1. INTRODUCTION
1.1 Definition:
Diarrhoea includes increase in volume or fluidity of stools, change in consistency and increase frequency of defecation. The measurement of stool fluid content is impractical and assessment of stool frequency is preferred for diagnostic purpose. World Health Organisation defines diarrhoea as the “passage of loose or watery stools at least three times in a 24 hours period” (Gilman, 1996, Jing et al., 2009). Diarrhoea involves both an increase in the motility of the gastrointestinal tract, along with increased secretion, and a decrease in the absorption of fluid and thus a loss of electrolytes and water (Mbagwu et al., 2008, Suleiman et al., 2008). The rapid movement of faeces through the intestine results in abnormally frequent and watery stools (Fine 1998). Absorption of water, nutritive elements, and electrolytes is decreased and the patient usually complains of abdominal cramps and generalized weakness. The normal daily stools of a healthy adult weigh 100 – 200 gm and contain 60% water. Even small variation in weight (excretion of more than 20 gm) and content (60 – 90%) of water causes diarrhoea (Farthing et al., 2000).

In the early 1980s, diarrhoeal disorders were the biggest child killers responsible for an estimated 4 - 6 million death world-wide every year (Adeyemi et al., 2008). Despite widespread use of oral rehydration therapies (ORT) and an increased understanding of the pathogenesis of diarrhoea, 2 -5 million children still die from these illness every year, almost all of them in developing countries (Abdulkarim et al., 2005, Wendel et al., 2008, Adeyemi et al., 2009).

1.2 Pathogenesis of Diarrhoea:
Diarrhoea is mainly due to one of the following reason:

- Abnormal motility
- Disturbances in intestinal permeability
- The presence of osmotically active, non absorbable substance in human gut
- Local irritation by infectious or chemical substance
- Emotional disorders that increase peristalsis

Diarrhoea commonly results from gastroenteritis caused by viral infections, parasites or bacterial toxins. Diarrhoea can also be a symptom of more serious diseases, such as
dysentery, cholera or botulism and can be indicative of a chronic syndrome such as Crohn’s disease. Diarrhoea can also be caused by dairy intake in those who are lactose intolerant (Margaret et al., 1982).

Many things can cause diarrhoea, which can make diagnosis complex. A list of established cause of diarrhoea follows (Kruszka et al., 2002, Das, 2001, Claudia et al., 2009, Jaw-Chyun et al., 2007):

- Lactose intolerance
- Pancreatic disease
- Short bowel syndrome
- Postgastrectomy syndrome
- Hyperthyroidism
- Cholestasis
- Celiac disease (gluten intolerance)
- Other malabsorption syndromes
- Inflammatory bowel disease
- Viral infection (*Norwalk virus, Rota virus, Adenovirus*)
- Bacterial infection (*Salmonella, Shigela, Campylobacter, Vibrio cholera, Enteroaggregative Escherichia coli, Entero-Toxic Escherichia coli, Yersinia enterocolitica, Vibrio parahemolyticus*)
- Protozoal infection (*Giardia lambia, Entamoeba histolytica, Blastocystis, Dientamoeba fragilis, Cryptosporidium, Isospora, Cyclospora, Toxoplasmosis*)
- Multicellular parasitic diseases (*Ascaris, Trichuris, Strongyloides, Filarisis, Tapeworm, Schistosoma, Hookworm, Pinworm*)
- Fungal diseases (*Candida*)
- Ischemic colitis
- Radiation colitis
- Secretory diarrhoea
- Irritable bowel syndrome
- Laxative abuse
- Bacterial toxins
- Drugs and poisons
- Neuroendocrine tumors
• Neoplasia (Colorectal cancer)
• Addison’s disease.

1.3 Symptoms of diarrhoea (Das et al., 2001):

• Frequent, loose and watery stools
• Loss of appetite
• Nausea
• Vomiting
• Stomach pains
• Fever
• Abdominal pain
• Abdominal cramps
• Dehydration
• Pricking sensation
• Bloody stools because of bacterial or parasitic infection

1.4 Mechanisms of diarrhoea:

The digestive system in human body functions to provide body cells with water, electrolytes, vitamins and nutritive substances. During passage through the gastrointestinal tract, ingested carbohydrates, fats and proteins are converted to smaller absorbable units by the action of digestive enzymes, aided by specialized secretions such as bile and hydrochloric acid. The luminal contents of the digestive tract are transported and effectively mixed with digestive secretions and mucus by specialized muscular movements. Gastrointestinal motility and secretions are affected by a complex interaction of intrinsic and extrinsic neural influences and by several peptide hormones (Bhise et al., 2009).

The gastrointestinal tract provides the body with continual supply of water, electrolytes and nutrients. The stomach normally is sterile because of the acidity. This acidity generally destroys most organisms which are not stable at this pH. The rest of the gastrointestinal tract has normal bacterial flora, which inhibits the growth of other organisms. Gastrointestinal wall is lined by cells, which produce mucus. This mucus forms barrier to the bacterial invasion of the gut wall (Gennaro et al., 1976).
1.4.1 Anatomy and physiology of gastrointestinal tract

Anatomically the gastrointestinal tract consists of the mouth, pharynx, esophagus, stomach, small intestine, large intestine, rectum and anal canal. When food is taken into the mouth it is masticated and mixed with saliva to form soft mass which is pushed into the pharynx. The esophagus is the muscular tube that rapidly transfers food from the pharynx to the stomach. It’s walls include all the anatomical layers, which are characteristics of the digestive tract in general (Waugh et al., 2001).

The stomach, whose function is to store and digest food, reduces solid food to fluid by virtue of the contraction of its muscular wall and the admixture of food with secretions from the glands of its mucous membrane. When the content of the stomach has been reduced to pulp like fluid mass, known as chyme, it is soft enough to be transferred to the intestine in small portions (Bowman et al., 1980).

The small intestine is the part of the alimentary tract between the stomach and the large intestine. It is made up of the duodenum, jejunum and ileum. The wall of the small intestine consists of five strata. These are starting from the inside wall, mucosa, submucosa, circular smooth muscle layer, longitudinal smooth muscle and serosa. The mucosa consists of a single epithelial layer, lamina propria and muscularis mucosa. The submucosa, a connective tissue, contains an autonomic nervous plexus, known as Meissner’s plexus, influences peristalsis. Auerbach’s plexi is located between the well developed circular and longitudinal smooth muscle layer and supplies the mucous membrane and secretory glands. The serosa, a layer of mesothelial cells and loose connective tissues, forms the outer surface of the intestinal wall.

Meissner’s and Auerbach’s plexi constitute the intrinsic neuronal control of the gastrointestinal functions. The extrinsic nerve endings in to the intestinal wall consist of preganglionic vagal fibers and postganglionic fibers of the sympathetic. The role of this extrinsic nervous system in normal gastrointestinal functions is unknown (Waugh et al., 2001).

The principal functions of the small intestine are (Bever et al., 1976):

- Forward movement of the chyme received from the stomach.
- Continued digestion by means of special secretions from its intrinsic and accessory glands.
• Absorption of nutrients released by digestion into blood and lymph vessel of the mucosa

The large intestine, the extension of the small intestine, is not folded except in the region of its terminal portion, the rectum. The absorption of water from the chyme discharged into the colon consolidates the material and transforms it to fecal masses. The mucin, secretion of colon helps to bind the fecal material and lubricates its passage through the terminal parts of the large intestine. Local movements of the colon aid the absorption of water and help to form the faeces by providing a kneading action. These movements are brought about by contractions of segments of circular muscle and the adjacent portions of the taeniae coli. These movements are termed segmentation. Defecation involves involuntary contraction of the muscle of the rectum and relaxation of the internal anal sphincter (Sengupta et al., 1969).

The movement of the gastrointestinal tract is due to the activity of smooth muscles. This tissue possesses extraordinary properties, in that it can maintain constant tension over widely differing lengths. This property accounts for the fact that a large meal can be ingested in a short time without much alteration in intragastric or intraintestinal pressures as the alimentary tract adopts itself to its content whatever the bulk may be.

The alimentary tract is supplied by nerves from both divisions of the autonomic nervous system, i.e. parasympathetic and sympathetic, having antagonistic actions. Parasympathetic stimulation causes smooth muscle contraction and the secretion of digestive juices. Sympathetic stimulation reduces smooth muscle contraction and glandular secretion (Chatterjee C.C., 1984).

1.4.2 Absorption and secretion

The normal small intestine contains particularly no fluids in the fasting state. However, following the ingestion of the meals, large volumes of essentially isotonic fluids enter the lumen of the proximal bowel. The fluids contain liquids of the meal and to the larger extent endogenous secretions of the upper digestive tract. The volume of the fluids entering the proximal bowel exceeds the extracellular volume and it is equivalent to a major proportion of the total body water. However more than 90% of these fluid is reabsorbed thereby completing an efficient enterosystemic cycle (Lawrence et al., 1997).
Total daily input into the gut amounts to 9 liter of essentially isotonic fluid. It includes saliva, intestinal secretions and also variable quantities of fat, carbohydrate and protein from diet, proteins in digestive secretions, and an unpredictable contributing by desquamated epithelial cells. Finally electrolytes and water are secreted into the lumen of the bowel, presumably by transepithelial movement, even in areas devoid of specific secretory glands. Adequate digestion and absorption of dietary macromolecules is essential to normal intestinal functions. Disturbances of water absorption and secretion provide the major clues to the pathophysiology of diarrhoea (Waugh et al., 2001).

![Figure 1.Absorption of water and electrolytes in GI tract.](image)

Of the 9L of fluid entering the digestive tract, about 7 lit are absorbed in the small intestine (absorbing efficiency 75%), and except for 0.1 - 0.2 lit lost in the faeces, the rest is absorbed in the colon (absorbing efficiency 90%). Normally, the overall efficiency of absorption of water from the digestive tract is 98% (Figure 1).
1.4.2.1 Decreased absorption of water and electrolytes.

A. Loss of functional absorptive area.

Causes of loss of functional absorptive area shown in Table 1. The small intestine is the most common site of disease caused by ingested pathogens and food constituents (Ramaswamy 2001, Baur et al., 1966, Cruickshank, 1968, Gerald et al., 2007, Vanderhoof, 2000).

B. Decreased intraluminal digestion

Maldigestion of nutrient seen in exocrine pancreatic insufficiency (e.g., Cystic fibrosis, chronic pancreatic) and congenital and acquired deficiencies of digestive enzymes. These enzymes are usually present in secretions into the intestinal lumen or within the brush border of intestinal epithelial cells. Abnormalities in synthesis, secretion or deconjugation of bile salts can result in malabsorption of fats. Undigested substrates cannot take in coupled absorption and they remain in the intestinal lumen and give rise to osmotic diarrhoea (Russo et al., 2002).

C. Decreased enterocyte cellular absorptive function

Some substrates absorbed via specific intestinal transporters. These substrate include glucose, galactose, amino acids, triglycerides, sodium chloride, and folate. Congenital defects in such transporters that result in osmotic diarrhoea (Sherman et al., 2004).

D. Decreased intestinal transit

Some physiological states (anxiety), drugs and toxins have a direct effect on the enteric nervous system. Thus, intestinal motility is increased, intestinal transit time is reduced and there is poor absorption of water and substrates giving rise to diarrhoea (Reinshagen et al., 2002).
Table 1. Mechanisms for loss of functional intestinal absorptive area.

