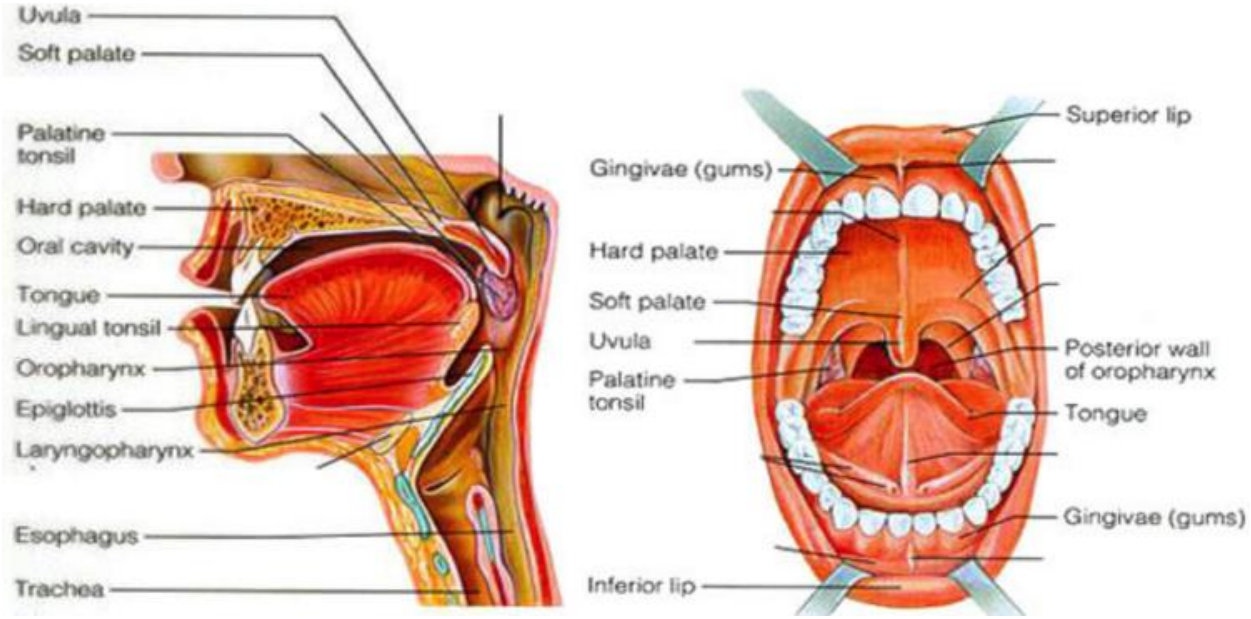

Figure 2. Anatomy of the oral cavity. Image retrieved from http://www.tarleton.edu/anatomy/oralcavity.html.

ii. Pharynx

The pharynx is made of 3 parts, the nasopharynx (which runs from the base of the skill to the soft palate), the oropharynx (located from the soft palate to the hyoid bone) and the laryngopharynx (from the hyoid bone to cricoid cartilage) (Figure 2) (Donner, Bosnia, & Robertson, 1985). The pharynx plays an important role during swallowing of the bolus and passage of food into the esophagus (Donner, Bosnia, & Robertson, 1985).

iii. Esophagus

The esophagus is a muscular tube (Figure 2) divided into cervical, thoracic, and abdominal parts, and is lined by moist stratified squamous epithelium (Long & Orlando, 1999). After mechanical processing of food and bolus formation in the oral cavity, the esophagus is responsible for transferring the bolus from the mouth into the stomach (Barrett, 2014). The esophagus contains both an upper and lower esophageal sphincter (UES and LES respectively). The upper esophageal sphincter lies between the pharynx and the cervical esophagus. It is responsible for preventing the entry of food into the airways, and the entry of air into the digestive tract (Sivarao & Goyal, 2000). A primary muscle in the UES is the circopharyngeus muscle, which plays a key role in the transient relaxation of the UES that occurs during the swallowing of bolus to allow it to enter the esophagus (Sivarao & Goyal, 2000). The LES is responsible for keeping the esophagus closed to prevent the reflux of acidic contents from the stomach, and also opening to allow the entry of bolus from the esophagus into the stomach (Daniel, 1992). Failure of the LES to close can lead to gastroesophageal reflux disease and damage to the esophageal epithelium (Barrett, 2014).

iv. Stomach

The stomach is a muscular structure that acts as a reservoir that stores, grinds, and controls the rate of delivery of the partially digested contents into the intestine for further digestion and absorption (Barrett, 2014). The surface of the stomach contains folds called rugae, and microscopically contains structures called pits further increase the surface area and serve as entrances to deep gastric glands (Figure 3) (Barrett, 2014). The pits are deepest in the fundus, and become shallower through the antrum (Barrett, 2014) which coincides with the exocrine function of the fundus (Figure 4). The ability of the stomach to serve as a reservoir is achieved through a process called receptive relaxation. While the stomach is being filled, it is capable of stretching and thus preventing significant increases in pressure that could otherwise lead to reflux of gastric contents into the esophagus (Barrett, 2014). The stomach is anatomically divided into the fundus, antrum, and body (corpus), while functionally it is divided into the exocrine or glandular portion, and the endocrine (hormone-secreting) regions (Leung, 2014). Another region, the cardia, overlaps with the LES and secretes mucus and bicarbonate to protect the gastric mucosa from the acidity of gastric contents (Barrett, 2014). A primary function of the stomach is to secrete hydrochloric acid (through the action of parietal cells) which facilitates protein digestion by converting pepsinogen into pepsin (Reinus, 2014). Gastric acid also plays a role in the absorption of iron, calcium, vitamin B12, some medications, and helps to prevent bacterial overgrowth and infections (Reinus, 2014).

