REVIEW OF LITERATURE
According to Bhan and Bhandari (1989) persistent diarrhoea is an important problem among children during the first two years of life. They observed that the incidence of chronic diarrhoea was 6.3% per year among those aged 0-71 months and highest incidence 31% per year among those aged 0-11 months. There was no significant sex related difference in the incidence of disease. They also observed that there was similar seasonal distribution between acute and chronic diarrhoea. 3-20% of acute diarrhoeal episodes in children in developing countries are persistent (Bhan, 1993).

According to Huttly et al (1989), highest incidence of persistent diarrhoea was among children under 6 months of age. Bhan et al (1989) and Ebrahim et al (1990) also stated that mean age of persistent diarrhoea was between 8-9 months.

In a recent study, Deivanayagam et al (1993) reported that the mean age of children with persistent diarrhoea under 2 years of age was 8.5 months.

Diarrhoea in childhood may be accompanied by secondary alterations in the intestinal mucosa and some deficiencies in the disaccharidase activities. The ingestion of disaccharide during any stage of illness may lead to increased severity of diarrhoea, acidosis and carbohydrate intolerance which improves on elimination of the offending carbohydrate from diet.
Carbohydrate intolerance may be defined as the development of symptoms after the ingestion of carbohydrate either in specific foods or as a specific tolerance test. The symptoms are the result of inadequate digestion and absorption of the sugar. Intolerance may be judged positive when (1) Diarrhoea is induced by feeds containing the offending sugar, (2) Stool pH is below 6, (3) Stool contains more than 0.5% of reducing agent (Lofshutz, 1910).

The developments that have led to an increased understanding and interest in disorders of disaccharide digestion and in disaccharidase deficiencies have come from laboratories involved in both basic sciences and clinical investigations.

About eighty years ago, Finbelstein and Meyer (1910) advocated the feeding of milk with high protein content "BIWELSSMILCH" to infant with gastro-intestinal disturbances. These authors believed that the protein was the substance responsible for the gastro-intestinal disturbances. Later they stated that not only a reduction of whey protein in milk was necessary but also a reduction in milk sugars was required for a complete remission of diarrhoea.

The use and abuse of carbohydrate in infant feeding was discussed by Grulee et al (1912) and Ostheimer et al (1912).

Howland (1921) described congenital intolerance to carbohydrate and temporary intolerance following
diarrhoea. He advocated removal of carbohydrates from
the diet of children with prolonged or severe diarrhoea.
Renewed interest in diarrhoeal syndromes, associated with
maldigestion of specific disaccharides, arose at several
pediatric centres. Holzel, Schwartz and Sutcliffe (1959)
and Weigers (1962) proposed that a secondary disaccharidase
deficiency would be encountered in association with any
process which damaged the intestinal cells, such as active
or chronic enteritis.

In 1960, Heworth and Ford demonstrated the lack of
elevation in blood sugar following ingestion of lactose
in patients with gastroenteritis. The fact that intestinal
disaccharidases were concentrated in the small intestinal
mucosa and more specifically in the microvilli was
emphasized by Dahliquist (1960).

Durand et al (1961) used chromatography to
demonstrate sugar in stools. They observed that if there
was an absolute deficiency of lactose, only then lactose
was found in stool while if enzyme deficiency was partial,
the respective monohydrates were also found.

In 1962 Giardet described oral lactose tolerance
test. Bowce et al (1963) emphasized that the activity of
intestinal enzymes was depressed in some acute diarrhoeas.
They suggested that high protein diet could, in part,
compensate for the decrease in dietary carbohydrate
absorption. They noted that changing from milk to
carbohydrate free diet resulted in a dramatic decrease
in stool weight, in 69% patients.

Malcolm et al (1965) suggested that the finding of large amounts of sugar and lactic acid in the stool was due to fermentation of sugar.

Michael et al (1966) reported that lactose activity was lower than maltose or sucrose activity and was the most vulnerable and last to recover. Law and Neole (1966) studied radiographic changes in lactose malabsorption. They found characteristic changes. The small intestine appeared distended by dilute contrast medium, peristalsis was very active, the contrast medium reached the transverse or descending colon within 1 hour while the Haustral pattern was strikingly prominent. Changes of pneumatosis intestinalis may be seen in very severe cases.