<table>
<thead>
<tr>
<th>i) Decreased intestinal length.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrotising enterocolitis</td>
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<tr>
<td>Inflammatory bowel disease</td>
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<tr>
<td>Tumors</td>
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<td>Surgical removal of nonviable or dysfunctional bowel</td>
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<tr>
<th>ii) Loss of intestinal villi and absorptive enterocytes</th>
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<tbody>
<tr>
<td>Rotavirus</td>
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<tr>
<td>Enteric adenovirus</td>
</tr>
<tr>
<td>Norwalk viruses</td>
</tr>
<tr>
<td>Lytic distruption of enterocytes often with little host inflammation</td>
</tr>
<tr>
<td>Malnutrition</td>
</tr>
<tr>
<td>Zinc deficiency</td>
</tr>
<tr>
<td>Vitamin A deficiency</td>
</tr>
<tr>
<td>Relative immunodeficiency and delayed intestinal repair. Substantial risk of persistent diarrhoea and motility.</td>
</tr>
<tr>
<td>Cytopathic bacterial pathogens</td>
</tr>
<tr>
<td>(Enteropathogenic E. coli, Enteroinvasive, E. coli, Giardia, Salmonella spp, Shigella spp, Campylobacter spp, Yersinsia spp)</td>
</tr>
<tr>
<td>Invasion and immune mediated destruction of enterocytes. More invasive pathogens associated with systemic manifestations.</td>
</tr>
<tr>
<td>Celiac disease (gluten sensitive enteropathy)</td>
</tr>
<tr>
<td>Abnormalities in cell mediated and humoral immunity arising in genetically susceptible individuals.</td>
</tr>
<tr>
<td>Autoimmune enteropathy</td>
</tr>
<tr>
<td>Associated with presence of gut auto-antibodies, usually anti-enterocyte, in the absence of an identifiable trigger.</td>
</tr>
<tr>
<td>Allergic (cow’s milk protein sensitive) enteropathy</td>
</tr>
<tr>
<td>Immune mediated damage resulting in partial villous atrophy.</td>
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<tr>
<th>iii) Disruption of colonic mucosa</th>
</tr>
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<tbody>
<tr>
<td>Salmonella spp, Shigella spp, Campylobacter spp, E. coli and Amoeba</td>
</tr>
<tr>
<td>Invasion and destruction of host cells largely mediated by bacterial proteins. Induction of inflammatory response with mucosal ulceration and hemorrhage.</td>
</tr>
</tbody>
</table>
1.4.2.2 Increased secretion or loss of water and electrolytes into the intestinal lumen

A. Net increase in secretory cells

To replace loss of villous absorptive cells, intestinal crypts undergo hyperplasia and the number of immature cryptal ‘secretory’ cells will increase. This cause of increased secretory loss into the intestinal lumen is noted in illness where there is enterocyte destruction and villous atrophy such as viral enteritis, celiac disease and food allergic enteropathy (Cash et al., 1970).

B. Stimulation of secretory pathway

Most bacteria pathogens elaborate enterotoxins and the rotavirus protein NSP4 acts as a viral enterotoxin. Bacterial enterotoxins can selectively activate enterocyte intracellular signal transduction and the second messenger pathways. Toxins may also act through cytoskeletal rearrangements which have also been shown to regulate water and electrolyte fluxes across enterocytes. Up regulation of these pathways results in inhibition of NaCl-coupled transport and increased efflux of chloride resulting in net secretion and loss of water into the intestinal lumen. Coupled transport of sodium to glucose and amino acid is largely unaffected. Plasma nitrate concentration as a marker of endogenous nitric oxide production is significantly higher in infections compared with non-infectious diarrhoea (Guandalini et al., 1982).

Four main pathways seem to be involved in the intestinal secretion of water and electrolytes: cAMP, cGMP, Ca\(^{2+}\), and cytoskeleton (Figure 2). These pathways are activated by several enteric pathogens, either directly or through the elaboration of enterotoxic products. CT=cholera toxin; LT=heat labile enterotoxin; TDH=thermostable direct haemolysin; CD=\textit{Clostridium difficile}; EAST1= enteroaggregative \textit{E. coli} heat stable toxin 1; STa=heat stable toxin a; AC=adenylatecyclase; GC=guanylatecyclase; CM=calmodulin; PKC=protein kinase C; ZOT=Zonulaoccludens toxin; EGF-r=epidermal growth factor receptor; ECM=extracellular matrix (Thapar et al., 2004).
Mucosa is normally an effective barrier but any disruption can lead to increased leakiness of the epithelium and if severe, results in mucosal ulceration and bleeding (Ramaswamy, 2001).

There are four main mechanisms of epithelial disruption (Thapar et al., 2004):

- Distortion of enterocyte cytoskeleton – eg. *E. coli* enterotoxin
- Effects on protein synthesis – *S. dysenteriae* toxins, *Staphylococcal* enterotoxin
- Inflammation – Usually via upregulation of proinflammatory cytokines and infiltration by host inflammatory cells, a response that eliminates pathogens and prevents bacterimia at the expense of damage to mucosa.

D. Osmotic shift and loss of fluid across the epithelium

The osmolarity of meals varies widely. Hypotonic saliva and isotonic gastric secretions modify the ionic strength of the gastric contents. Hypotonic meals are rendered isotonic by the movement of water from the lumen and the concomitant movement of ions, mainly sodium and chloride into lumen. Dietary macromolecules are also hydrolysed to smaller, osmotically active compounds. Water also moves rapidly into the small bowel to dilute the...
hypertonic contents. The duodenum reduces the osmolarity of its contents much faster than does the ileum. These rapid changes render the chyme essentially isotonic by the time it reaches the jejunum where more absorption seems to occur. Throughout the intestine chyme contains sodium as a major cation but potassium concentration increases distally and can be greater than those of sodium in faeces. Chloride is the major anion of jejuna contents but its concentration decreases distally where it is partially replaced by bicarbonates in the ileum and organic anions in the colon (Alam et al., 1999, Tripathi 1999).

Malabsorption or maldigestion can result in the presence of osmotically active molecules within the intestinal lumen. These molecules draw water into the lumen at a rate directly proportional to their concentration. This fluid loss is exacerbated in the colon where bacterial digestion and fermentation propagate osmotic diarrhoea and interfere with sodium absorption thus lowering luminal pH. The increased volume in the lumen then stimulates peristalsis (Thapar et al., 2004).

1.4.3 Intestinal fluxes of water and electrolytes

The proper flux of nutrients, wastes, electrolytes and water through the intestine depends on a balance of absorption and secretion of water and electrolytes by the intestine in response to osmotic gradients that result from uptake and secretion of ions and the absorption of nutrients (mainly sugar and amino acids). Neuronal mechanisms, pathogens and drugs can alter uptake and secretory processes and the osmotic gradients for water flux such that excessive absorption or net secretion of water occurs, contributes to constipation or diarrhoea, respectively. Additionally drugs can stimulate or reduce intestinal motility and thereby alter the transit time of compounds through the intestine. Since the extension of absorption generally parallels transit time, altered motility also contributes to diarrhoea or constipation (Sengupta et al., 1969, Heinrich et al., 2005).

In the intestine, water absorption follows active and passive sodium and nutrient absorption. In the small intestine, sodium is co-transported with chloride and nutrients such as glucose, in the terminal ileum, sodium is co-transported with bile salts, in the colon sodium is absorbed via sodium channels and by the electroneural sodium chloride absorptive mechanism used in the small intestine. The co-transport mechanism for sodium and nutrient depends on Na\(^+\)-K\(^+\) ATPase pump of basolateral membrane by a facilitated transport mechanism. Water absorption follows passively to maintain iso-osmoalarity in
the intracellular space. Because the sodium glucose co-transport mechanism remains unaffected by most diarrhoeal diseases, administration of a glucose salt solution is useful clinically for the management of diarrhoea and dehydration regardless of the cause (Binder, 1992).

In addition to its absorptive function, the intestine has a secretory function. Chloride can be secreted by intestinal crypt cells via an electromagnetic mechanism, with sodium, potassium and water following passively through the tight junctions. As in the small intestine, sodium absorption mechanism exists in the colon (Waugh et al., 2001).

Intestinal lining undertakes both absorptive and secretory functions under the control of regulators (Table 2). The colon and the rectum are innervated by nerve that release noradrenalin, acetylcholine and other neurotransmitters. Parasympathetic nerve stimulates peristaltic contraction and electrolyte secretion where as adrenergic tone inhibits cholinergic stimulation and increases electrolyte absorption. Additional regulation is provided by local reflex arcs in the autonomous enteric nervous system and intrinsic contractile responses of the colonic smooth muscle.

Table 2. Regulators of intestinal water and electrolyte transport (Thapar et al., 2004):

<table>
<thead>
<tr>
<th>Stimulators of absorption</th>
<th>Stimulators of secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin</td>
<td>Vasoactive intestinal polypeptide</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>Serotonin</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>Neuropeptide Y</td>
<td>Substance P</td>
</tr>
<tr>
<td>Mineralocoricoids</td>
<td>Prostaglandins</td>
</tr>
<tr>
<td></td>
<td>Calcitonin</td>
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<tr>
<td></td>
<td>Acetylcholine</td>
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<tr>
<td></td>
<td>Guanylin</td>
</tr>
<tr>
<td></td>
<td>Neurotensin</td>
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</tbody>
</table>

The colon absorbs relatively few nutrients. It does however absorb short chain fatty acids (two to four carbon atoms in the length) by diffusion. The absorption of these fatty acids increases the absorption of fluids and electrolytes, in contrast to the effects of longer chain fatty acids (greater than 12 carbon atoms) and dehydroxy bile acids, which decrease
colonic absorption of fluids and electrolytes and may contribute to diarrhoeal illness (Burks, 1987).

### 1.4.4 Sodium and water absorption

Absorption and secretion of water and electrolyte occurs through the intestine probably as separate process. Absorption is the function of the cells of intestinal villi and is also responsible for active secretion of water. Water follows the osmotic gradients that result from shift of electrolytes across the intestinal epithelium and sodium and chloride transport mechanisms are central to the causation and management of diarrhoea (Bever, 1976).

Absorption of sodium into the epithelium is affected by

i) Sodium – glucose coupled entry:

Glucose stimulates the absorption of sodium and the resulting water flow also sweeps additional sodium chloride along with it. This important mechanism remains active in diarrhoea of various etiologies and improvement of sodium and water absorption by glucose is the basis of oral rehydration. Thus, sodium can be absorbed across intestinal mucosal preparations by means of an energy dependent phenomenon that is able to transport sodium from the lumen against gradients of chemical concentration and against the electrical charge of intestinal mucosa (Margaret et al., 1982).

ii) Sodium ion coupled entry

Sodium and chloride enters the epithelial cell either as a pair or by double exchange sodium (extracellular) with hydrogen (intracellular) and chloride (extracellular) with hydroxyl or carbonate ion (intracellular). Thus in the ileum and colon a less permeable membrane restricts the passive movements of sodium (and other water soluble solutes) but active sodium absorption is more effective.

Secretion is the opposite process to that of absorption. In response to various stimuli, crypt cells actively transport chloride into the gut lumen and sodium and water follow. This stimulates secretion where coupling is modulated by cyclic AMP, GMP, PGs and leukotrienes (Harison, 1997, Tripathi, 1999).
1.4.5 Maintenance of water balance

Water is the most abundant of all chemical compounds in the human body which constitutes approximately 2/3rd of the entire body weight. Its importance has been emphasized by the fact that if 20 – 25% of body water is lost death usually results.

One of the principal factors in the maintenance of water balance among the components is the osmotic pressure of electrolytes and the selective ion permeability of cellular membranes. The plasma proteins cannot diffuse through the capillary wall because of their large particle size. Thus, they act as a force in holding water in the blood through the osmotic pressure which they exert.

Extracellular fluid contains sodium chloride in isotonic concentrations. Hence the ingestion of 9 gm of sodium chloride will necessitates the holding in the intestinal fluid of 1 liter water to maintain the normal osmotic balance. Conversely the loss of sodium will require the loss of water to compensate for the diminished osmotic pressure (Krantz, 1965).

1.4.6 Absorption of other electrolytes:

Fecal matter contains high concentrations of potassium. Potassium excretion occurs commonly in diarrhoea. Potassium movement across the jejunum and ileum can be explained by passive electrical (passive difference) and chemical concentration gradients.

Intestinal absorption of anion is complex. Movements of chloride and bicarbonate are closely coupled particularly in the distal bowel. Chloride and bicarbonate exchange in the ileum is related to sodium and hydrogen ion transport. Chloride and bicarbonate can be absorbed together in the jejunum. However, in the ileum and colon chloride is usually absorbed while bicarbonate is secreted. As chyme passes distally chloride concentration decreases and bicarbonate concentrations and the pH rises. Organic anion (acetate, propionate, butyrate and others) are prominent constituents of stool and comprise 70% of fecal anions (Margaret et al., 1982).

Under certain pathological conditions secretion of water and electrolytes is highly relevant to the production of diarrhoea and has demonstrated under variety of conditions:

i) Abnormal physical conditions such as mechanical bowel obstruction, lowered pH and post irradiation conditions.
ii) In the presence of chemical stimulants such as dihydroxy bile acids in the small intestine and colon, hydroxylated fatty acids like ricinolic acid from castor oil, hydroxyl stearic acid and cathartics of anthraquinone group.

iii) In the presence of bacterial toxins such as those of *Vibrio cholerae*, *Staphylococcus*, *Clostridium perfringens*, certain *Shigellae* and *E. coli*.

iv) Stimulation by humoral factors, mineralocorticoids which augment sodium absorption and stimulate potassium secretion in the human colon, prostaglandins, gastrin, secretin, cholestochynin and newer polypeptide substances recently isolated from gut mucosa induce secretion in the variety of experimental models (Bever, 1976).