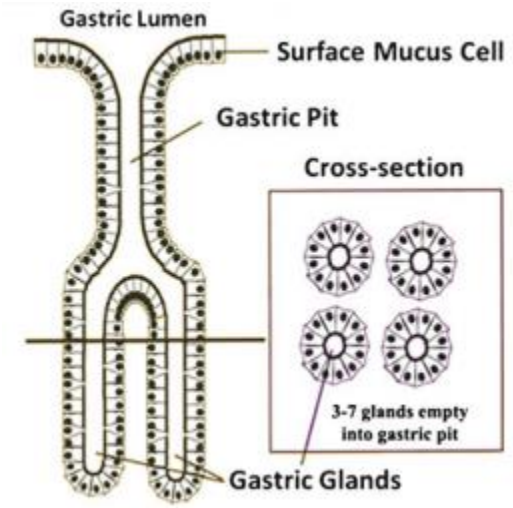

Figure 3. Side and cross-sectional illustrations of the gastric gland. Image reproduced from Leung (2014).

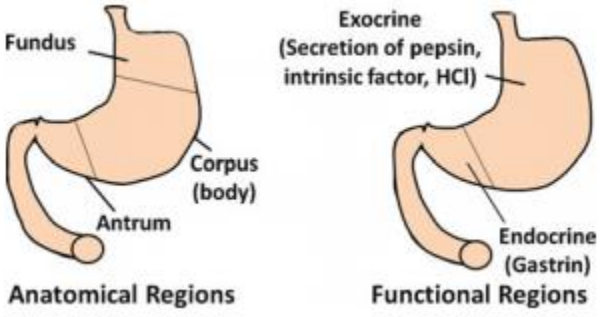

Figure 4. The anatomical and functional regions of the stomach. Image reproduced from Leung (2014).

iv. Duodenum

The beginning of the small intestine, approximately 12 inches in length, is called the duodenum. The duodenum is divided into four parts, namely the superior, descending, horizontal, and ascending parts, and is the primary regulator of digestion and absorption (Barrett, 2014). The superior portion is connected to the liver by the hepatoduodenal ligament (Barrett, 2014). Digestive enzymes and other products that aid in digestion are secreted into the duodenal lumen by the exocrine pancreas and the biliary system (such as bile from the gall bladder) through the sphincter of Oddi (Figure 5) (Ellis, 2013). Endocrine cells and chemosensitive and mechanosensitive nerve endings monitor luminal contents and emit signals that serve to coordinate other areas of the GI tract (Barrett, 2014).

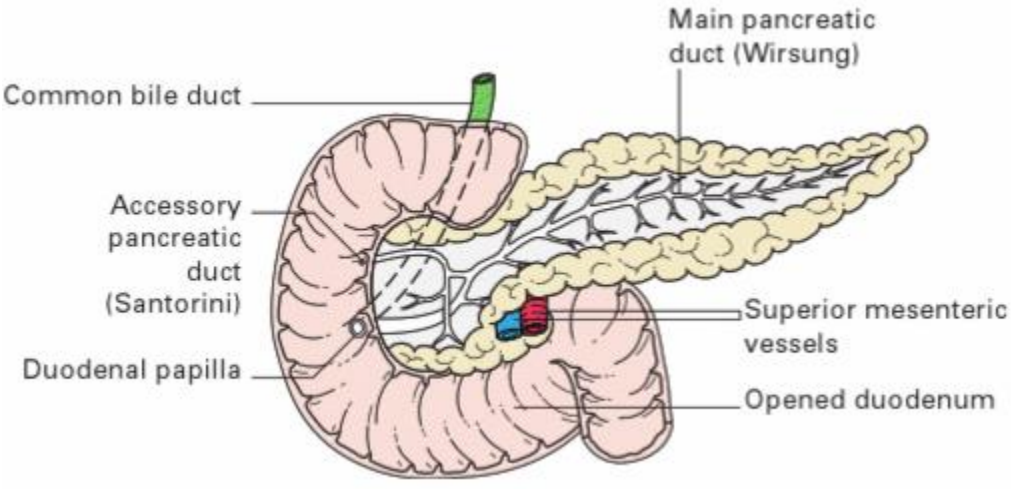

Figure 5. Illustration of the duodenum and its proximity to the pancreas. Image reproduced from Ellis (2013).

B. The Lower Gastrointestinal Tract

i. The Small Intestine

Aside from the duodenum, the remaining components of the small intestine are the jejenum and ileum. The small intestine overall is approximately 6 to 7 metres long and is adapted to maximize its absorptive surface area through circular folds, intestinal villi, and microvilli (Figure 6) (Barrett, 2014). The villi contain absorptive cells and goblet cells which secrete mucus (Figure 6) (Kwok, 2015). Membrane bound enzymes of the brush border secrete enzymes such as maltase, sucrase, lactase, aminopeptidase, and enterokinase (Kwok, 2015). The jejunum is primarily responsible for the absorption of digested products, electrolytes, water, and vitamins, while the ileum is primarily responsible for the absorption of bile salts and vitamin B12 (Kwok, 2015). The ileum has fewer folds and sparser villi, thus rendering it less involved in the nutrient absorption process (Barrett, 2014).

The small intestine engages in segmentation activity which serves to mix dietary nutrients with pancreatic, biliary, and small intestine secretions during a meal to further the digestion of fats, carbohydrates, and proteins (Kwok, 2015). After segmentation, the migrating motility complex propagates contents further down the small intestine to clear undigested food, desquamated epithelial cells, bacteria, and digestive juices out of the small intestine (Kwok, 2015). When contents reach the end of the ileum, the ileocecal valve and sphincter prevent the reflux of bacteria from the large intestine (Kwok, 2015).