The next development that expanded the understanding of disordered disaccharide digestion was the availability of peroral biopsy method that could easily and safely provide jejunal mucosal tissue for assay of disaccharidase activities. This was regarded as the most reliable diagnostic means. The technique, difficulties, fallacies and limitations were discussed by Anderson (1966). One such limitation was that only a tiny fragment of intestinal mucosa would be examined and that could provide misleading information particularly in disaccharidase deficiency secondary to disease of small gut, with patchy lesions.
Enzyme activity is expressed in units per gram of protein. Each unit splits 1 micromole of substance per minute. Burke (1966) gave the normal range of disaccharidase activity in jejunal mucosa in children as follows:

<table>
<thead>
<tr>
<th>Lactase</th>
<th>Sucrose</th>
<th>Isomaltase</th>
<th>Maltase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>14 - 132</td>
<td>32-228</td>
<td>31 - 177</td>
</tr>
<tr>
<td>Mean</td>
<td>49</td>
<td>95</td>
<td>89</td>
</tr>
</tbody>
</table>

Dahlgquist (1966) described a single step ultra-micro method for the assay of intestinal disaccharidases which was most suitable for small quantities of mucosa removed by the peroral biopsy method.


Majority of the carbohydrate malabsorption syndrome are related to alterations in the function integrity of intestinal mucosa, and its epithelial cells. Additional intolerance to carbohydrates particularly lactose could be due to other etiologies. Generally 3 classes of intolerance types are recognised (Norbert, 1980).

(1) Ontogenic lactase deficiency, also called the physiological deficiency. In this condition the person has either not developed the enzyme or else has lost most of the enzymes function. It could, thus, be seen in premature babies and adults or older children (Cook, 1967). The lactose enzyme develops immediately before birth and
around the age of 3 years, it declines to about 10% of its peak values. This decline, increasing with age, takes place in the majority of ethnic groups who consume very little milk. Northern Europeans, Americans, Mongols and the Tusi falani, Nasi Tribes of Africa maintain high levels of lactase throughout adulthood (Delmont 1968).

At birth jejunal lactase is high in all ethnic groups, irrespective of the status of the enzyme in the adult. In a population where adult hypolactasia prevails fall in the lactase levels takes place in the first 3-5 years of life. In some cases, an early fall, in the first 6-12 months, has been recorded that doubtless accounts for many cases of marasmus (Schrieber et al, 1973). Authors opined that lactase from the breast milk does not get absorbed and that leads to significant energy loss for the infant.

Zambian population have almost a 100% incidence of adult hypolactasia, and infant diarrhoea during breast feeding is common. After the weaning diarrhoea is reported to stop (King, 1960).

(2) Primary Lactase deficiency - First described by Holzel (1967) and his associates. Primary or congenital lactase deficiency is very rare. Only a few reports of its incidence in the western world are available and incidence in India is unknown. Most physicians, however, agree that its incidence is less than one in one thousand. Primary deficiency usually becomes manifest very early in life, though it may have a late onset in adults. Patients have a virtual absence of hydrolytic capacity towards lactase,
but no other abnormality of intestinal structure or function. The precise biochemical defect responsible for the absence of enzymatic activity has not been characterised. The deficiency may be associated with a complete depletion of enzyme protein or with the presence of an abnormal biologically inactive enzyme molecule. The mode of inheritance of this abnormality has not been clarified. Males are at greater risk (McNair, 1972).

(3) Secondary lactase deficiency - Damage to the brush border of the enterocytes and loss of mucosal integrity leads to secondary lactase deficiency. A wide variety of agents are known to cause specific damage to the lactase enzyme while diverse systemic and gastrointestinal disorders are known to damage villi primarily, leading to reduction of lactase levels. Severe or total villi damage leads to deficiency of all disaccharidases and monosaccharide transport mechanisms (Lindenbaum, 1975).