**1.4.7 Mucosal disease**

Patients with nontropical sprue, intestinal scleroderma and regional enteritis secrete sodium and water into the jejunum. Bacterial enterotoxins invade the mucosa and produce changes in villus architecture and cause secretion of water. In such conditions mucosal structure is abnormal (Bever, 1976).

**1.5 Gastrointestinal motility and secretions**

**1.5.1 Gastrointestinal (GI) motility:**

The GI tract generates motility using smooth muscle subunits linked by gap junctions. These subunits fire spontaneously in either a tonic or a phasic fashion. Tonic contractions are those contractions that are maintained from several minutes to hours at a time. These occur in the sphincters of the tract, as well as in the anterior stomach. The other type of contractions, called phasic contractions, consist of brief periods of both relaxation and contraction, occurring in the posterior stomach and the small intestine, and are carried out by the muscularis externa (Waugh et al., 2001, Bennet, 1992, Borelli et al., 2004).

**1.5.1.1 Stimulation:**

The stimulation for these contractions likely originates in modified smooth muscle cells called interstitial cells of Cajal. These cells cause spontaneous cycles of slow wave potentials that can cause action potentials in smooth muscle cells. They are associated with the contractile smooth muscle via gap junctions. These slow wave potentials must reach a threshold level for the action potential to occur, whereupon Ca$^{2+}$ channels on the smooth
muscle open and an action potential occurs. As the contraction is graded based upon how much Ca$^{2+}$ enters the cell, the longer the duration of slow wave, the more action potentials occur. This in turn results in greater contraction force from the smooth muscle. Both amplitude and duration of the slow waves can be modified based upon the presence of neurotransmitters, hormones or other paracrine signaling (Wang et al., 2000, Lamba et al., 1969).

1.5.1.2 Contraction Patterns:

The patterns of GI contraction as a whole can be divided into two distinct patterns, peristalsis and segmentation. Occurring between meals, the migrating motor complex is a series of peristaltic wave’s cycles in distinct phases starting with relaxation followed by an increasing level of activity to a peak level of peristaltic activity lasting for 5 – 15 minutes. This cycle repeats every 1.5 – 2 hours but is interrupted by food ingestion. The role of this process is likely to clean excess bacteria and food from the digestive system (Rang et al., 2003, Bolton 1979).

1.5.1.3 Peristalsis:

Peristalsis is the second of the three patterns and is one of the patterns that occur during and shortly after a meal. The contractions occur in wave patterns traveling down short lengths of the GI tract from one section to the next. The contractions occur directly behind the bolus of food that is in the system, forcing it toward the anus into the next relaxed section of smooth muscle. This relaxed section then contracts, generating smooth forward movement of the bolus at between 2 – 25 cm per second. This contraction pattern depends upon hormones, paracrine signals, and the autonomic nervous system for proper regulation (Bolton 1979).

1.5.1.4 Segmentation:

The third contraction pattern is segmentation, which also occurs during and shortly after a meal within short lengths in segmented or random patterns along the intestine. This process is carried out by longitudinal muscles relaxing while circular muscles contract at alternating sections thereby mixing the food. This mixing allows food and digestive enzymes to maintain a uniform composition, as well as to ensure contact with the epithelium for proper absorption (Waugh et al., 2001).
1.5.1.5 Gastrointestinal contractility reducing agents:

Alfa-2 adrenoceptor agonists, botulinum toxin, calcium channel blockers, muscarinic receptor antagonists and nitrates (Rang et al., 2003, Das, 2001).

1.5.1.6 Gastrointestinal contractility augmenting agents:

Alfa-2 adrenoceptor antagonists, erythromycin, GABAB receptor agonists, muscarinic receptor agonists, neostigmin, nifedipine, nitric oxide synthase inhibitors and substituted benzamides (Rang et al., 2003, Das, 2001).

1.5.2 Gastrointestinal fluid secretion (Intraluminal fluid secretion):

1.5.2.1 Secretion:

Every day, seven liters of fluid are secreted by the digestive system. This fluid is composed of four primary components: ions, digestive enzymes, mucus, and bile. About half of these fluids are secreted by the salivary glands, pancreas, and liver, which compose the accessory organs and glands of the digestive system. The rest of the fluid is secreted by the GI epithelial cells (Waugh et al., 2001).

1.5.2.2 Ions:

The largest component of secreted fluids is ions and water, which are first secreted and then reabsorbed along the tract. The ions secreted primarily consist of $\text{H}^+$, $\text{K}^+$, $\text{Cl}^-$, $\text{HCO}_3^-$ and $\text{Na}^+$. Water follows the movement of these ions. The GI tract accomplishes this ion pumping using a system of proteins that are capable of active transport, facilitated diffusion and open channel ion movement. The arrangement of these proteins on the apical and basolateral sides of the epithelium determines the net movement of ions and water in the tract.

$\text{H}^+$ and $\text{Cl}^-$ are secreted by the parietal cells into the lumen of the stomach creating acidic conditions with a low pH. $\text{H}^+$ is pumped into the stomach by exchanging it with $\text{K}^+$. This process also requires ATP as a source of energy; however, $\text{Cl}^-$ then follows the positive charge in the $\text{H}^+$ through an open apical channel protein (Gilman, 1996).
HCO$_3^-$ secretion occurs to neutralize the acid secretions that make their way into the duodenum of the small intestine. Most of the HCO$_3^-$ comes from pancreatic acinar cells in the form of NaHCO$_3$ in a watery solution. This is the result of the high concentration of both HCO$_3^-$ and Na$^+$ present in the duct creating an osmotic gradient to which the water follows (Donowitz et al., 1987).

1.5.2.3 Digestive enzymes:

The second vital secretion of the GI tract is digestive enzymes that are secreted in the mouth, stomach and intestines. Some of these enzymes are secreted by accessory digestive organs, while others are secreted by the epithelial cells of the stomach and intestine. While some of these enzymes remain embedded in the wall of the GI tract, others are secreted in an inactive proenzyme form. The release of the enzymes is regulated by neural, hormonal, or paracrine signals. However, in general, parasympathetic stimulation increases secretion of all digestive enzymes (Krantz, 1965).

1.5.2.4 Mucus:

Mucus is released in the stomach and intestine, and serves to lubricate and protect the inner mucosa of the tract. It is composed of a specific family of glycoproteins termed mucins and is generally very viscous. Mucus is made by two types of specialized cells termed mucus cells in the stomach and goblet cells in the intestines. Signals for increased mucus release include parasympathetic innervations, immune system response and enteric nervous system messengers (Bhende et al., 1969).

1.5.2.5 Bile:

Bile is secreted into the duodenum of the small intestine via the common bile duct. It is produced in liver cells and stored in the gall bladder until release during a meal. Bile is formed of three elements: bile salts, bilirubin and cholesterol. Bilirubin is a waste product of the breakdown of haemoglobin. The cholesterol present is secreted with the faeces (Horwitz et al., 1996, Bhende et al., 1969).
1.5.3 Regulation of gastrointestinal motility and secretion:

The digestive system has a complex system of motility and secretion regulation which is vital for proper function. This task is accomplished via a system of long reflexes from the central nervous system (CNS), short reflexes from the enteric nervous system (ENS) and reflexes from GI peptides working in harmony with each other (Bennet, 1992).

1.5.3.1 Long Reflexes:

Long reflexes to the digestive system involve a sensory neuron sending information to the brain, which integrates the signal and then sends messages to the digestive system. While in some situations, the sensory information comes from the GI tract itself; in others, information is received from sources other than the GI tract. When the latter situation occurs, these reflexes are called feed forward reflexes. This type of reflex includes reactions to food or danger triggering effects in the GI tract. Emotional responses can also trigger GI response such as the butterflies in the stomach feeling when nervous. The feed forward and emotional reflexes of the GI tract are considered cephalic reflexes (Brunton, 2000).

1.5.3.2 Short Reflexes:

Control of the digestive system is also maintained by ENS, which can be thought of as a digestive brain that can help to regulate motility, secretion and growth. Sensory information from the digestive system can be received, integrated and acted upon by the enteric system alone. When this occurs, the reflex is called a short reflex. Although this may be the case in several situations, the ENS can also work in conjunction with the CNS; vagal afferents from the viscera are received by the medulla, efferents are effected by the vagus nerve. When this occurs, the reflex is called vagovagal reflex. The Myenteric plexus and Submucosal plexus are both located in the gut wall and receive sensory signals from the lumen of the gut or the CNS (Burks, 1987).

1.5.3.3 Gastrointestinal Peptides:

GI peptides are signal molecules that are released into the blood by the GI cells themselves. They act on a variety of tissues including the brain, digestive accessory organs, and the GI tract. The effects range from excitatory or inhibitory effects on motility
and secretion to feelings of satiety or hunger when acting on the brain. These hormones fall into three major categories, the gastrin and secretin families, with the third composed of all the other hormones unlike those in the other two families (Brunton, 2000).

1.5.4 Potassium channels in gastrointestinal tract (K⁺):

In gastrointestinal epithelia, K⁺ channels are involved in a different physiological and pathophysiological processes and their large molecular diversity allows precise adaptation to the complex needs. The consequences of K⁺ channel activity includes the electrical effect on the membrane potential and effects related to the transport of K⁺ as an ion and osmolyte. Such vital functions of K⁺ channels encompass (Rudy, 1988):

- The K⁺ channel-mediated hyperpolarization is a prerequisite of vectorial transport across the epithelial cells. By this mechanism, many different K⁺ channels energize voltage-driven transport processes, e.g., electrogenic glucose reabsorption in small intestine, colonic Na⁺ reabsorption by epithelial Na⁺ channels, and Cl⁻ secretion in crypt cells or exocrine glands. Moreover, the polarized activation of K⁺ channels in basolateral or luminal membranes is a critical factor for the establishment of a transepithelial voltage difference that is needed to drive ion transport across the paracellular pathway (Sun et al., 1994).

- Luminal potassium channels in the colonic surface cells act as an exit pathway for K⁺. These mineralocorticoids controlled channels play a significant role for the fine-tuning of the electrolyte homeostasis.

- Several K⁺ channels act in concert with K⁺-transporting ATPases by allowing K⁺ recycling across the plasma membrane. A prominent example for this function is the gastric K⁺ channels, whose activity is indispensable for gastric acid secretion by the H⁺-K⁺-ATPase.

- K⁺ channels play a role in cellular volume regulation. During reabsorption of nutrients, epithelial cells transport vast amounts of osmolytes and, therefore, they are continuously challenged by changes of cell volume. Cell volume dependent activation of K⁺ channels is needed to counterbalance the cellular increase in osmolytes (Meisher et al., 1988).

- K⁺ channels are involved in the control of cell differentiation, proliferation, and carcinogenesis. Unfortunately, in many cases it is not clear whether changes in K⁺ function are causative or secondary (Ruddy, 1988, Flavia et al., 1999).
1.5.5 Calcium channels (Ca\(^{2+}\)) in gastrointestinal tract:

Actin-myosin interaction:

Smooth muscle cells of the gut behave as unitary types. Three types of filaments exist: thin actin, thick myosin and intermediate desmin filaments. These filaments interdigitate with each other. Following electric or mechanical coupling, the essential first step in smooth muscle contraction is generated: phosphorylation by myosin light chain kinase. Several steps lead to the activation of the enzyme. Cytoplasmic calcium sequentially binds to the regulatory protein, calmodulin, which eventually greatly enhances the ability of actin to activate myosin Mg\(^{2+}\)-ATPase and bring about the hydrolysis of adenosine triphosphate (ATP) bound to the myosin head. The interaction of myosin and actin with hydrolysis of ATP occurs in a cycle, the essential feature of which is a shift in the affinity of myosin for actin (Fleckenstein, 1977, Horowitz et al. 1996, Murphy 1998).