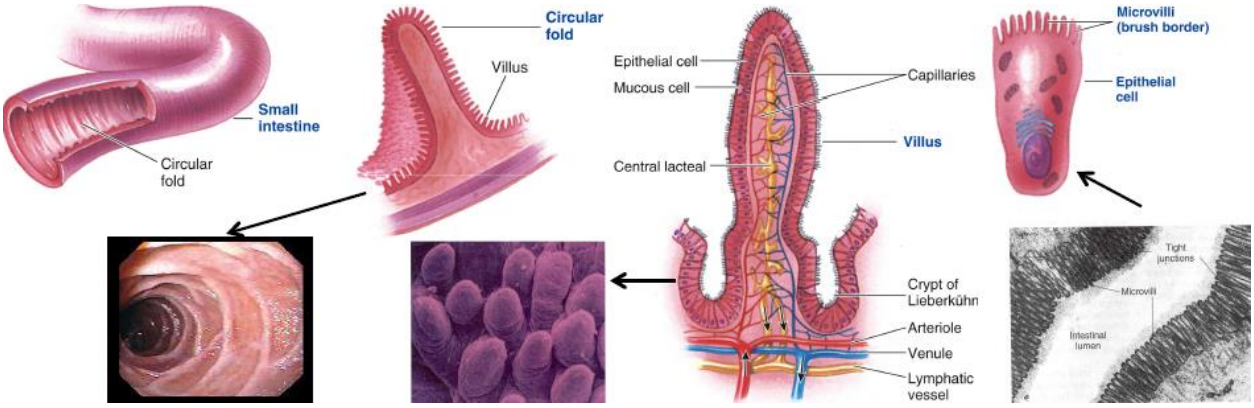

Figure 6. Anatomy of the small intestine. Image reproduced from Kwok (2015).

ii. The Large Intestine (Colon)

The large intestine is about 2.4 metres long and is comprised of the cecum, appendix, colon, and rectum (Figure 7) (Kwok, 2015). The colon is further divided into the ascending, transverse, descending, and sigmoid colon (Figure 7) (Kwok, 2015). Structurally, it is larger in diameter than the small intestine and possesses a thicker wall with folds called haustrae (Figure 7) (Barrett, 2014). The large intestine primarily serves as a reservoir for the storage of wastes and indigested materials in preparation for excretion (Barrett, 2014) and does not partake in the digestion process (Kwok, 2015). Epithelial cells in this region do not possess absorptive transporters for nutrients (monosaccharides, peptides, amino acids, and vitamins) (Barrett, 2014).

The absorption of water and electrolytes from chyme and the production of feces occurs in the proximal colon (Trowers, 2014). In order to propel bowel contents toward the sigmoid colon, signals induced by distension of the stomach or duodenum after a meal result in mass movements (Trowers, 2014). Mass movement of fecal materials into the rectum can cause rectal distension, which induces the defection reflex (Kwok, 2015). The anus is controlled by both an internal (involuntary) and external (voluntary) sphincter (Figure 7) which play key roles in one's voluntary control over defecation (Kwok, 2015).

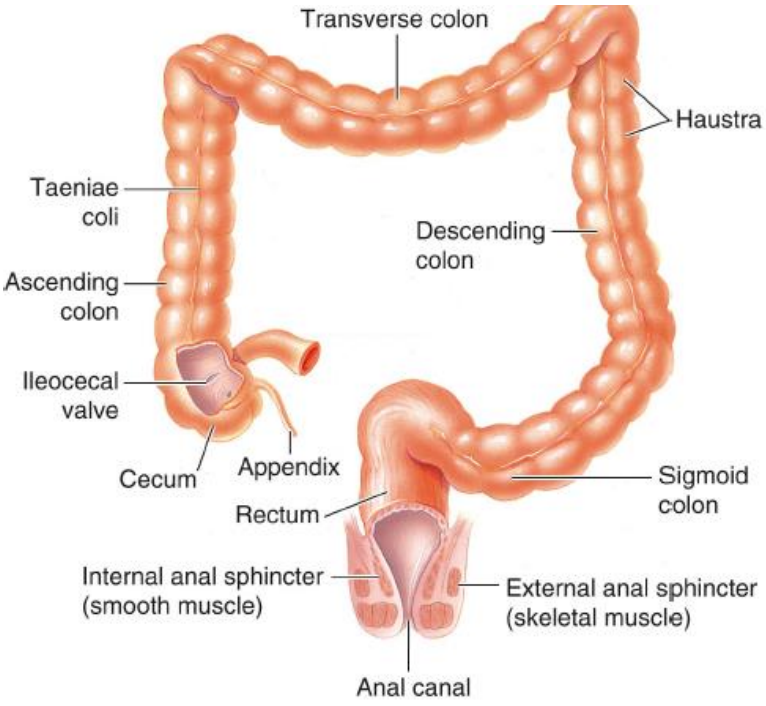

Figure 7. Anatomy of the large intestine.

III. Disruption of Normal Physiological Functioning

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).

Upon ingestion, sufficient numbers of *E. coli* and *C. jejuni* must pass through the stomach in order to infect the small or large intestine. In order successfully infect the GI tract, both bacteria utilize various bacterial factors to invade tissues, avoid and resist the host immune response, disturb normal gut flora, damage host cells, and multiply.

A. Disruption caused by *E. coli*

Various strains of *E. coli* commonly reside in the large intestine of warm blooded animals and humans. Among the five classes of *E. coli* associated with diarrheal diseases, of interested to this case are enteropathogenic E. Coli (EPEC) which induce watery, and sometimes bloody diarrhea

(Todar, n.d.). A plasmid encoded protein called EPEC adherence factor in combination with non fimbrial adhesion intimin (an outer membrane protein) plays a key role in the pathogen's adherence to intestinal cells (Todar, n.d.) (Figure 9). The diarrhea and abdominal cramps experienced by Ronnie is attributed to the pathogens invasion of host intestinal cells and interference of normal cellular signal transduction (Figure 9) (Todar, n.d.). Various plasmid encoded factors such as pili allow *E. coli* to colonize intestinal mucosa and induce the host inflammatory response as well as the influx of lymphocytes which contribute to the resultant bloody diarrhea (Evans, 1996). Binding of the bacteria to intestinal epithelium followed by the loss of microvilli due to rearrangement of host cytoskeleton leads to malabsorption and osmotic diarrhea, often accompanied by fever (Evans, 1996).