Lactase is the most superficial of the intestinal oligosaccharidases. Its activity is the rate limiting step for absorption and its concentration is lower than that of other disaccharidases. While decrease in the lactase levels is the main cause of secondary deficiency, other factors such as changes in motility or reduction in absorption surface reduces the exposure time of disaccharides to mucosal enzymes (Ferguson, 1976). Further the author adds that inflammation or anatomical disturbances
could also interfere with enzyme substrate binding, reducing the rate of hydrolytic action to produce a syndrome very similar to secondary deficiency.

Secondary lactase deficiency is thus caused by many factors, the most important of which are mentioned below:

Viral: (1) Rotavirus, (2) Norwalk like agent, Norwalk (3) Non-specific virus, (2) Measles virus (5) Hepatitis virus.

Bacteria: Streptococci, shigella, staphylococci, E.coli, Klebsiella, Pseudomonas.

Mycobacteria: Mycobacterium tuberculosis.

Protozoa: Amoeba, giardia (Quinter, 1980).

Candida: it has been associated with chronic diarrhoea and subsequent lactose deficiency (Kane, 1976).

1) Rotavirus Infection

Rotavirus infection is a common case of secondary lactase deficiency and since it occurs in young infants it is a major cause of infant diarrhoea (Flewett, 1976). Viral infection may causes varying degrees of structural changes, ranging from spotty subtotal atrophy to severe flattening of villi and derangement of surface epithelium (Hamilton, 1976).

According to Gall (1978) virus invades the mature cells which have high levels of lactase, consequently immature cells from the crypts migrate towards the tip to take the place of damaged cells. The immature cells
tips are lactase deficient, thus leading to intestinal lactase deficiency and diarrhoea.

Systemic viral infections can also cause secondary hypolactasia and malabsorption (Conard, 1978). Hyam's et al (1981) reported that lactose intolerance develops in 50% of cases with Rotavirus infection. Karabucuoğlu et al (1994) noticed in their study that rotavirus is known to be the most frequent condition leading to lactase intolerance.

2) Protozoa

The precise cause of malabsorption caused by amoebiasis or giardiasis is not known though a few factors are believed to be involved (Das, 1979). They are: bacterial colonization of the upper small bowel, parasitic injury to mucosa and tissue invasion, mechanical barriers to absorption and bacterial overgrowth with subsequent bile salt deconjugation.

In patients with giardiasis with secondary lactase intolerance, symptoms may subside immediately after elimination of the parasite (Terruzzi, 1980).

3) Bacteria

Majority of the intestinal bacteria cause damage to the brush border and may produce secondary deficiency. In bacterial diarrhoeas, the malnutrition - gastroenteritis cycle is of great importance since malnutrition predisposes an individual to infection (Chandra, 1982).
Bhan and Bhandari et al (1989) observed enteric pathogens during initial illness in 46.4% of persistent and 55.4% of acute episodes. They reported that the pathogens isolated during persistent episodes include enterotoxigenic E. Coli 9.3%, Salmonellae species 4.7%, Campylobacter 4.7%, Shigella 2.3%, Entamoeba histolytica 2.3% and Rotavirus 2.3%.

Multiple pathogens were isolated in 7% of persistent diarrhoea. E. coli that manifested aggregate adherence was more common 34.9% and it was significantly associated with persistent diarrhoeal episodes. They further identified several risk factors for persistent diarrhoea viz (1) Malnutrition (2) Age <1 years (3) Impaired nutritional status, (4) Introduction of animal milk in diet (5) Occurrence of recent diarrhoeal episodes.

Sazawal et al (1992) reported that a much higher risk of persistent diarrhoea with liquid animal milk than spray dried infant formula when compared to breast feeding.

According to Thapa (1994) etiological agents isolated from stool culture in their study were E. coli 18%, Klebsiella 9%, Shigella species 6%, Salmonella 2%, Cholera mitschikom 1%, Giardia lamblia 6% and E. histolytica 1%.