The signal transduction pathway:

In smooth muscle undergoing contraction or relaxation, agonists act mainly by means of intracellular messengers to induce the release or stimulate the sequestration of calcium (Ca\(^{2+}\)). The signal transduction pathway of an external neurohumoral signal into an internal signal is a process that involves sequential activation of at least three membrane proteins: a receptor, a guanosine triphosphate (GTP) binding protein, and phospholipase C (PLC), which is capable of mobilizing intracellular Ca\(^{2+}\). Production of cyclic adenosine monophosphate (cAMP, e.g. by adrenergic agonists), cyclic guanylate monophosphate (cGMP, e.g. by nitric oxide, NO) or both (e.g. by vasoactive intestinal polypeptide, VIP), leads to activation of protein kinase A and C, respectively (Gabriel et al., 1999). These kinases cause a decrease in cytosolic Ca\(^{2+}\) and in the sensitivity of contractile proteins to Ca\(^{2+}\). PLC hydrolyses inositol phospholipids located in the plasma membrane, generating several metabolites, one being 1, 4, 5-trisphosphate (IP\(^3\)) and another being diacylglycerol (DG). IP\(^3\) regulates Ca\(^{2+}\) influx into the cell and its reuptake into the intracellular store. Accordingly, the exposure of smooth muscle cells derived from the circular muscle layer to a contractile agonist induces rapid contraction accompanied by an increase in IP\(^3\), cytosolic Ca\(^{2+}\), and net Ca\(^{2+}\) influx. The peak responses of IP\(^3\), cytosolic Ca\(^{2+}\), Ca\(^{2+}\) efflux and contraction are concentration dependent and closely correlated with each other (Bolton, 1979, Burk 1987, Andrew et al, 2003).
Electrical properties:

The resting membrane potential of muscle cells of the gut is in the range of −40 to −80 mV and is largely determined by activity of the Na⁺-K⁺ pump and K⁺ channels. In addition to passive ion-selective channels, the plasma membrane contains ion-selective channels that can be regulated by membrane potential and by various neurohumoral agents. Especially, voltage-gated Ca²⁺ and several types of K⁺ channels have been identified. High conductance channels with mixed selectivity for K⁺ and Na⁺ carry an inward depolarizing current and are activated at membrane potentials negative to −70 mV, known as the pacemaker potential. Ca²⁺ channels and Ca²⁺ activated K⁺ channels constitute the electrical apparatus that sustains rhythmicity in the smooth muscle. The cycle speed, amplitude and duration depends on the relative proportions of active Ca²⁺ and K⁺ channels, modulated by neurohumoral agents, participation of other voltage-gated or ligand-gated channels, and coupling of muscle cells to each other and to pacemaker cells (Ward et al., 1998, Fleckenstein, 1977, Gilani et al., 2000).

Contractile activity of intestinal smooth muscle generates the peristalsis that determines effective digestion and propulsion of digesta. This activity is controlled by neuronal reflexes and by pacemaker cells of smooth muscle precursor origin, that is, interstitial cells of Cajal (ICC), involving both electromechanical and pharmaco-mechanical coupling. Electromechanical coupling is mediated by the opening of voltage-dependent Ca²⁺ channels, which is initiated by electrical activity conducted from the ICC to smooth muscle cells via gap junctions. The Ca²⁺ channel is essential for electromechanical coupling and important for pharmaco-mechanical coupling in intestinal smooth muscle (Dar et al., 1999, Horowitz et al., 1999).

1.5.6 Nitric oxide (NO) in gastrointestinal tract:

NO mediates multiple physiological functions in the gastrointestinal tract, including mucosal blood flow, maintenance of mucosal integrity, and maintenance of vascular tone. NO is synthesized by the conversion of L-arginine to equimolar amounts of L-citrulline and NO. Once NO is generated, it binds to the haeme group of soluble guanylyl cyclase, which catalyzes the conversion of GTP to cGMP, leading to an intracellular increase in cGMP concentration. cGMP then binds to and modifies the target domain of specific proteins, including protein kinases, ion channels, and phosphodiesterases, to elicit cellular responses. However, NO can also act in a cGMP-independent manner, in which redox
derivatives of NO mediate cellular activities by post-translational modifications or oxidation of proteins and/or lipids. NO works in the gastrointestinal tract to help maintain homeostasis and, when disrupted, can perpetuate pathologic conditions (Uchida et al., 2000, Mascolo et al., 1993).

NO is released through conversion of L-arginine to NO and L-citrulline by three isoforms of NOS. Two isoforms are calcium dependent and constitutive, with one predominantly present in the brain (neuronal NOS, nNOS) and the other in the endothelium (endothelial NOS, eNOS). The third isoform, inducible (inducible NOS, iNOS), is calcium independent and found largely in cells of the macrophage line. The inducible enzyme (iNOS) is present in very low concentrations in normal states, but is rapidly transcribed at times of immune activation, and active transcription can last for several days with significant increases in the total amount of NO synthesized. The induction of iNOS in tissues can lead to the sustained production of high concentrations of NO that may exert pro-inflammatory effects including vasodilatation, edema, cytotoxicity, and the mediation of cytokine-dependent processes (Philippe et al., 2005).

Nitric oxide helps to protect the gastrointestinal tract:

NO has numerous functions in the GI tract. NO that is produced by neuronal Nitric Oxide Synthase (nNOS) in neurons that innervate the GI tract and helps to regulate GI motility. The phasic pattern of contractile activity in the gut (migrating motor complex) is controlled by inhibitory and excitatory motor neurons that innervate smooth muscle layers. NO produced by nonadrenergic, noncholinergic inhibitory motor neurons relaxes smooth muscle cells, which counter contractile activity to ensure normal peristalsis and sphincter function. Deficient NO generation is observed in various GI motility disorders with non-relaxing esophageal, gastric, and bowel segments or sphincters, such as achalasia, hypertrophic pyloric stenosis, diabetic enteropathy, and slow-transit constipation (Katzung et al., 2001, Curro et al., 1994).

Nitric oxide serves to protect the integrity of the mucosal barrier:

The GI tract is constantly assaulted by ingested irritants (eg, food components, alcohol, and drugs), endogenous secretions (eg, stomach acid, bile, and proteolytic enzymes), and enteric microbes. The GI mucosa forms a barrier between the lumen of the GI tract and the
rest of the body. NO serves to protect the integrity of the mucosal barrier in the GI tract through several mechanisms (Mascolo et al., 1992).

Nitric oxide increase blood flow to the GI mucosa:

The vasodilator action of endothelial derived NO helps to increase the flow of blood to the GI mucosa during periods of injury. The inhibitory effect of NO on leukocyte adhesion to the endothelium and on platelet aggregation also acts to prevent vascular stasis and ischemic injury. Aside from these effects on the vasculature, NO also stimulates gastric mucus secretion by GI epithelial cells, which helps further protect the mucosal barrier from injury (Mascolo et al., 1996). In addition to the protective effects in response to injury, experimental models of colitis have shown that NO enhances mucosal repair and healing (Jing et al., 2009).

NO is an extremely unstable free radical. A persistent and large quantity of NO could induce nitrosative and oxidative stress, which could cause mucosal damage through an indirect reactive interaction with biological molecules. Compounds that scavenge free radicals and elevate the level of superoxide enzymes could reduce NO effectiveness by shortening its half-life (Mascolo et al., 1996).

1.5.7 $\alpha_2$ adrenergic receptors in gastrointestinal tract:

Activation of the sympathetic innervations of the intestines results in inhibition of peristaltic activity and a reduction in tone (Ruwart et al., 1990). This inhibitory effect is mediated mainly by $\alpha_2$ adrenoceptors. Activation of the pre-junctional $\alpha_2$ adrenoceptors on parasympathetic terminals also may play an important role in the inhibitory action of sympathetic nerve stimulation of gastrointestinal motility by acetylcholine release. The sympathetic nervous system also controls the balance between absorption and secretion in the ileum through activation of mucosal $\alpha_2$ adrenoceptors. Stimulation of these receptors in the ileum results in a decrease in ion fluxes, consistent with the ability of $\alpha_2$ adrenoceptor agonists to inhibit intestinal fluid secretion (Mbagwu et al., 2008, Berthelsen et al., 1977). This is in view of the fact that adrenergic agonists with actions at $\alpha_2$ receptors can promote fluid and electrolyte absorption (Burks, 1991). Adrenergic agonists stimulate sodium and fluid absorptions via a reduction in intracellular cyclic adenosine monophosphate. They also reportedly have antimotility effects (Bart et al., 1995, Field et al., 1973).
1.5.8 Muscarinic receptors and ganglionic (nicotinic) receptors in gastrointestinal tract:

The chemical compound acetylcholine (Ach) is a neurotransmitter in both the peripheral nervous system (PNS) and central nervous system (CNS) in many organisms including humans. Acetylcholine is one of many neurotransmitters in the autonomic nervous system (ANS) and the only neurotransmitter used in the motor division of the somatic nervous system (sensory neurons use glutamate and various peptides at their synapses). Acetylcholine is also the principal neurotransmitter in all autonomic ganglia (Kim et al., 2003, Valiollah et al., 2000).

There are two main classes of acetylcholine receptor (AChR), muscarinic acetylcholine receptors (mAChR) and nicotinic acetylcholine receptors (nAChR). They are named for the ligands used to activate the receptors (Kim et al., 2003).

Muscarinic receptors:

Muscarinic receptors are metabotropic, and affect neurons over a longer time frame. They are stimulated by muscarine and acetylcholine, and blocked by atropine. Muscarinic receptors are found in both the central nervous system and the peripheral nervous system, in heart, lungs, upper GI tract and sweat glands (Gilman et al., 1996).

Acetylcholine is a neurotransmitter released by the parasympathetic nervous system, mediates its action in the gut by stimulation of M₃ muscarinic receptor subtypes. Through this mechanism acetylcholine plays an important physiological role to regulate the peristaltic movements of the gut (Gilani et al., 2005).

Nicotinic receptors:

Nicotinic AChRs are ionotropic receptors permeable to sodium, potassium, and chloride ions. They are stimulated by nicotine and acetylcholine. They are of two main types, muscle type and neuronal type. The former can be selectively blocked by curare and the latter by hexamethonium. The main location of nicotinic AChRs is on muscle end plates, autonomic ganglia (both sympathetic and parasympathetic), and in the CNS (Jing et al., 2009, Gilani et al., 2000).
GI secretory and motor functions are regulated by enteric nervous system. Stimulation of enteric cholinergic neurons within the gut wall as well as those originating in the vagus increases intestinal motility by promoting peristalsis (Gilani et al., 1997).

1.5.9 Histamine receptors in gastrointestinal tract:
Histamine occurs throughout the gastrointestinal tract, in enterochromaffin like cells, restricted to the fundic mucosa of the stomach, mast cells and nerves. Histamine is actively produced and released in enterochromaffin like (ECL) cells, rich in the synthesis enzyme, histidine decarboxylase (HDC), while it is mainly stored in mast cells (Shi et al., 2001).

Histamine regulates multiple functions at the gastrointestinal level. Contraction of intestinal smooth muscle is described as one of the best characterized responses mediated by H1 receptors. Throughout the gastrointestinal tract, contractile effects are also exerted on vascular smooth muscle and on endothelial cells, this latter resulting in an increase in vascular permeability. H2 receptors, located on parietal cells, are potent stimulants of gastric acid secretion. The role of H3 and H4 receptors is less well defined. Prevention of acute gastric injury, stimulation of mucus production and increase in gastric epithelial cell proliferation appear to be regulated by H3 receptors. Antagonists of H4 receptor have been recently shown to reduce tissue damage and inflammation in colitis, suggesting a role of the receptor in gut inflammation (Sharif et al., 1994, Arul et al., 2004).

1.6 Dysfunctions causing diarrhoea

Three major categories of dysfunctions can be distinguished (Samuel et al., 2007):

- Osmotic retardation of water absorption
- Abnormal electrolyte and water transport
- Disorders of transit

1.6.1 Osmotic retardation of water absorption

1.6.1.1 Overload

Intakes in excess of capacity cause diarrhoea. The presence of certain unabsorbed dietary components in the bowel constitutes an abnormal osmotic load. When certain substances cannot be absorbed in to the blood stream, they remain in the intestine. These substances cause excessive amounts of water to remain in the stool, leading to diarrhoea specifically
called osmotic diarrhoea. Certain foods (some beans and fruits), hexitol, sorbitol and mannitol (used as sugar substitutes in diabetic foods, candy and chewing gum) can also cause osmotic diarrhoea. Also lactase deficiency can lead to osmotic diarrhoea. Lactase is an enzyme normally found in the small intestine that converts milk sugar (lactose) to glucose and galactose so that it can be absorbed into the blood stream. When people with lactase deficiency drink milk or dairy products, it causes osmotic diarrhoea because lactase is not converted to glucose and galactose it accumulates in the intestine. The severity of the osmotic diarrhoea depends on how much of the osmotic substance is consumed (Alam et al., 1999).