Another strain that is relevant to Ronnie's case is enterohemorragic *E. coli* (EHEC) (Figure 8). EHEC (particularly *E. coli* O157:H7) primarily cause hemorrhagic colitis and bloody diarrhea which may lead to haemolytic uremic syndrome (Todar, n.d.). The production of verotoxin or Shiga toxins (Stx) are primary factors in causing gastrointestinal illness by initiating an extreme inflammatory response leading to subsequent tissue damage (Todar, n.d.). In addition, the toxins directly damage mucosal cells and vascular endothelial cells of the gut wall (Bush & Perez, 2014). Some toxins are cytotonic, leading to the secretion of water and electrolytes, and thus contributing to the diarrhea observed in infected individuals (Evans, 1996). Shiga toxins can also cause diarrhea by increasing intracellular cGMP levels, which lead to a decrease in intestinal fluid uptake and thus net fluid secretion (Evans, 1996). A consequence of *E. coli* infection is the development of HUS (Bush & Perez. 2014).

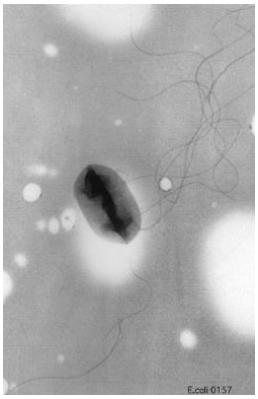

Figure 8. Electron microscopy image of *E. Coli* O157:H7. Image reproduced from Todar (n.d.).

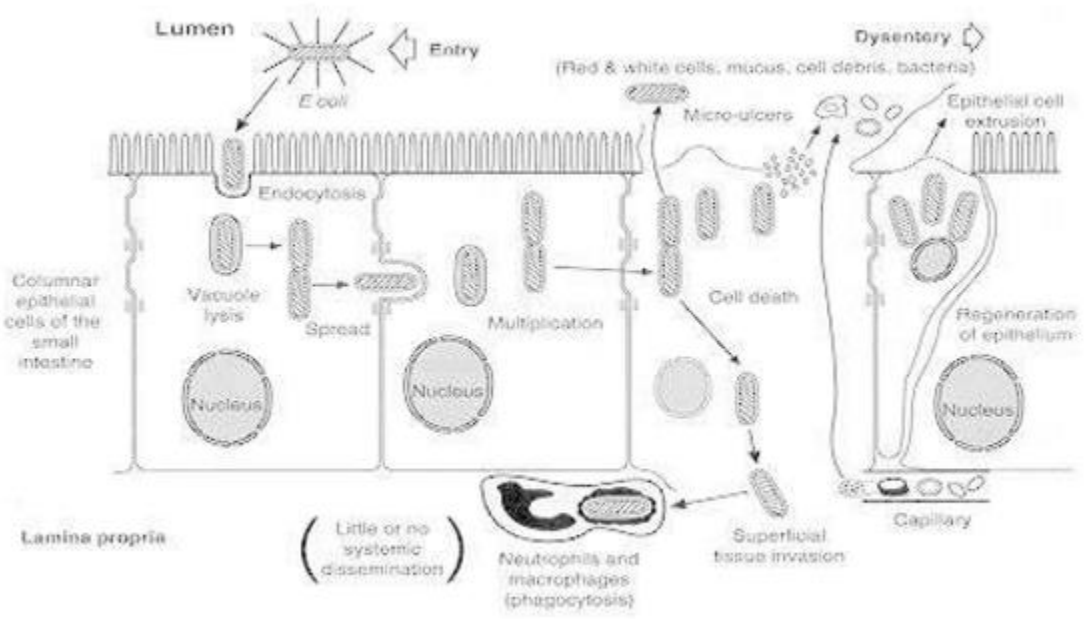

Figure 9. Pathogenesis of *E. coli*. Image reproduced from Evans (1996).

B. Disruption caused by *C. jejuni*

C. jejuni in a food-borne enteric pathogen that causes gastroenteritis, leading to diarrhea, abdominal pain, fever, nausea, and vomiting after an incubation period of about 24-72 hours; however, the severity of symptoms is dependent on the ingested dose (Perez & Blaser, 1996). In addition, it is regarded as the most prevalent cause of bacterial-mediated diarrheal disease worldwide, in which children (like Ronnie) are the most susceptible (Zillbauer, Dorrell, Wren & Bajaj-Elliot, 2008). Predominantly *C. jejuni* colonize the small and large intestine causing significant hemorrhagic inflammation and enteritis in humans (Young, David & DiRita, 2007). In the small intestine, *C. jejuni* has been detected in the proximal small intestine and lesions of the jejunum and in mucuosal edemas (Black, Levine, Clements. Hughes & Blaser, 1988). Ulceration and colo-rectal inflammation of the large intestine is also commonly observed (Black, Levine, Clements. Hughes & Blaser, 1988).

Bacterial adhesion and invasion of the intestinal epithelium is vital to ensure pathogenic success of *C. jejuni* (Figure 10) and explains the cause of the symptoms experienced by Ronnie. Many bacterial factors play key roles in the pathogen's success and the initiation of inflammatory processes and diarrheal development. For example, capsular polysaccharides (CPS's) are crucial in allowing *C. jejuni* to survive and persist in the human host due to its structural variability, similarity to host antigens, and its resistance to phagocytosis and complement-mediated killing (Zillbauer, Dorrell, Wren & Bajaj-Elliot, 2008). In addition, recent studies indicate that the capsule is capable of protecting the pathogen from epithelial antimicrobial peptides (Zillbauer, Dorrell, Wren & Bajaj-Elliot, 2008).

C. jejuni's flagellum also plays a key role in its damage to the host. The flagellum enables the bacteria to overcome peristalsis and enter into the mucus layer, thus rendering it vital for colonization in the host (Zillbauer, Dorrell, Wren & Bajaj-Elliot, 2008). In addition, the flagellum is capable of undergoing N and O-linked post translational glycoslation pathways to alter flagellum gene expression, allowing it adapt to the host's immune response (Zillbauer, Dorrell, Wren & Bajaj-Elliot, 2008). Bloody diarrhea indicates the progression of the infection into the tissues of the colon and rectum (Tracz et al., 2005). Invasion of intestinal epithelium through the bacterial factors described is responsible for mucosal damage and inflammatory lesions (Tracz et al., 2005). An additional factor that plays a key role in the development of bloody diarrhea by supporting *C. jejuni* epithelial cell invasion is pVir virulence plasmid (Tracz et al., 2005).