4) **Malabsorption syndrome**

Individuals living in the tropics may show non-specific villous damage due to diet, environmental pathogens, nutritional status etc. Such non-specific villus damage can cause malabsorption of all foods including carbohydrate (Gray, 1982).
5) **Hypoxia**

Lifshitz et al (1982) have demonstrated, in rats, that hypoxia could cause long lasting depression of lactase activity. Neonatal hypoxia and respiratory distress have also shown to cause lactase deficiency.

6) **Surgical resection of small intestine leads to lactase deficiency** (Gudmen, 1983).

7) **Cow’s milk intolerance**

Smith et al (1984) have demonstrated that the incidence of lactase intolerance with milk protein intolerance was as high as 92%. They have suggested that allergic reaction in the intestine led to mucosal damage and depletion of lactase.

8) **Helminthic infection**

Anchylostomiasis, strongyloidiasis are associated with lactase intolerance (Tandon, 1976).

**Development of Disaccharidase activity**

Maltase, sucrase and isomaltase in the fetus reached the lower range of normal adult levels by 28-37 weeks of gestation. In both the pre-term and the full term infants their digestion is adequate. In contrast the major digestive enzyme lactase is present at a low level of activity at 28 weeks and then at term the lactase level doubles or triples and reaches adult levels. Theoretically premature infants may be milk intolerant for a few
days until their lactase levels reach adequate levels to digest lactose in their milk formula (Stanley, 1950).

Newborn infants nursed on breast milk which contains 7% lactose are said to have several soft acid stools per day, whereas those fed on Cow's milk formulas containing 4% lactase have only one or two alkaline stools. This is presumably due to relative lactose intolerance (Kistler, 1956).

A post weaning decrease in lactase activity occurs in most animal species. Experimentally this decrease can be prevented for several additional weeks if lactose is provided as the only source of carbohydrate (Perkin, 1960).

Contrary to the concept that the intestinal disaccharidases are secreted into the succus entericus, digestion of disaccharides occurs intracellularly. This was first shown by Cejori (1962). It appears that all the enzyme activities are highest in the distal part of the villi and epithelial cells are regenerated in the bottom of the crypts and migrate up the sides of the villi and the highest enzyme activity is obtained at the tips of the villi. Galactosidase or lactase activity has been localized in the microsomes by Doell and Kretchmer (1962) while Dehlquist and Brun (1962) associated their activity with cytoplasmic granules.
**Disaccharidase distribution along the small intestine**

Enzyme assays in mucosal specimens obtained by peroral intestinal biopsy indicate that sucrase, isomaltase and lactase are less active in the first part than in the remainder of duodenum. In the upper jejunum and the last segments of the ileum, the disaccharidase activity is of the same order and magnitude (Hansen, 1963).

**Sugar Transport**

Assuming that the disaccharidase splitting enzymes are intracellular, the means by which sugars enter the mucosal cells is obscure. This could be by diffusion, if for instance rapid hydrolysis of the disaccharide within the cell maintained a gradient between it and the intraluminal medium. For glucose and galactose, there also exists an active carrier system (Sinclair, 1963).

A further essential requisite is the presence of sodium ions on the membrane of the mucosal cell. The driving force is regarded, as a form of biological pump, with adenosine triphosphate (ATP) providing the immediate energy source (Burgess, 1964).

Littmann and Hammond (1965) have proposed that sugars enter the intestinal cell by means of a tertiary sugar-sodium carrier complex. This carrier would possess two specific binding sites, one for the substrate and one for sodium ion. The rate of sugar transport seems to be dependent on the difference between intra and extra-cellular
sodium concentration and is also mediated by ATP dependent pump.

The probable mechanisms by which diarrhoeal disease leads to malabsorption can be classified as (Twinly, 1966).

A. **Intraluminal events** which includes
   - Bacterial over growth
   - Competition
   - Fermentation
   - Cross production
   - Osmotic effects.

B. **Cellular events**
   - Pharmacotoxic
   - Cytotoxic

C. **Villous abnormalities**

A. **Intraluminal events**

Malabsorption could occur because of events in the lumen which interfere with normal digestive and absorptive process. Due to the bacterial overgrowth the bacterial mass competes with the host for the intake of ingested nutrients (Donaldson, 1967).