1.6.1.2 Malabsorption

Malabsorption of carbohydrate, protein and fat due to different gastrointestinal disease cause diarrhoea. In generalized malabsorption, fats left in the large intestine because of malabsorption cause secretory diarrhoea. Carbohydrate malabsorption occurs in primary disorders of digestion (lactase deficiency), hereditary disorders of monosaccharides transport (glucose, galactose malabsorption). Malabsorption of protein is a frequent cause of diarrhoea. A rare congenital deficiency of the mucosal enzyme enterokinase results in incomplete activation of trypsinogen and leads to protein maldigestion, malabsorption and diarrhoea (Bowman et al., 1980).

1.6.2 Abnormal electrolyte and water transport:

Small and large intestine sometime secrete salts (especially sodium chloride) and water into the stools resulting in diarrhoea called secretory diarrhoea. Certain toxins such as the toxin produced in the cholera infection and those produced in other infectious diarrhoea can cause these secretions. The diarrhoea can be massive more than a quart an hour in cholera. Other substances that cause salt and water secretion include certain laxatives such as castor oil. Certain tumors such as carcinoid, gastrinoma and vipoma also can cause secretory diarrhoea (Berkow et al., 1997).

1.6.2.1 Bacterial diarrhoea:

Bacterial overgrowth (the growth of normal intestinal bacteria in abnormally large numbers or the growth of bacteria normally not found in the intestines) can lead to diarrhoea. Normal intestinal bacteria play an important role in digestion. Thus, any disruption of the intestinal bacteria can cause diarrhoea.
Bacterial enteritis involves two separate pathogenesis for a wide variety of bacterial diarrhoea (Das et al., 2001, Rang et al., 2003):

1) Elaboration of filterable enterotoxins without mucosal damage.

2) Mucosal injury by direct penetration.

1.6.2.2 Bile acids:

Dihydroxy bile acids inhibit water absorption reversibly in the canine colon and provide secretion in the human colon without producing morphological damage. This effect is independent of conjugation, is concentration related and is specific for dihydroxy compounds. Dihydroxy bile acids and their conjugates also provoke secretion in the jejunum (Waugh et al., 2001, Brunton et al., 2000).

1.6.2.3 Fatty acids:

Fatty acids appear to induce diarrhoea by impairment of sodium and water absorption. Ricinolic acid (active principal of castor oil) can be considered as a representative compound. This hydroxyl fatty acid alters intestinal motility increases mucus secretion, produces “chemical gastroenteritis” and also decreases sodium transport in vitro. Bile acid malabsorption can produce steatorrhea. Bile acids inhibit colonic water reabsorption which is responsible for the diarrhoea of ileal resection (Bhende et al., 1969).

1.6.2.4 Humoral and chemical factors:

Prostaglandins when administered by arterial infusion provoke secretion of isotonic fluid in to the lumen of intestinal loops also stimulate secretion of mucosal adenyl cyclase. Other gastrointestinal hormones such as gastrin, secretin, cholecystokinin and glucagon are also capable of modifiying water absorption in man and experimental animals. Hypersecretion of gastric juice is associated with diarrhoea in many instances of the Zollinger Ellison syndrome. Changes in ileal function may aggrevate diarrhoea where an acid pH has been shown to impair vitamin B₁₂ and water absorption. Gastrin may impair mucosal transport of electrolyte and water directly and may also influence intestinal motility. Among other chemical agents that modify water transport are certain absorbable cathartics, some diuretics and antidiuretic hormones (Bhende et al., 1969, Brunton et al., 2000).
1.6.2.5 Miscellaneous diseases:

When the lining of the large intestine becomes inflamed, ulcerated or engorged, it releases proteins, blood, mucus and other fluids which increase the bulk and fluid content of the stool resulting in exudative diarrhoea. This type of diarrhoea can be caused by many diseases including ulcerative colitis, Chron’s disease (regional enteritis), tuberculosis, lymphoma and cancer. When the lining of the rectum affected the person often feels an urgent need to defecate and has frequent bowel movements because the inflamed rectum is more sensitive to distension by stools (Bowman et al., 1980).

1.6.3 Disorders of transit

Altered intestinal transit can cause diarrhoea. In order to allow normal absorption, the chyme must be mixed, properly digested and adequately exposed to the mucosal surface for a critical minimum time. To have normal consistency it must remain in the large intestine for a certain amount of time. Stools that leave large intestine too quickly are watery while stools that stay too long are hard and dry. Many conditions and treatments can decrease the amount of time that stools stays in the large intestine including hyperthyroidism, surgical removal of part of intestine, large intestine or stomach, treatment for ulcers in which the vagus nerve is cut, bypass of part of the intestine and drugs such as antacids and laxatives containing magnesium, prostaglandins, serotonin and caffeine (Bennett, 1992).

1.6.3.1 Hypomotility:

Normal intestinal motor activity is an important determinant of the relative sterility of the small bowel. The consequences of hypomotility relate to bacterial overgrowth in the small bowel. Diarrhoea has been related to excess of fat in the lumen of the small bowel and the colon, possibly mediated by hydroxyl fatty acids. An inhibitory action of free bile acids on jejuna water absorption and changes in jejuna morphology produced by unconjugated bile acids could also be responsible (Burks, 1987, Bennett, 1992).

1.6.3.2 Hypermotility:

When rapid transit and malabsorption co-exit, increased volume of the lumen due to incomplete absorption may accelerate transit. Fatty acids, bile acids and humoral agents also affect the function of the intestinal smooth muscle (Bennett, 1992, Bhise et al., 2009).
1.7 Consequences of diarrhoea:

Clinical consequences of gastrointestinal infection lead to fluid loss that is extracellular fluid loss, and extensive potassium loss. Watery diarrhoea originates in the small bowel and is modified by transit through the lower ileum and colon. The consequence of acute saline loss is extracellular volume depletion which continued and unreplaced leads to hypotension, shock and death. The acute loss of fluid equally 10 – 12% of body weight (5 – 6 lit. in 50 kg person) is close to being fatal (Rang et al., 2003).

The consequence of acute bicarbonate loss is metabolic acidosis, manifested by deep, rapid breathing and in severe cases, disorientation and hypotension. The consequences of extensive potassium loss are cardiac arrhythmia, muscular weakness and ileus, obstruction of the bowel with severe colic pain, vomiting, fever and dehydration. Pathological changes in sodium chloride deficiency shows loss of the extracellular fluid with slight depletion of the fluid in the plasma compartment. There is no disturbance of osmotic equilibrium between the extracellular and intracellular fluid compartments. Water may flow into the cells (cellular hydration) because of the greater concentration of sodium in them and aggravate the depletion of the extracellular fluid. These changes decrease the venous return and the cardiac output and cause a fall in the arterial pressure. The clinical manifestations are nausea, vomiting, muscular cramps, loss of weight and signs of dehydration. To compensate for the depletion of cellular potassium, sodium and hydrogen ions from the extracellular fluid enter the cells. This shift causes extracellular alkalosis.

Replacement of diarrhoeal fluid loss therefore consists of glucose saline with added bicarbonate and potassium ions in the fluid composition (Wendel et al., 2008, Katzung et al., 2001, Wagman, 1983).

Fever, toxicity, sepsis:

Many patients with diarrhoea due to invasive bacteria feel quite ill with fever, headache, myalgia, abdominal pain, malaise and tenesmus. In children and young adults with dysentery due to *Shigella bacillus* a syndrome characterized by a leukamoid response and falling haematocrit may occur as the diarrhoea improves (Alam et al., 2003).

Intestinal damage and malabsorption:

Common manifestation of intestinal damage during and after diarrhoea is intolerance to the milk sugar lactose due to loss of the intestinal enzyme lactase. This enzyme splits
lactose which can be absorbed. When the intestine fails to hydrolyse lactose, bacteria in the intestine ferment the sugar producing acid, gas and osmotically active carbon fragments (which pull more fluid to the intestine). Other sugars, fats and vitamins are also malabsorbed during and shortly after diarrhoea (Amstrong et al., 1999, Bowman et al., 1980).

Enteric blood and protein loss:

Anemia and hypoproteinemia may be serious consequences of any of the invasive diarrhoea, especially in-patients already malnourished (Harvey et al., 1976).

1.8 Classification of diarrhoea:

Diarrhoea is a symptom associated with too rapid passage of fecal material which may be with or without blood or mucus, diarrhoea with blood is usually due to known cause such as amoebic or bacillary dysentery. In all the cases of severe or prolonged diarrhoea, the rapid and complete correction of water and electrolyte loss is one of the utmost importance (Satoskar et al., 1997, Tetali et al., 2009).

Diarrhoea can be categorized on the basis of onset and duration (Alam et al., 2003)

a) Acute diarrhoea
b) Chronic diarrhoea

1.8.1 Acute diarrhoea (Bodhanakar et al., 2010, Prarthana et al., 2007):

According to WHO acute diarrhoea is an attack of sudden onset, which usually last few days or upto a week. It is caused by the infection of bowel. The term gastroenteritis is more frequently used to describe acute diarrhoea (Berkow et al., 1997, Harper et al., 1983).

Causes of acute diarrhoea (Park, 1995):

It may be infectious or non-infectious


a) Bacterial: *E. coli*, *Vibrio cholerae*, *Shigella species*, *Salmonella species*, *Staphylococcus aureus*, *Clostridiaspecies*, *campylobacter jejuni*. 
b) Viral: *Rota virus*, *Astro virus*, *Calci virus*, *Corona virus*.

c) Protozoal: *Entamoebica histolytica*, *giardia lambia*.

d) Helminthes: *Trichuris trichura*, *Strongiloids stercoalis*.

Acute infectious diarrhoea is a major cause of protein calorie malnutrition and dehydration, the latter is condition in which water content of the body is reduced because water output exceeds water intake and body is in negative water balance. Contributing factors of infectious diarrhoea include inadequate sewage disposal and water supplies, lack of refrigeration, overcrowding and lack of personnel hygiene, poverty, lack of personnel hygiene, lack of access to health care and lack of education as shown in Table 3 and 4 (Harison, 1997, Casburn-Jones et al., 2004, Das et al., 2001).
Table 3. Pathophysiological mechanisms and causes of diarrhoea

<table>
<thead>
<tr>
<th>Pathophysiological mechanism</th>
<th>Examples</th>
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<tbody>
<tr>
<td>I) Toxin production</td>
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<tr>
<td>Preformed toxin</td>
<td><em>Bacillus cereus</em></td>
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<td></td>
<td><em>Clostridium species</em></td>
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<tr>
<td></td>
<td><em>S. aureus</em></td>
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<td>Enterotoxin</td>
<td><em>Aeronomas species</em></td>
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<td></td>
<td><em>Vibrio cholera</em></td>
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<tr>
<td>Cytotoxin</td>
<td><em>Clostridium difficile</em></td>
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<td>II) Enteroadherence</td>
<td><em>Cryptosporidiosis</em></td>
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<td></td>
<td><em>Helminthis</em></td>
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<td></td>
<td><em>Giardia</em></td>
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<td>III) Mucosal invasion</td>
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<td>Minimal</td>
<td><em>Norwalk virus</em></td>
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<td></td>
<td><em>Rota virus</em></td>
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<td></td>
<td><em>Adeno virus</em></td>
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<td></td>
<td><em>Astro virus</em></td>
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<td></td>
<td><em>Calci virus</em></td>
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<td></td>
<td><em>Corona virus</em></td>
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<tr>
<td>Viable</td>
<td><em>Aeronomas species</em></td>
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<td></td>
<td><em>Camphylobacter species</em></td>
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<tr>
<td></td>
<td><em>Salmonella species</em></td>
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<tr>
<td>Severe</td>
<td><em>E. histolytica</em></td>
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<td></td>
<td><em>Shigella species</em></td>
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<td>IV) Systemic infection</td>
<td><em>Viral hepatitis</em></td>
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<tr>
<td></td>
<td><em>Rocky mountain</em></td>
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<tr>
<td></td>
<td><em>Spotted fever</em></td>
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</tbody>
</table>

Most infectious diarrhoea are acquired by fecal oral transmission by way of water or food contaminated by human waste as a result of poor sewage systems or by wild or domestic animal faeces in inadequately purified water (Bhan., 2000).