Enterotoxin production has been observed in some isolates of *C. jejuni* (Perez & Blaser, 1996). In particular, cytolethal distending toxin (CDT) has been found to be produced by *C. jejuni*. This toxin causes eukaryotic cells to arrest in the G2/M phase of the cell cycle, therefore inhibiting the cell from undergoing mitosis and ultimately leading to cell death (Zillbauer, Dorrell, Wren & Bajaj-Elliot, 2008). CDT consists of three membrane-associated protein subunits that are required for inducing the pro-inflammatory host response, particularly of the release of interleukin-8 and other cytokines that cause fever, tissue damage and diarrhea in the host (Zillbauer, Dorrell, Wren & Bajaj-Elliot, 2008).

Although the epithelial lining of the small and large intestine serves as a protective physical barrier for the underlying mucosa, *C. jejuni* possess numerous bacterial factors that enable it to successfully enter and adhere. Once *C. jejuni* have been recognized by the host innate immune response, chemokines, cytokines, and antimicrobial peptides are released (Figure 10). Ironically, this inflammatory response leads to tissue damage. For example, IL-8 serves as a potent chemoattractant. Upon release, various immune cells are recruited to the site of infection such as neutrophils which has been found to be a crucial component of diarrhea development as well as the clearance of the pathogen (Zillbauer, Dorrell, Wren & Bajaj-Elliot, 2008), thus serving as a double-edged sword. In addition infiltration of mononuclear cells and eosinophils as part of the host immune response can cause crypt abscess development in epithelial glands and ultimately ulceration of the mucosal epithelium (Acheson & Allos, 2001). The tissue damage and associated inflammatory response may be a key contributor to Ronnie's experienced fever, abdominal cramp, and bloody stool.

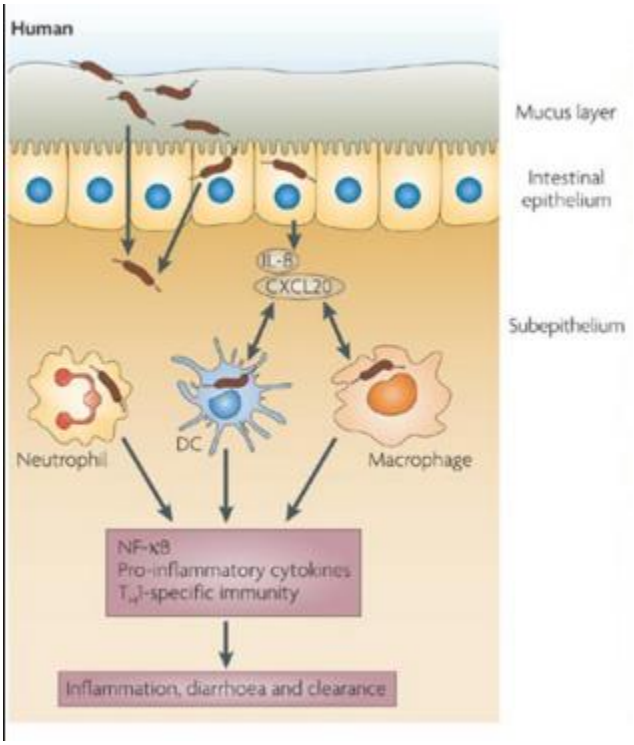

Figure 10. Inflammatory response and cytokine release stimulated by *C. jejuni* infection leading to inflammation, diarrhea, and subsequent clearance. Image retrieved from http://www.nature.com/nrmicro/journal/v5/n9/fig_tab/nrmicro1718_F5.html.

IV. Secondary Sites of Infection

A. Secondary Sites of Infection of *E. Coli*

Extra-intestinal infections of *E. Coli* O157:H7 rarely occur, and deep tissue invasion is not commonly observed (Coia, 1998). However, damage to renal endothelial cells is possible after HUS (Coia, 1998). HUS can be characterized by acute renal failure, microangiopathic haemolytic anemia, and thrombocytopenia (Paton & Paton, 1998). Damaged endothelial cells become swollen, and hypertrophy of mesangial cells and detachment from the underlying basement membrane is also observed (Coia, 1998). Furthermore, renal injury due to ischaemic glomerular and tubular necrosis is possible due to upregulated coagulation pathways and the formation of platelet thrombi and fibrin generation which narrow the glomerular capillaries and afferent arterioles (Coia, 1998). A variant form of HUS called thrombotic thrombocytopenic purpura can also impact some individuals (Figure 11) (Paton & Paton, 1998). In addition, after HUS, some individuals experience neurological symptoms such as lethargy, severe headache, convulsions, and encephalopathy (Paton & Paton, 1998). Even after the infection is cleared, studies report that permanent disabilities remain such as chronic renal insufficiency, hypertension, and neurological deficits (Paton & Paton, 1998).

Eukaryotic cell surfaces possess globotriaosylceramide receptors for Stx (Paton & Paton, 1998). After binding to the target cell membrane, toxin molecules are internalized by receptor-mediated

endocytosis (Paton & Paton, 1998). Clathrin-coated pit formation is also involved in the internalization process thus forming a sealed coated vesicle around the toxin as it is intracellularly transported and thus protected from host immune response (Paton & Paton, 1998).

Pathogenic factors of *E. Coli* that allow it to survive in different environments beyond the small and large intestine is StcE (secreted protease of C1-esterase inhibitor) (Yu, Worrall & Strynadka, 2012). StcE possesses zinc metalloprotease mediated mucinase activity toward mucin-type glycoproteins which allow it to degrade and reduce the viscosity of host mucus layers (Yu, Worrall & Strynadka, 2012). By targeting mucin 7 and glycoprotein 340 in the mucus layer, StcE is also simultaneously reducing the host immune response because these proteins serve as receptors for microbial adhesins and are part of the innate immune response system (Yu, Worrall & Strynadka, 2012). By destroying these molecules, *E. coli* is able to overcome the mucosal barrier and subsequently contact the epithelium and establish infection (Yu, Worrall & Strynadka, 2012).