The effects of bacterial metabolism of ingested nutrients are important. Bacterial fermentation of sugars occur with the production of gas and short chain fatty acids, both of which are capable of producing gastro-intestinal symptoms and increased water loss. Failure to digest and absorb sugars can also result in an osmotic
load in the gastro-intestinal tract and contribute to diarrhoea with secondary effects on vitamin and micro nutrient absorption. Finally, the correlation between carbohydrate malabsorption and bacterial counts in the intestine suggest that carbohydrate malabsorption may contribute to, as well as result from bacterial contamination of the gut (Lifshitz, 1972).

It is especially important to look for E. coli strains in the upper gut. E. coli have been isolated in several cases of lactose intolerance (Cufford, 1973).

Clinical lactose intolerance is an uncommon complication of bacterial dysentery indicating that these infections may be more damaging to colon than to the small intestine (Harry, 1975).

B. Cellular events

The second major category of pathogenesis relates to the intestinal epithelium and its response to toxins from the lumen of the small intestine. These toxins can be divided into two groups.

1) Pharmacotoxic agents

Studies of xylose and folic acid malabsorption were done by Lindenbaum (1975) in patients with cholera and other related diarrhoeal diseases. He documented that there is a finite period of malabsorption which may be associated with diarrhoea.

Current evidence however indicates that pharma-
cotoxins such as cholera enterotoxin do not affect the intestinal absorption of sugars and amino acids (Rosenberg, 1978).

ii) Cytotoxic agents

They produced damage with or without invasion of mucosa. Shigella toxin contribute to a cytotoxic effect which interrupts normal intestinal epithelial processes, resulting in defects in intestinal malabsorption. Acute intestinal infection from a variety of cases may be associated with morphological and even villous abnormalities of the intestinal mucosa similar to those associated with more severe chronic forms of malabsorption. There is often a loss of absorbing surface (Ostheimer, 1978).

Drugs

Oral contraceptives are known to depress mucosal lactase though the implication of the observations is not clear, as far as children on breast milk are concerned. Neomycin commonly used for control of diarrhoea has been associated with secondary lactase deficiency. It is believed that this is either a direct effect of the drug or it could be due to antibiotic induced enteropathy (Kistler, 1980).

C. Villous abnormalities

The major disaccharidases are located in the microvilli of the small intestinal mucosa and if the
microvilli are damaged, there is usually a resultant
decrease in the activity of all disaccharidases. Lactase
activity which is lower than maltose or sucrose is most
vulnerable and last to recover. Decrease in jejunal
maximal absorptive capacity may be caused by loss of
digestive absorptive cell mass, by permeability distur-
bances (external or internal), owing to defective
hydrolytic and transport mechanisms or as a result of
inhibition of brush border function (Rivera, 1980).

The general pattern of rotavirus infection
involves virus penetration and infection of the diffe-
rentiated enterocytes in the villus of small intestine.
Rotavirus multiplies in the cytoplasm of these cells and
causes damage to the digestive and absorptive functions
(Marykobestes, 1980).

Sequence of events in the small intestine consist
of replacement of the absorptive villous epithelial
columnar cells with cuboidal cells and shortening of villi
with lymphocyte infiltration. Available evidence suggests
that such damaged cells are sloughed into small intestine.
Lysis of the infected cells release virus into the
intestine. These studies suggest that diarrhoeas caused
by rota virus infection is due to malabsorption which also
includes impaired carbohydrate absorption. The highly
differentiated absorptive villous cells are replaced by
immature crypt cells that are not able to compensate for
absorption defect (Yates, 1980).
Such changes occur in a cephalo-caudal direction and suggests that much of the diarrhoea is due to loss of absorptive capacity. Histological abnormalities have ranged from mild flattening of the mucosa to complete mucosal atrophy. A decrease in the rate of intestinal cell turnover and decrease in the mitotic index have been noted. Enzyme studies after about 3 weeks of treatment show that the defects in the absorption of monosaccharides and hydrolysis of disaccharides (sucrose, maltose) tend to disappear. However, there is both histochemical and clinical laboratory evidence that the defect in lactose metabolism is the last to get corrected (Leichberg, 1980).