Clinical features:
Nauseas, vomiting, abdominal pain, fever and diarrhoea which may be watery, malabsorptive, or bloody depending on the specific pathogen (Satoskar et al., 1997, Das et al., 2001).

**Table 4. Pathogens frequently identified in children with acute diarrhoea.**

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Percent of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viruses:</strong></td>
<td></td>
</tr>
<tr>
<td><em>Rota virus</em></td>
<td>15 – 25</td>
</tr>
<tr>
<td><strong>Bacteria:</strong></td>
<td></td>
</tr>
<tr>
<td>Enterotoxigenic</td>
<td>10 – 20</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td></td>
</tr>
<tr>
<td><em>Shigella</em></td>
<td>5 – 15</td>
</tr>
<tr>
<td><em>Campylobacter</em></td>
<td>10 – 15</td>
</tr>
<tr>
<td><em>Vibrio cholera</em></td>
<td>5 – 10</td>
</tr>
<tr>
<td><em>Salmonell</em></td>
<td>1 – 5</td>
</tr>
<tr>
<td>Enteropathogenic</td>
<td>1 – 5</td>
</tr>
<tr>
<td><strong>Protozoans:</strong></td>
<td></td>
</tr>
<tr>
<td><em>Cryptosporidium</em></td>
<td>20 – 30</td>
</tr>
</tbody>
</table>

1.8.1.2 Acute non infectious diarrhoea:

1.8.1.2.1 Drug induced diarrhoea

Imbalance of opposing cholinergic and adrenergic inervation of the gut may result in diarrhoea. Antihypertensive agents like reserpine and adrenergic neuron blocking agents act by reducing adrenergically mediated relaxation. Anticholinesterase drug neostigmine enhances the cholinergically mediated contraction. Ergot alkaloids and their derivative produce diarrhoea. Beside these following drugs are responsible for diarrhoea (Bernstock et al., 1989, Alam et al., 2003).

a) Gastrointestinal drugs (magnesium containing antacids, laxative)

b) Cardiac drugs (digitalis, quinine and procainamide)

c) β- blockers

d) Antibiotics (clindamycin, ampicillin, cephalosporine)

e) Chemotherapeutic agents
f) Hypolipidemic agents

g) Others (theophylline, thyroid hormones)

1.8.1.2.2 Spurious diarrhoea:

Diarrhoea may alternate with constipation. This may be a result of the irritation of the mucous membrane by impacted hard faeces (Farthing, 2000).

1.8.1.2.3 Psychological diarrhoea:

Emotional strains or stress in adults and fright in children could also cause diarrhoea (Larry, 2001).

1.8.1.2.4 Allergic diarrhoea:

Allergies to common foods such as milk, wheat, eggs and sea-foods may contribute to diarrhoea (Farthing, 2000).

1.8.1.2.5 Traveller’s diarrhoea:

Tourist visiting foreign countries with warm climate and poor sanitation can acquire ETEC (Enterotoxigenic E. coli) by eating contaminated foods such as fruits, vegetables, sea-food, raw meat, water and ice cubes. Toxins produced by ETEC cause the sudden onset of diarrhoea, abdominal cramps, nausea and sometimes vomiting (Ramzan, 2001).

1.8.1.3 Acute bloody diarrhoea:

When the stool contains blood and mucus it is called acute bloody diarrhoea or dysentery. The blood is trace of an invasion of bowel tissue (Bhende et al., 1969).

Causes:

It is caused by microorganisms that thrive in the intestine of infected individuals. Most common are amoebic dysentery caused by amoeba and bacillary dysentery caused by bacteria. It may be caused by Shigella species, Entamoeba histolytica, Escherchia coli, Vibrio parahaemolyticus and Salmonella species. Of these Shigella species are responsible for majority of the episodes of acute bloody diarrhoea in children. Shigela dysentery type 1 is the only species responsible for epidemics (Fine, 1998).
Symptoms:
It is usually accompanied by diarrhoea with blood and pus in the stool, tenesmus, abdominal cramps, anorexia and fever.

The infection is spread from person to person through infected excrement that contaminates food or water and also spread by houseflies, which feed on faeces as well as on human foods. It is a common tropical disease and can occur wherever human excrement is not disposed off in a sanitary manner (Lawrence et al., 1997).

1.8.2 Chronic diarrhoea (Bodhanakar et al., 2010):

Diarrhoea that persists for week or months, whether constant or intermittent is considered as chronic diarrhoea and it may represent a manifestation of an underlying serious illness (Yao-Zong et al., 2004). Severe chronic diarrhoea is produced by various specific infections, ulcerative colitis and neoplasia of the colon, malabsorption, thyrotoxicosis, neurotic disorders, carcinoid syndrome and certain drugs. It is categorised as follows (Kruszka et al., 2002, Harison, 1997, Thapar et al., 2004):

1.8.2.1 Inflammatory diarrhoea:

It occurs when there is damage to the mucosal lining or brush border, which leads to a passive loss of protein rich fluids and a decreased ability to absorb these fluids. It can be caused by bacterial infections, viral infections, parasitic infections or autoimmune problems such as inflammatory bowel diseases.

Mechanisms:
Mucosal and submucosal inflammation, epithelium, in some cases impaired intestinal absorption and excessive secretion.

Clinical features:
Fever, abdominal pain, blood and/or leukocytes in the stool.

Examples:
Ulcerative colitis, Crohn’s disease, radition, enterocolitis, Eosinophilic gastroenteritis, infections associated with AIDS (Harison, 1997, Bodhanakar et al., 2010).
1.8.2.2 Osmotic diarrhoea:

Osmotic diarrhoea occurs when too much water is drawn into the bowel. This can be the results of maldigestion, in which the nutrients are left in the lumen to pull in water. It can also be caused by osmotic laxatives in healthy individuals. Too much magnesium or vitamin C or undigested lactose can produce osmotic diarrhoea and distension of bowel. Sugar alcohols such as sorbitol (often found in sugar free foods) are difficult for the body to absorb and, it’s large amounts, may lead to osmotic diarrhoea.

Mechanisms: Non-digested intraluminal solute.
Osmotic diarrhoea is produced when an orally ingested solute is not fully absorbed in the intestine and thereby exerts an osmotic force that draws fluid into the intestinal lumen. The increased luminal fluid volume overwhelms the capacity of the colon for reabsorption. The nonabsorbed solute can be a maldigested or malabsorbed nutrient or drug (Bodhanakar et al., 2010).

Clinical features:
Improvement of diarrhoea with fasting, bulky, greasy, fouling stools, weight loss, nutrient deficiencies and osmotic gap in the fecal water.

Examples:

1.8.2.3 Secretory diarrhoea:

Secretory diarrhoea means that there is an increase in the active secretion or there is an inhibition of absorption. There is little to no structural damage. The most common cause of this type of diarrhoea is a cholera toxin that stimulates the secretion of anions, especially chloride ions. Therefore, to maintain a charge balance in the lumen, sodium is carried with it, along with water.

Mechanism:
Excessive secretion of electrolytes.

Clinical features:
Watery diarrhoea persists with fasting, dehydration, other systemic effects of hormones, absence of osmotic gap in fecal water.
Examples:
Carcinoid syndrome, Zollinger-Ellison syndrome, vasoactive intestinal peptide secreting pancreatic adenomas and medullary carcinoma of thyroid, villous adenoma of rectum, microscopic colitis and cholerrheic diarrhoea (Chatterjee, 1984, Bodhanakar et al., 2010).

1.8.2.4 Altered intestinal motility:

Mechanisms:
Rapid transit, in some cases associated with bacterial overgrowth.

Clinical features:
Alternating diarrhoea and constipation, neurologic symptoms, bladder involvement.

Examples:
Irritable bowel syndrome, fecal impaction and neurologic diseases (Chatterjee, 1984).

1.8.2.5 Factitious diarrhoea:

Mechanism:
Self induced

Clinical features:
Usually occurs in women, watery diarrhoea with hypokalemic, weakness and oedema.

Examples:

Diarrhoea is generally viewed as a symptom of an underlying pathologic condition rather than a disease entity itself. Distinction must be made between acute diarrhoea and chronic diarrhoea. As significant differences exist between the two conditions with respect to etiology, potential danger to the patient and offered treatment. The major danger of severe acute diarrhoea is that it can quickly lead to dehydration and electrolyte imbalances, especially in pediatrics patients. Most episodes of acute diarrhoea are self-limiting, that is once the offending organism, food or medications are removed the symptoms subside (Attia et al., 2004, Brunton, 2000, Bhise et al., 2009).
1.9 Diarrhoea as a symptom of various disorders of gastrointestinal tract.

Diarrhoea an extremely common symptom is caused by wide range of conditions and it forms a symptom of several serious diseases.

1.9.1 Gastroenteritis:

Enteritis means infection caused either by a virus or by a bacteria in the intestinal tract. The term regional enteritis is used sometimes because the disease most often involves the terminal ileum, even though any part of the digestive tract can be involved. It is extensively in the entire large intestine and the distal end of the ileum. The mucosa become extensively irritated and its rate of secretion become greatly enhanced. In addition the motility of the wall usually increases manifold. As a result large quantities of fluid are made available for washing the infectious agent towards anus and at the same time strong propulsive movements propel this fluid forward. Regional enteritis is also called as Crohn’s disease (Bowman, 1980).

Gastroenteritis is the general term for group of conditions that are usually caused by infections and produce symptoms such as loss of appetite, nausea, vomiting, intermittent bloody diarrhoea, discomfort in abdomen and weakness. Later stages are marked by fever, increase bouts of diarrhoea, with resultant loss of weight and sharp lower abdominal pain on the right side (Guyton et al., 1996).

In the diarrhoea, caused by cholera toxin directly stimulates excessive secretion of electrolytes and fluid from the crypts of liberkuhn in the distal ileum and colon. The amount can be 10 - 12 liter per day and the colon can usually reabsorb a maximum of only 6 liter per day. Thus, loss of fluid and electrolytes can be so debilitating within a day or so that death ensues. *Vibrio cholera* affects the small intestine without inducing any histological abnormality of the mucosa. In many cases diarrhoeal stools are watery but if blood is visible in the stools, condition is called dysentery (Fine, 1998).

1.9.2 Crohn’s disease:

Crohn’s disease also called as regional enteritis or regional ileitis is an inflammatory disease usually affecting child and adults. It is characterized by abdominal cramps, diarrhoea, loss of weight, fever, anemia and fistulas. Colonic disease causes rectal bleeding more than ileal disease.
Common pattern of Crohn’s disease:

Symptoms differ among people with Crohn’s disease, but there are four common patterns:

1. Inflammation with pain and tenderness in the right lower part of the abdomen.
2. Recurring acute intestinal obstructions that cause severe painful spasms of the intestinal wall, swelling of the abdomen, constipation and vomiting.
3. Inflammation and chronic partial intestinal obstruction causing malnutrition and chronic debility.
4. Abnormal channels (fistulas) and pus filled pockets of infection (abscesses) that often cause fever, painful masses in the abdomen and severe weight loss (Satoskar et al., 1997).

1.9.3 Colitis (Ulcerative colitis):

Colitis is an inflammatory condition of the colon of uncertain origin and often chronic. The inflammation can cause spasms that damage the colon or can lead to bleeding ulcers that may be fatal.

In milder form colitis first appears as diarrhoea with red bloody streaks. As the disease process advances the diarrhoeal episodes become more frequent. More blood and mucus are present in the faeces. These are combined with abdominal pain, nausea and vomiting. Anemia results due to loss of blood. If there are ulcers craters in the mucosa the disease is called ulcerative colitis.

Ulcerative colitis is a chronic inflammatory disease involving primarily the mucosa of the colon. Extensive areas of the large intestine become inflamed and ulcerated. The onset of ulcerative colitis may be insidious with vague abdominal discomfort, anorexia or a gradual change in bowel habits.

Actually both ulcerative colitis and Crohn’s disease are included under chronic inflammatory bowel disease and both are of uncertain etiology (Guyton et al., 1996, Satoskar et al., 1997).

1.9.4 Psychogenic diarrhoea:

Diarrhoea also accompanies with nervous tension. This type of diarrhoea refers to emotional or psychogenic diarrhoea is caused by the excessive stimulation of the
parasympathetic nervous system which greatly excites motility and secretion of mucous in the distal colon. These two effects caused marked diarrhoea (Berkow et al., 1997).