StcE also contributes to *E. coli*'s immune evasion abilities by targeting and cleaving leukocyte surface glycoproteins CD45 and CD43 (Yu, Worrall & Strynadka, 2012). Cleavage of these glycoproteins prevents immune cells from initiating the host immune response and prevents them from migrating to sites of infection (Yu, Worrall & Strynadka, 2012). Furthermore, StcE recruits human C1-esterase inhibitor (C1-INH), a regulator of serine proteases in the complement pathway to the cell surface (Yu, Worrall & Strynadka, 2012). By recruiting C1-INH, the proteolytic activation of the complement cascade is inhibited, thus rendering *E. Coli* more resistant to complement-mediated cell lysis (Yu, Worrall & Strynadka, 2012). This improves the pathogen's chances of spread and survival in new sites.

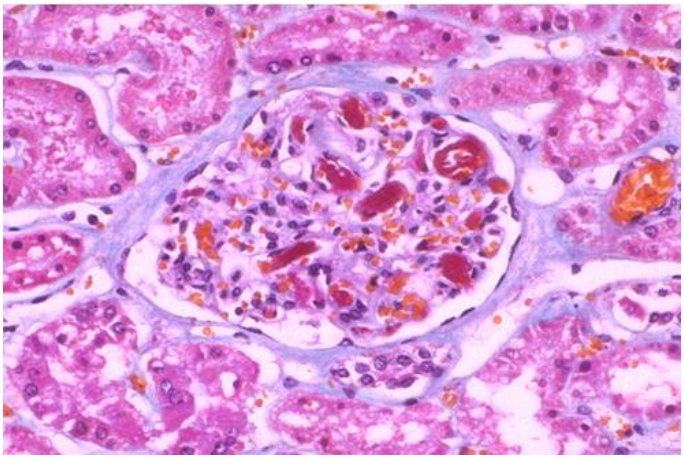

Figure 11. Fibrin thrombi formation in glomerular capillaries due to thrombotic thrombocytopenic purpura. Image retrieved from http://library.med.utah.edu/WebPath/RENAHTML/RENAL030.html

B. Secondary Sites of Infection of *C. jejuni*

Locally, *C. jejuni* can directly spread from the GI tract and cause cholecystitis, pancreatitis, peritonitis, and massive gastrointestinal hemmorhage (Figure 12) (Acheson & Allos, 2001). *C. jejuni* is commonly associated with intestinal manifestations; although it is capable of spreading to other sites leading to severe and potentially life-threatening infections such as Guillain-Barre syndrome (GBS) (Figure 13). GBS is a demyelinating disease that causes ascending paralysis that can affect peripheral and cranial nerves, particularly cranial nerve VII (the facial nerve) (Zillbauer, Dorrell, Wren & Bajaj-Elliot, 2008). *C. jejuni* lipooligosaccharide (LOS) molecularly mimics that of peripheral nerve gangliosides, leading to the production of autoreactive antibodies (Zillbauer, Dorrell, Wren & Bajaj-Elliot, 2008). These antibodies generate an inflammatory response, leading to tissue damage.

Other infections caused by *C. jejuni* include Reiter's reactive arthritis. Individuals with HLA-B27 histocompatibility antigen are more prone to developing reactive arthritis after infection with *C. jejuni* (Acheson & Allos, 2001). Additional post-infectious complications of *C. jejuni* include uveitis, haemolytic anemia, haemolytic uremic syndrome, carditis, and encephalopathy (Acheson & Allos, 2001). Bacteremia is rare, occurring in less than 1% of patients (Acheson & Allos, 2001). Overall, serious systemic illnesses is also rare, but can lead to sepsis and death (Acheson & Allos, 2001).

As discussed previously, *C. jejuni* motility and infection capabilities are dependent on its flagellum and other bacterial factors such as CPS. CPS allows *C. jejuni* to evade the host immune response and persist due to its structural variability and similarity to host antigens (Zillbauer, Dorrell, Wren & Bajaj-Elliot, 2008). In addition the capsule is resistant to phagocytosis and complement-mediated killing (Zillbauer, Dorrell, Wren & Bajaj-Elliot, 2008) which allows the pathogen to spread from one site to the other without being detected or eliminated. CPS structural variability renders it well suited for survival in new host environments. *C. jejuni* flagellum is important for motility, and also contributes to that pathogen's ability to evade and adapt to the host response due to post-translational pathways. The flagellum is capable of undergoing both O-linked and N-linked post-translational glycosylation pathways, which allow it to rapidly alter flagellum gene expression in response to the immune response of the host (Zillbauer, Dorrell, Wren & Bajaj-Elliot, 2008). Particularly, N-linked glycosylation has been shown to be important for bacterial virulence, while O-linked glycosylation has been found to be important for flagellin assembly and motility, and therefore important for successful adhesion, invasion, and virulence (Zillbauer, Dorrell, Wren & Bajaj-Elliot, 2008).