In cases of malnutrition where the gut is previously damaged, gastrointestinal infection or infestation may be a factor in producing an acquired disaccharide intolerance (Valman, 1980).

Normal lactase activity in the jejunum requires more protein than what is necessary for maltase activity. So it will be more easily influenced by the combined effect of malnutrition and gastrointestinal infections. As soon as the inciting cause of mucosal damage subsides, as in acute gastroenteritis, enzyme activity increases. Although lactose tests may become normal, lactase levels remains abnormally low for years. The continued ingestion of lactose may aggravate the acute gastroenteritis (Barnes, 1982).
The excess of volatile organic acids especially acetic and lactic acid produced by bacterial fermentation irritate the intestine, which induce peristalsis and excretion of fluid and mucous. Thus, absorption is disturbed with subsequent diarrhoea. Once diarrhoea is present mono-saccharides are also poorly absorbed (Naser, 1983).

Diagnosis of carbohydrate intolerance is suspected at a time when in the history of a diarrhoeal episode there are increasing number of motions and consequent dehydration. The stool are watery, frothy and explosive, accompanied by irritability, abdominal distension and perianal soreness with high stool weight (Lifshitz et al., 1980).

In carbohydrate intolerance (due to lactase deficiency) significant improvement of symptoms occur and a decrease in the stool weight occurs on withdrawal of milk from the diet. Diarrhoea recurs on reintroduction of milk to the diet. Withdrawal of milk from diet decreases the stool weight by 69% (Bowie et al., 1981).

The finding of abnormally large amounts of lactic acid and sugar in the stool while on milk suggests that there is fermentative diarrhoea (Barker, 1981).

Fermentative diarrhoea may be due to malabsorption of mono, di, or polysaccharides. The unabsorbed carbohydrate is subjected to bacterial action which produces organic acid in large quantities as an end product (Weijer, 1982).
and Harry et al (1983) demonstrated the association of
disaccharide intolerance and protein calorie malnutrition.

**TABLE 1**
Showing percentage cases of carbohydrate
intolerance in different studies (Ashoka, 1988).

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Author</th>
<th>Year</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Chandra R. K.</td>
<td>1968</td>
<td>54.0</td>
</tr>
<tr>
<td>2.</td>
<td>Reddy</td>
<td>1972</td>
<td>37.0</td>
</tr>
<tr>
<td>3.</td>
<td>Udani, P.M.</td>
<td>1976</td>
<td>9.32</td>
</tr>
<tr>
<td>4.</td>
<td>Archer</td>
<td>1977</td>
<td>12.0</td>
</tr>
<tr>
<td>5.</td>
<td>Ansari</td>
<td>1976</td>
<td>10.0</td>
</tr>
<tr>
<td>6.</td>
<td>Hirschorn</td>
<td>1980</td>
<td>50.0</td>
</tr>
<tr>
<td>7.</td>
<td>Ghai, O.P.</td>
<td>1982</td>
<td>23.0</td>
</tr>
<tr>
<td>8.</td>
<td>Bhate</td>
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<td>37.0</td>
</tr>
<tr>
<td>9.</td>
<td>Clifford</td>
<td>1983</td>
<td>12.0</td>
</tr>
<tr>
<td>10.</td>
<td>Davidson</td>
<td>1984</td>
<td>50.0</td>
</tr>
<tr>
<td>11.</td>
<td>Trounce</td>
<td>1985</td>
<td>10.9</td>
</tr>
</tbody>
</table>

**Clinical consequences of lactose intolerance**

1. **Prolongation of diarrhoea:** Average duration of rota virus diarrhoea, is 5-7 days. It may get prolonged to 10-14 days due to lactose intolerance according to Hyams and Krause (1970).

2. **Metabolic acidosis:** Lactose on fermentation yields lactic acid which is absorbed partially and may stimulate bicarbonate secretion (Rivera et al, 1972).
orally and blood sugar estimated at 15, 30, 60, 90, 120 minutes. If the lactose level was low, blood glucose rise and less than 1.1 m mol/l

3) **Presence of reducing substances in the stool**

Diagnosis of carbohydrate intolerance could be made with Benedict’s reagent when reducing substances such as lactose, glucose and galactose are excreted in stools in concentration above 0.25%. The presence of reducing substances could be determined by a change in the colour of diluted fresh stool sample (Joseph, 1976).