1.9.5 Pancreatic diarrhoea:

It is a form occasionally found in the children of imperfect development in consequences of failure by the pancreas to secrete its proper digestive fluid. Diarrhoea may also be a symptom of ulceration of gangrene of bowels and is then associated with the passage of blood and mucus or even of shreds of membrane produced by the destruction of the inner surface of the bowels (Guyton et al., 1996).

1.10 Diarrhoea as an adverse effect:

According to FDA, adverse drug effect is defined as noxious, unintended effect that occurs at doses normally used in man for prophylaxis, diagnosis or therapy of the disease (Tripathi, 1999, Razina et al., 2001, Harvey et al., 1976).

Antibiotic induced diarrhoea and colitis have become a serious concern in antibiotic therapy. Antibiotics like chlortetracycline, chloramphenicol, ampicillin, amoxicillin and many others including clindamycin produce colitis called as antibiotic associated colitis. The condition is always accompanied by diarrhoea. Diarrhoea is a much more common side effect of antibiotic therapy than in colitis (Bowman et al., 1980).

Broad spectrum antibiotics produce greater suppression of a bacterial flora because of their wide range of antimicrobial activity. With suppression of normal non-pathogenic bacterial flora, drug resistant organisms or fungi (Candida albicans) can more easily initiate superinfection in gastrointestinal tract. Symptoms of gastrointestinal superinfection usually include oral burning, stomatitis, glossitis, cheilosis, diarrhoea, enteritis and colitis.

Adrenergic neuron blocking drugs (guanithine, debrisoquine) reduce the blood pressure by preventing the release of noradrenalin from postganglionic sympathtic nerves. Diarrhoea is a common side effect of treatment with these drugs and is presumably due to loss of adrenergically mediated inhibition of intestinal activity. In some patients, the diarrhoea can occur with such urgency and violence that the use of the drugs must be discontinued (Harvey et al., 1976).
Cardiac glycoside toxicity leads to diarrhoea accompanied by abdominal pain. It is the first indication of overdose. It also produces hemorrhage necrotic lesions of the whole gastrointestinal tract (Tripathi, 1999).

Prostaglandins (PGE$_2$ and PGE$_{2α}$) enhance gastrointestinal motility, diarrhoea and abdominal cramps are common side effects in patients given intravenous prostaglandin.

Anthelmentic drugs (bithinol, niclosamide) are also responsible for diarrhoea as a side effect (Satoskar et al., 1997).

Irritant purgative castor oil produce diarrhoea due to stimulation of peristalsis either by an irritant action on intestinal mucosa or by acting directly on sensory nerve ending or by facilitating reflex action in the myenteric plexus. Magnesium compounds used as antacids also act as purgatives and may produce diarrhoea (Atta et al., 2005, Mujumdar et al., 2000).

Sulphonylureas which are hypoglycemic agents (tolbutamide, tolazamide, chlorpropamide and glibenclamide produce the common side effects like anorexia, epigastric discomfort, nausea, vomiting or diarrhoea in 3 – 5% of patients (Bowman et al., 1980).

1.11 Treatment of diarrhoea

Diarrhoea can be caused by a variety of conditions varying from infections and allergy to emotional disturbances.

Treatment of diarrhoea consist of (Satoskar et al., 1997):

- Specific treatment
- Treatment of dehydration
- Symptomatic and protective treatment

1.11.1 Specific treatment

Depending upon the cause of the diarrhoea treatment can be done. Diarrhoea resulting from the presence of an infectious organism may best be treated by use of an appropriate antibiotic. Drug induced diarrhoea can often be corrected by simply discontinuing the offending drug. Successful treatment of secondary disease state associated with diarrhoea usually reduces or eliminates the accompanying episodes of diarrhoea. Treatment of infectious diarrhoea may first involve antimicrobials and treatment of chronic
inflammatory bowel disease first involves anti-inflammatory agents. Treatment of osmotic diarrhoea first involves avoidance of the offending osmotic agents (lactose in lactase intolerance) or correction of the underlying malabsorptive process (pancreatic enzyme for the pancreatic insufficiency, gluten-free diet for gluten sensitive enteropathy). Treatment of secretory diarrhoea (carcinoid syndrome) is likely to require hormonal therapy (Satoskar et al., 1997, Feldman et al., 1981, Burks, 1991).

A number of drugs are now available to treat the bacterial and protozoal infections but no specific antiviral agent is available at present for known or presumed viral diarrhoea (Wagman et al., 1983).

### 1.11.2 Non specific treatment

As acute onset diarrhoea is usually self limiting due to its infectious origin the treatment of diarrhoea is generally non specific. It includes (Satoskar et al., 1997):

- Treatment of dehydration
- Symptomatic and protective treatment

#### 1.11.2.1 Treatment of dehydration:

The main risk in acute diarrhoea is dehydration. Thus the common therapies are aimed at reducing fecal water loss and replacing the fluid and electrolytes. Oral rehydration therapy with glucose electrolyte solution began soon after the onset of diarrhoea. It is an effective component of therapy regardless of the origin of the diarrhoea. It is sufficient to treat the vast majority of the episodes of watery diarrhoea. As a simple, effective, cheap and readily administered therapy for a potentially lethal condition, oral rehydration therapy must rank as a major advance in dehydration therapy. It is effective because glucose coupled sodium transport continues during diarrhoea and so replacement of water and electrolyte losses in the stools (Nizami et al., 1996, Claudia et al 2006).
1.11.2.1.1 Oral rehydration salts (ORS):

The WHO/UNICEF recommended formulation is:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium chloride</td>
<td>2.6 g/lit</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>1.5 g/lit</td>
</tr>
<tr>
<td>Sodium citrate</td>
<td>2.9 g/lit</td>
</tr>
<tr>
<td>Anhydrous glucose</td>
<td>13.5 g/lit</td>
</tr>
</tbody>
</table>

This provides sodium 75 m. mol., potassium 20 m. mol., chloride 65 m. mol., citrate 10 m. mol., and glucose 75 m. mol.

The higher sodium content of WHO/UNICEF formulation is based on sodium concentrations in diarrhoeal stools, but low sodium and high glucose formulation may be preferred for infants for their fecal losses of sodium are less (Bodhanakar et al., 2010).

The glucose may be replaced by another substrate (glycine ORS, rice power ORS). Almost every household in the world can find the essential component of an effective oral rehydration mixture as cereals and salt. Fluid and electrolyte depletion is especially dangerous in children for whom hospitalization and intravenous replacement may be needed.

Oral rehydration fluid vary in sodium and sugar content and are must be taken in choice so as to avoid hyponatremia due to low sodium content or osmotic diarrhoea caused by high sugar content (Alam et al., 1999, Bhattacharya, 1994).

1.11.2.2 Symptomatic and protective treatment:

Infections in which diarrhoea is a prominent sign and for which there is specific treatment include giardiasis, amoebic dysentery and typhoid. Other infection in which there is severe diarrhoea but for which specific irradiation of the causative organism cannot be achieved include cholera, viral gastroenteritis. In these cases, treatment is symptomatic (Hilbrand et al., 1996).

Symptomatic treatment is usually aimed at reducing the discomfort and inconvenience of frequent bowel movements. It includes the use of

i) Systemically acting drugs
ii) Drugs acting on GI motility

Protective treatment includes the use of gastrointestinal protectives. Agents useful against diarrhoea may (Alam et al., 2003):

- Act locally by providing a protective coating of the gut.
- Decrease the propulsion of the intestinal contents.
- Act on intestinal microcirculation and lowering the hydrostatic pressure in favour of water absorption
- Act directly on mucosal transport processes thus reducing fluid accumulation in the intestinal lumen.

1.11.2.2.1 Systemic antidiarrhoeals:

The systemic antidiarrhoeals comprise the opiates, principally camphorated tincture of opium (paregoric), anticholinergic and two opiates (meperidine) derivatives, diphenoxylate and loperamide that are claimed to have a less CNS effects and reduced addiction liabilities compared to other opiates (Murphy et al., 1993, ).

1.11.2.2.1.1 Opiates

Main opiates used in diarrhoea are codeine, diphenoxylate and loperamide. Although codeine and tincture of opium have been used for many years to treat diarrhoea, the synthetic opioids, diphenoxylate and loperamide are now preferred because it penetrate poorly into the CNS and can produce antidiarrhoeal effects at doses that produce less central effects (Bowman et al., 1980).

Mode of action:

Opioid agonist can affect gastrointestinal function via both central and peripheral sites of action. They act at $\mu$ and $\delta$ receptor in the gastrointestinal tract to alter both motility and secretion. Activation of both receptors may lead to enhanced sodium chloride and water absorption. It also acts on the intestinal epithelial cells and smooth muscle cells. Thus, opioids slow intestinal transit (permitting more time for absorption) and reduce secretion and stimulate absorption. The net effect is a reduction in the quantity of fluid presented to the large intestine by the small intestine so that the absorptive capacity of the colon is not overwhelmed. Thus, opioids act by diminishing both biliary and pancreatic secretions and increasing the resting tone of small intestine (Xiao et al., 2009, Angelo et al., 1999).
Contradictions:
Chronic ulcerative colitis, acute bacillary or amoebic dysentery.

Opiate withdrawal symptoms:
It includes severe abdominal cramps, hypokalemia. Severe diarrhoea may result in serious electrolyte and acid base imbalance. Dehydration hypochloremic alkalosis is to be expected (Satoskar et al., 1997, Pasricha 2006).

1.11.2.2.1.1 Diphenoxylate hydrochloride with atropine sulphate

Marketed products:

Preparations:
Tablets: 2.5 mg diphenoxylate hydrochloride and 0.025 mg atropine sulphate.

Liquid: 2.5 mg diphenoxylate hydrochloride and 0.025 mg atropine sulphate per 5 ml

Indications:
Adjunctive therapy in the treatment of diarrhoea

Mechanisms:
It slows intestinal motility by an action on gastrointestinal smooth muscles ($\mu$ receptors in gastrointestinal tract) it may exert an antisecretoy action as well. Little or no analgesic effect (Andrew et al., 2003).

Fate:
Well absorbed when taken orally. Onset of action is 30 – 60 min. It is rapidly and extensively metabolized by ester hydrolysis to dipenoxylic acid which is biologically active and the major circulating metabolites are excreted over 4 days in the urine and 49% in the faeces. Serum half life of the parent drug is about 2.5 hours, elimination half life is approximately 12 – 14 hours.

Average daily doses
2 yr. – 5 yr.: 2 mg 3 times a day.
5 yr. – 8 yr.: 2 mg 4 times a day.
8 yr. – 12 yr.: 2 mg 5 times a day.
Significant adverse reactions (usually with larger doses):
Abnormal discomfort, vomiting, anorexia, headache, dizziness, restlessness, depression, malaise, numbness of extremities, pruritis, urticaria, angioneurrotic oedema, paralytic ileus, toxic megacolon, respiratory depression. Atropine side effects are common in children and include flushing, diminished secretions, hyperthermia, tachycardia, urinary retention, hypotonia, miosis and nystagmus blurred vision.

Contraindications:
Hypersensitivity to diphenoxylate or atropine, obstructive jaundice, diarrhoea associated with pseudomembranous enterocolitis following therapy with antibiotics. Children under two years because of less margin of safety (Gilman et al., 1996).

Drug interactions:
Chemical structure is similar to that of meperidine, concurrent use with monoamine oxidases inhibitors may precipitate hypersensitive crises. Diphenoxylate may potentiate depressant action of barbiturates, tranquillizers and alcohol.

Adverse reactions:
Atropine effects such as dryness of skin and mucous membranes, flushing, hyperthermia, tachycardia and urinary retention may occur.

Other reported adverse reactions are as follows:
Gasrointestinal tract: anorexia, nausea, vomiting, abdominal discomfort, paralytic ileus and toxic megacolon.
Allergic: pruritis, swelling of gums, angioneurotic oedema and giant urticaria.
Central nervous system: dizziness, drowsiness, sedation, headache, malaise, lethargic, restlessness, euphoria, depression, respiratory depression, coma and numbness of extremities (Pasaricha 2006, Andrew et al., 2003).

1.11.2.2.1.2 Loperamide hydrochloride

Marketed product: Imodium
Capsules: 2 mg.

Indications:
Control and symptomatic relief of acute nonspecific diarrhoea associated with inflammatory bowel disease. Also indicated for reducing volume of discharge from GI tract.