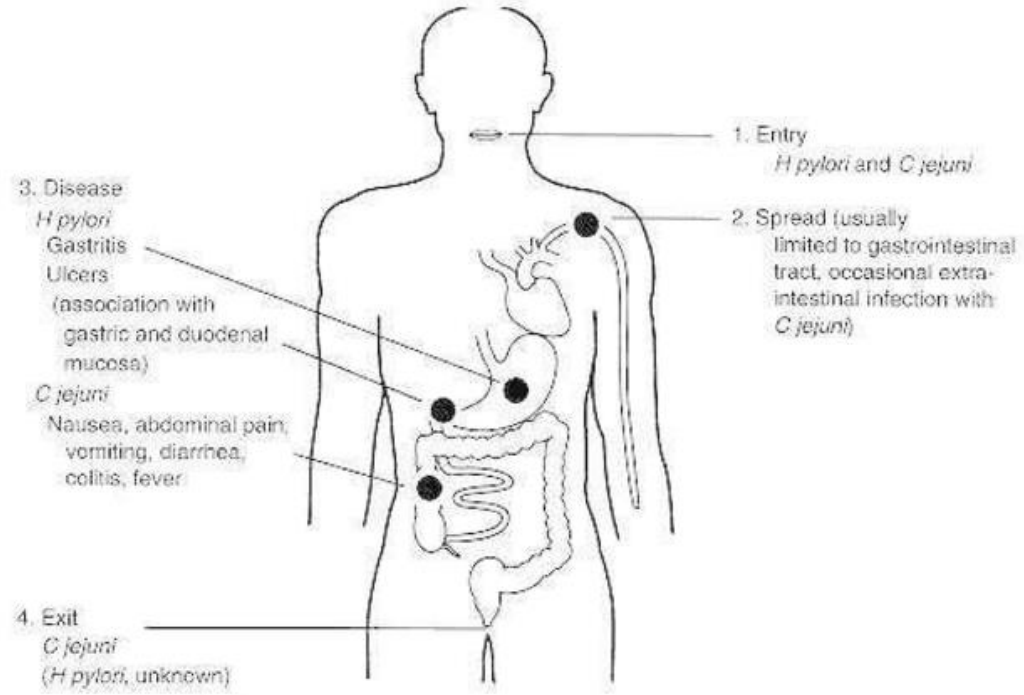

Figure 12. Pathogenesis of *C. jejuni.* Image reproduced from Perez & Blaser (1996).

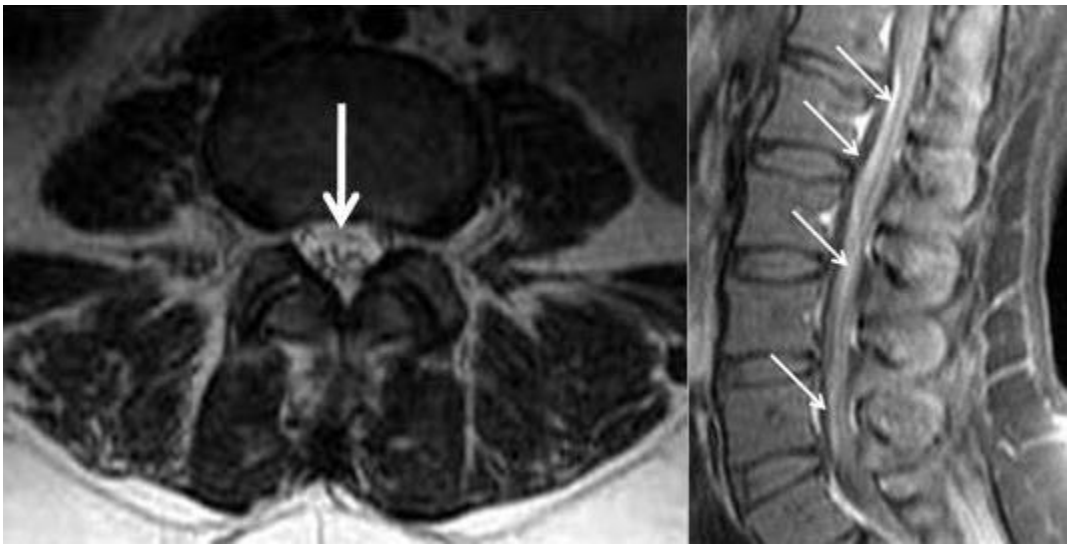

Figure 13. MRI imaging of the spinal cord of a patient with GBS. Disc herniation at T12-L1 is shown. Image retrieved from http://www.radiologycases.com/casereports/jrcr-tp.cgi?case=153#.Vu3cDuIrLIU

V. Routine Blood Work Tests

Performing blood tests when infection with *E.coli* or *C. jejuni* is suspected is important in the identification of the pathogen as well as to determine the health of other areas in the body, like renal function.

Complete Blood Count

The complete blood count (CBC) test is used to measure the number of red blood cells, white, blood cells, platelets, haemoglobin, hematocrit, red cell distribution width, and mean corpuscular volume (Figure 14) ("Types of Blood Tests", 2012). This test can help identify blood diseases, anemia, the presence of infection, excessive menstrual bleeding, internal bleeding, or problems with blood clotting ("Laboratories and Blood Tests", n.d.). For example, red cell distribution width measures the variation in size of red blood cells; when levels are elevated, it corresponds iron deficiency and anisocytosis (Spell, Jones, Harper, & Bessman, 2004). Studies indicate that neoplastic lesions of the colon are often discovered in individuals with iron deficiency with or without anemia (Spell, Jones, Harper, & Bessman, 2004). Abnormal red blood cell levels may indicate anemia, dehydration, and bleeding ("Types of Blood Tests", 2012). In Ronnie's case CBC test results can help determine if he is dehydrated (due to diarrhea) and if there are any other diseases or blood abnormalities cause by his infection (such as haemolytic anemia) present in his body.