In case of sucrose, preliminary hydrolysis using HCl was done so as to split sucrose into glucose and fructose (Vincent, 1979).

Estimation of stool reducing agents was unreliable techniques in the diagnosis of lactose intolerance as opined by Rossi (1990).

4. **Rubner's test**

This test has been used to detect reducing substances in the stool.

According to Singh et al (1985) incidence of false positive tests was considerably reduced in Rubner's method as compared to the conventional Benedict's test. To the liquid stool sample lead acetate was added and boiled cooled and then 2 ml of liquid ammonia was added. A pink or red precipitate showed lactose in the stool.
3. **Malnutrition**: Carbohydrates form the major source of energy especially in the infant. Since 50% of the calorie requirements are derived from lactose, loss of the sugar to the system leads to caloric defects, even when the diarrhoea is mild.

Presence of unabsorbed carbohydrate in the lumen also enhances protein and nitrogen loss. Unhydrolysed carbohydrate also interferes with fat malabsorption due to dilution of bile salts (McNair, 1972).

4. **Bacterial proliferation**: The presence of unabsorbed carbohydrates and fermentation products in the small bowel lumen and proliferation of enteric bacteria in the upper segment of intestine. Such overgrowth of faecal flora in the upper segment of small intestine leads to a state of chronic diarrhoea. Altered motility, presence of free carbohydrate in the lumen, and other metabolic alterations (luminal pH) are among other factors that influence enteric bacterial dissemination. Bacterial over-population of the upper bowel may generate additional injurious factors such as deconjugated bile salts, hydroxy fatty acids which aggravate intestinal malfunction and worsen diarrhoea (Berr, 1981).

5. **Pneumatosis intestinalis** may result from carbohydrate intolerance since unabsorbed carbohydrates generate large quantities of gas in the intestinal lumen, which
if not expelled may lead to distension of gut with increasing pressure, leading to ischemia or necrosis of the intestinal mucosa. Thus, providing access for the gas into the tissue spaces and resulting in pneumatosis intestinalis (Vázquez and Amador, 1983).

5. **Macromolecular absorption**: An increased macromolecular absorption occurs resulting into development of hypersensitivity and allergy to food stuffs. Experimentally it is proved that elevated luminal osmolarity leads to enhanced rate of transport of macromolecular traces across the intestinal epithelium (Teichbergs, 1985).

**EPITHELIAL AND BASEMENT MEMBRANE ABNORMALITIES**

Goulet Oliver et al (1995) studied 6 children with watery diarrhoea in the neonatal period requiring total parenteral nutrition. Repeated duodenal and jejunal biopsies had revealed villous atrophy with normal or hyperplastic and regenerative cryptae, normal cellularity of lamina propria, no signs of T cell activation. The main histological features observed by them were epithelial dysplasia with focal crowding and disorganisation of surface enterocyte, pseudocystic formation of glands abnormal regenerative cryptae.

The basement membrane component were studied with polyclonal antibodies on frozen specimen and were compared with biopsy specimen from patients with coeliac disease, or
autoimmune enteropathy. Relative to control subjects there was faint and irregular deposition of lamina at the epithelial lamina mesentrii propria interface, whereas deposits of heparin sulphate proteoglycan were large and lamellar.

Primary and secondary nature of their modifications of basement membrane remains to be determined, but the modifications might be related to epithelial abnormalities and to the severity of this neonatal diarrhoea which resisted all treatment and required permanent total parenteral nutrition.

INVESTIGATIONS IN CARBOHYDRATE INTOLERANCE

1. **Stool pH**

Stool pH was first suggested by Davidson in 1967. Opinions vary remarkably on the reliability of stool pH in the diagnosis of lactose intolerance.