Mechanisms:
It slows intestinal motility and inhibits peristalsis by a direct depressant effect on intestinal smooth muscle. Its antidiarrhoeal effect is partly due to decrease in intestinal hyperperistalsis and partly due to decrease in intestinal hypersecretion. Acts predominantly on μ receptors in the gastrointestinal tract by slowing intestinal motility and by affecting water and electrolyte movement through the bowel. Inhibits peristaltic activity by direct effect on the circular and longitudinal muscles of the intestinal wall. Loperamide prolongs transit time of intestinal contents, reduces daily fecal volume, increases the viscosity and bulk density and diminishes loss of fluid and electrolytes. Tolerance to its antidiarrhoeal effect is not seen (Bart et al. 1995, Couper, 1997, Theoderau et al., 1991).

Fate:
Well absorbed when taken orally. Onset is 30 – 60 min. and duration is 3 – 4 hr. Elimination half life is about 10 – 12 hr. Metabolized by the liver and excreted in the faeces as both unchanged drug and metabolites with small amounts in the urine.

Dose recommended:
Initial dose is 4 mg followed by 2 mg after each unformed stool. Daily dosage should not exceed 16 mg.

Common side effects:
Generally observed with prolonged therapy and includes abdominal discomfort and drowsiness.

Significant adverse reactions:
Abdominal cramps, distention, paralytic ileus, constipation, drowsiness, dizziness, dry mouth, nausea, vomiting, hypersensitivity reactions.

Contraindications:
Hypersensitivity, those in whom constipation must be avoided.

Interactions:
It may enhance the sedative effects of other central nervous depressants (Satoskar et al., 1997, Friedi et al., 1980, Andrew et al., 2003).

1.11.2.2.1.3 Opium tincture, camphorated (paregoric):

A mixture containing 0.04% anhydrous morphine, alcoholic benzoic acid, camphor and anise oil. Its antidiarrhoeal effectiveness is due to its morphine content.

Mechanisms:

Decrease gastrointestinal motility and peristalsis, reduce digestive secretions, and increase intestinal smooth muscle tone thus showing passage of intestinal contents.

Uses:

Treatment of acute diarrhoea.

Dosages:

Adults 5 – 10 ml, 4 times a day, children 0.25 ml to 0.5 ml/kg.

Significant adverse reactions:

Allergic reactions (rash, urticaria, pruritis), vomiting, dizziness, sweating and constipation.

Interactions:

Paregoric can enhance the depressive effects of alcohol, barbiturates, tranquilizers and other central nervous system depressants (Satoskar et al., 1997, Tripathi, 1999).

1.11.2.2.1.2 Anticholinergics:

They decrease gastrointestinal motility by impairing parasympathetic nerve stimulation to intestinal smooth muscle. They also act by decreasing smooth muscle tone and decreasing secretions. They are also responsible for delay in gastric emptying (Kim et al., 2003, Tripathi, 1999).

1.11.2.2.2 Locally acting antidiarrhoeals:

A large number of compounds exhibiting diverse pharmacologically effects have been employed in the treatment of diarrhoea. Locally acting antidiarrhoeals are primarily non
absorbable chemicals that act within the lumen of the gastrointestinal tract by a variety of mechanisms.

These locally acting drugs include adsorbents, antiseptics and bacterial cultures. Although they are essentially safe in recommended doses, they have not been conclusively demonstrated to be clinically effective. Since they are readily available and relatively safe, they are the most often the initial agents tried in cases of occasional, uncomplicated diarrhoea and in many instances provide sufficient relief. It includes (Satoskar et al., 1997):

1.11.2.2.2.1 Adsorbents and gastrointestinal protective:

These agents are mainly useful by virtue their ability to adsorb noxious substances, such as gases, bacteria and bacterial toxins. In addition, some of these possess an astringent action, while others protect the mucous membrane from the irritants by coating it physically. They are cheap, devoid of any adverse effects but their usefulness are limited to the treatment of mild episodes of diarrhoea. Charcoal, kaolin and pectin are used in proprietary antidiarrhoeal mixture because of their presumed ability to absorb preformed toxins responsible for some types of food poisoning.

Limitations:

The adsorptive capacity of these compounds is not selective for irritants or toxins. They may also adsorb other drugs found in the intestinal tract. Thus, adsorbents can potentially interfere with the normal absorption of many drugs and this possibly should be noted whenever an adsorbent substance is given to a patient receiving medications for other conditions (Rang et al., 2003, Satoskar et al., 1997).

The most frequently encountered adsorbents in commercial preparations are:

1.11.2.2.2.1.1 Bismuth salts:

The commonly employed bismuth salts are bismuth subcarbonate and bismuth subsalicylate. These salts have an astringent, protective and adsorbent effect. Orally they are devoid of serious toxic manifestations. They are expensive.

Bismuth subsalicylate binds toxins produced by Vibrio cholera and E. coli, an antimicrobial action have been demonstrated both in vitro and in vivo. In case of
subsalicylate salt of bismuth, it is possible that salicylic acid is liberated which in turns inhibits the synthesis of prostaglandin responsible for intestinal inflammation and hypermotility. Salicylate may also exert an antisecretory action and stimulate absorption of fluid and electrolytes across the intestinal wall. It is supplied as a suspension containing 262 mg/ml or tablet 262 mg (Satoskar et al., 1997).

1.11.2.2.2.1.2 Prepared chalk (Crepta preparate):

It is often used as an antacid as well as in the treatment of diarrhoea. In diarrhoea it probably acts as a protective by covering the intestinal mucous membrane. It is generally administered in the dose of 1 gm in the form of suspension. It is quite cheap (Satoskar et al., 1997, Tripathi, 1999).

1.11.2.2.1.3 Light kaolin:

It is hydrated aluminium silicate (clay) purified and free from gritty particles. When employed in the treatment of diarrhoea, it is believed to act as an adsorbent of bacteria and bacterial toxin. It is recommended orally in the dose of 2 – 4 gm 4 hourly as a thick flavoured suspension for 4 – 6 days (Nizami et al., 1996, Sengupta et al., 1969).

1.11.2.2.1.4 Pectin:

It is a purified carbohydrate product obtained from the dilute extracts of citrus fruit or apple pomace. It consists of chiefly methoxylated polygalactouronic acid.

The mechanism of antidiarrhoeal effect of pectin is not clear. When ingested it passes into the intestinal tract where it probably acts by physical coating. It helps to produce formed stools. It is decomposed in the colon by bacterial action. It may be administered either as a colloidal solution alone or with kaolin or in the form of apple or over ripe banana (Sengupta et al., 1969, Hilbrand et al., 1996).

1.11.2.2.1.5 Activated wood charcoal:

The preparation is the residue from the destructive distillation of vegetable matter such as saw dust, cellulose residue and coconut shells treated with zinc chloride to increase its adsorptive power. It is employed in the treatment of flatulence, dyspepsia and various types of diarrhoea.
So far there has been no rigorous demonstration that these gastrointestinal tract protectives and adsorbents help in diarrhoea although their administration may result in a more formed stools (Sengupta et al., 1969, Hilbrand et al., 1996, Satoskar et al., 1997).

**1.11.2.2.2 Miscellaneous:**

**1.11.2.2.2.1 Antiseptics and astringents:**

Drugs such as phenosulphonate, phenyl salicylate and zinc sulphocarbonate are included in several proprietary antidiarrhoeal mixtures based on their astringent and reputed antiseptic action (Satoskar et al., 1997).

**1.11.2.2.2.2 Bacterial cultures:**

Cultures of wide strains of *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* have been used in the treatment of diarrhoea resulting from a disruption of normal intestinal microorganism balance. Seeding the bowel with bacterial cultures is believed to re-establish the normal intestinal flora and suppress the growth of undesired microorganisms thus improving those gastrointestinal disturbances including diarrhoea, resulting from an altered intestinal flora. While possibly effective in those cases of diarrhoea induced by treatment with antibiotics that can upset the normal bacterial population of gastrointestinal tract, lactobacillus preparations are not recommended for most episodes of diarrhoea (Satoskar et al., 1997, Yao-Zong et al., 2004, Kieran et al., 2003).

**1.11.2.2.2.3 Agents which modify fluid and electrolyte transport:**

Drugs which reduce secretion and or stimulate absorption is useful in the diarrhoea. Zaldaride maleate inhibits calmodulin and therefore reduces secretion of water and electrolytes. It is reported to be effective in traveller’s diarrhoea. Non steroidal anti-inflammatory agents such as aspirin and indomethacin have been shown to have significant antidiarrhoeal action both in experimental animals in man. The effect is probably largely due to inhibition of prostaglandin synthesis (Ramzan, 2001).

**1.11.2.2.2.4 Others:**

Among the other types of locally acting products that have been used in the treatment of diarrhoea are the bulk producing laxatives or hydrophilic colloids (CMC, polycarbophil, psyllium seeds) the rational behind this apparently paradoxical action is that these
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substances have the ability to absorb excess fecal fluid as they swell in the intestinal tract. Their suitability for most of the forms of diarrhoea however remains speculative (Satoskar et al., 1997).

1.12 Proper use of the drugs in the treatment of diarrhoea.

The frequent passage of fluid or semisolid stools is a serious matter and investigation must be undertaken to determine the cause of the diarrhoea and to eliminate it by appropriate treatments for severe dehydration. The following types of diarrhoea indicate medical supervision (Alam et al., 2003, Casburn et al., 2004):

- Diarrhoea in infants
- Moderate or severe diarrhoea in young children
- Diarrhoea associated with blood
- Diarrhoea that continues for more than two days
- Diarrhoea that is associated with more general illness such as non-cramping abdominal pain, fever, weight loss etc.
- Diarrhoea in travelers, since they are more likely to have exotic infections such as parasites.
- Diarrhoea in food handlers because of the potential to infect others.
- Diarrhoea in institutions such as hospitals, child care centers or geriatric and convalescent homes.

The modern concept of diarrhoea is that an attempt on the part of the alimentary tract to rid itself of some irritating or toxic substances and therapy should be aimed at aiding this process. Acute diarrhoea is usually of short duration and is self limiting lasting from 12 – 72 hrs. If it persists for more than 3 days, it is possibly of a serious nature and investigation of faeces for ova and parasitic enteric pathogens should be made in addition to a gastrointestinal examination (Chaterjee, 1984).

A number of substances have been suggested for the treatment of diarrhoea, but the majority of them are relatively ineffective. Charcoal, kaolin, bismuth and chalk have been used extensively but are of no particular value. Astringent materials are substances which precipitate proteins and by forming an insoluble layer of protein precipitate on the mucous membrane protect the tissues from irritating substances and lead to inhibition of secretions. Vegetable drugs containing tannic acid have been employed in diarrhoea due to
its astringent effect (Parimala et al., 2002, Tripathi, 1994, Ashish et al., 1999). The cathartics such as castor oil or one of the saline groups have been frequently used to assist in clearing the gastrointestinal tract of the irritant. However, the use of such substances is not usually necessary (Capasso et al., 1994). Opium preparations and systemic antidiarrhoeals have been used successfully to check diarrhoea (Bowman et al., 1980).

**1.13 Factors in assessing a new treatment for diarrhoea:**

1. A good safety profile is vital.

2. The drug should act by inhibiting hypersecretion by the intestinal mucosa rather than simply by decreasing gastrointestinal motility.

3. Stool output and diarrhoeal duration must be substantially decreased during the initial phase of the diarrhoea to reduce the risk of dehydration and the overall morbidity.

4. Restoration of appetite following early recovery with drug treatment would render the child less listless and enable complementary feeding. This is particularly important given that malnutrition is a key determinant of diarrhoea-related mortality.

5. Drug administration should reduce the proportion of diarrhoeal episodes that extend past 4 – 5 days to reduce the burden placed on the doctor by patient’s dissatisfaction with treatment.

6. Promotion of pathogen excretion is a desirable, but not essential, property.

7. The use of the drug should not, in any way, decrease the use of oral rehydration solution and other fluids or dilute the focus on this vital component of treatment.

8. The drug should be affordable.

Previous attempts to develop antisecretory agents for the treatment of diarrhoea have been frustrated by lack of efficacy, high side-effects, and activity on the central nervous system. However, a truly novel compound that provided substantial benefit in terms of reduction in stool output and diarrhoeal duration combined with safety and selectivity of action would merit consideration as a part of the treatment (Bhan, 2000).