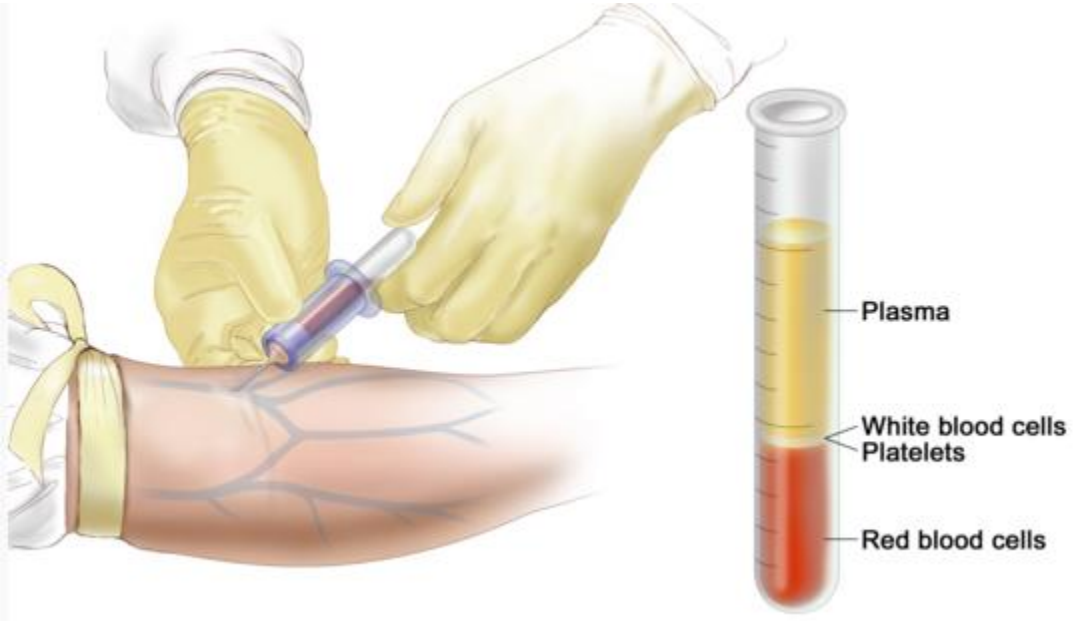

Figure 14. Image showing how blood samples are collected. A needle is inserted into a vein and the blood sample collected into a tube. The blood sample contents: red blood cells, white blood cells, and platelets are counted which can then be used diagnose and monitor different conditions. Image retrieved fromhttps://my.pearlpoint.org/cancer-education/chronic-myeloproliferative-disorders-treatment-general-information-about-chronic-myeloproliferative-disorders.

Electrolyte Test
This test measures the amount of electrolytes in the body such as sodium, potassium, and chloride. These minerals are involved in maintaining water balance in cells; therefore, changes in levels of electrolytes can indicate dehydration and acid-base imbalance ("Blood Tests", 2016). In addition, abnormal electrolyte levels may suggest disturbed kidney function ("Blood Tests", 2016).

Blood Chemistry Tests/Basic Metabolic Panel (BMP)
The basic metabolic panel (BMP) measures blood glucose, calcium, electrolytes and kidney function based on levels of blood urea nitrogen, and creatinine ("Types of Blood Tests", 2012). Abnormal levels of blood urea nitrogen and creatinine may indicate kidney disease. Overall BMP tests provide information about muscles in the body, the heart, bones, and organs such as the kidneys and liver ("Types of Blood Tests", 2012). This is important in Ronnie's case since infection by *E. Coli* can lead to renal complications as discussed previously. Additionally this test can help detect early-stage metabolic syndrome, diabetes, and provide information on cardiovascular health based on the levels of cholesterol, high density lipoprotein (HDL), low density lipoprotein, triglyerides, and total cholesterol/HDL ratios (Figure 15) ("Types of Blood Tests", 2012).

	Current Laboratory Reference Range	Optimal Range
Glucose	65-99 mg/dL	70-85 mg/dL
Cholesterol	100-199 mg/dL	180-200 mg/dL
LDL	0-99 mg/dL	Under 100 mg/dL
HDL	40-59 mg/dL	Over 55 mg/dL
Triglycerides	0-149 mg/dL	Under 100 mg/dL

Figure 15. Optimal ranges of glucose, cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides in blood. Image reproduced from Barron (2006).

Blood Enzyme Tests
Blood enzyme tests provide information on the levels of various enzymes in the blood that may be involved in vital processes and can indicate the health state of an individual ("Types of Blood Tests", 2012). For example, elevated liver enzymes (such as alanine transaminase or aspartate transaminase) suggest inflammation or damage to the liver cells (Barron, 2006).

Reticulocyte Count
This test is often used in conjunction with the CBC test and can evaluate anemia and haemolytic states ("Types of Blood Tests", 2012). This test compares the RNA levels of newly released red blood cells to those of mature red blood cells.

Peripheral Blood Smear
Peripheral blood smear tests are performed by spreading a thin film of a blood sample onto a slide, and then staining it with Wright's stain ("Types of Blood Tests", 2012). This allows the haematologists to observe and evaluate the morphology of the red blood cells, white blood cells, and platelets ("Types of Blood Tests", 2012), thus aiding in the identification of any blood abnormalities.

Erythryocyte Sedimentation Rate (ESR)
This test measures the number of red blood cells in the blood sample that settle to the bottom of a test tube within one to two hours ("Types of Blood Tests", 2012). Erythrocyte sedimentation rate test results help to diagnose conditions associated with acute and chronic inflammation such as arthritis, the presence of infections, cancers, and autoimmune diseases ("Blood Tests", 2016). A very high ESR suggests infection, which may be what we expect in Ronnie's results.

C-Reactive Protein (CRP) Test
Similarly to ESR tests, the C-reactive protein test also helps to diagnose conditions that cause inflammation ("Blood Tests", 2016). C-reactive protein is an acute phase serum protein made by the liver and released into the blood within a few hours after tissue injury or the beginning of an infection (Black, Kushner & Samols, 2004). Concentrations of C-reactive protein rise above optimal ranges (Figure 16) during inflammatory states due to its role in the innate immune response (Black, Kushner & Samols, 2004).

Current Laboratory Reference Range	Optimal Range
MALE 0-3 mg/L	MALE <0.55 mg/L
FEMALE 0-3 mg/L	FEMALE <1.5 mg/L

Figure 16. Optimal ranges for C-protein concentrations in males and females. Image reproduced from "Blood Tests" (2016).

Liver Function Test
The liver function test helps screen for potential liver damage and abnormal function by measuring the levels of enzymes and proteins such as alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase, and albumin ("Blood Tests", 2016). Usually,

this test is used when patients exhibit symptoms such as diarrhea, vomiting, nausea, bloody stools, fatigue, and pain in the bell (“Blood Tests”, 2016). Although Ronnie does not experience all of these symptoms, this test may be recommended by his physician to ensure proper functioning of his liver and screen for the potential of other diseases.

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