Measurement of stool pH in lactose intolerance is unreliable, full of fallacies and subject to wide fluctuations according to Martino and Lifshitz (1960). On the other hand Durand (1960) stated that measurement of stool pH was reliable and stool pH was less than 6 in all cases of lactose intolerance.

2. **Oral lactose loading test**

In 1962, Giardet described oral lactose loading tests, after taking a fasting blood sugar sample. Fifty grams of lactose dissolved in 400 ml of water was given
5. **Stool chromatography**

It is one of early techniques used in diagnosing cases of carbohydrate intolerance and it continues to be one of the most specific and reliable methods.


Thin layer chromatography can pin point the exact offending sugar. It is extremely useful in the diagnosis of monosaccharide malabsorption where there are rapid changes in the type of food given as observed by Udani (1976).

Bhave et al (1983) observed that stool chromatography was extremely reliable in the diagnosis of lactose intolerance though it was painstaking and time consuming method.

Karabucuoglu et al (1994) reported that thin layer chromatography when done in conjunction with fecal pH determination and clinitest tablet assay method was suggested as a useful method in confirming and supplementing the results of these tests.

6. **Clinitest method**

In 1964 Kerry and Anderson developed a new and easy method for the diagnosis of sugar in stool. To 15 ml of stool suspension an indicator tablet was added and a
chemical reaction similar to that of urine was seen. This test was not intended to provide conclusive evidence of defective carbohydrate digestion, but indicated that patient could be investigated for sugar malabsorption more intensively.

7. **Jejunal biopsy**

Quantitative, biochemical assay of disaccharides in per oral biopsy of intestinal mucosal specimen is regarded as one of the most reliable diagnostic means.

Direct estimation of lactase concentration and the morphology of the biopsy specimen give the idea of the type of hypolactasia. In specific primary hypolactasia the villi are basically normal, together with other disaccharidase concentration (Reddy, 1975).

Small bowel biopsy according to Byrne (1981) is not justified in the diagnosis of carbohydrate intolerance. Since it can be diagnosed better by other non-invasive technique.

8. **Breath hydrogen test**

Cochet et al (1981) introduced the breath hydrogen test for children with lactose 1 gm/kg as syrup was given orally. Expired breath samples were collected at 0, 60, 90 minutes and analysed for hydrogen concentration. An increase in breath hydrogen, more than 20 parts per million was considered as positive result.
Unabsorbed lactose on fermentation liberates hydrogen and carbon dioxide. These gases are finally eliminated through the breath. This technique has the advantage of being non-invasive (Moffei et al, 1982).

According to Bufford et al (1982) breath hydrogen test permits the study of intestinal malabsorption of disaccharidase activity after diarrhoea and may help in deciding the re-introducing of certain carbohydrates into the diet.

Solomon et al (1983) have pointed out that there may be lower hydrogen production in some patients with severe diarrhoea and carbohydrate malabsorption because the frequency of bowel movements may wash out the colonic bacteria, thus giving false negative results in hydrogen breath test.

9. **Radiography in Carbohydrate Intolerance**

Law and Neale (1966) described radiological changes in disaccharidase deficiency.

**TREATMENT**

Malcolm et al (1965) advocated the practice of withholding milk in protracted diarrhoea.

Opinion differs as to when milk diet should be restarted. According to Jeffrey et al (1974) it could be started after 10–14 days while Davidson et al (1978) advised a period of at least 4 weeks.
According to Shub and Walker (1980) oral feeding should be started as early as possible at least partially. The author opines that enteric feedings have a trophic effect on the hypoplastic or damaged intestinal mucosa facilitating early healing and inducing a more rapid return of disaccharidases.

Soyabean preparations were suggested as a milk substitute by Hill and Stuart (1980).

Larcher et al (1980), Bhan et al (1983) and Bhave et al (1983) have emphasized that there may be intolerance to low lactose formulae due to associated milk protein intolerance and gluten sensitivity. To cope with such situations, authors have devised some diets prepared from locally available ingredients.

In 1984 Bedline and Boylis suggested that one substrate like glucose could reverse the net secretion and the associated clinical symptoms induced by malabsorption of another substance like lactose.

Larcher et al (1984) have made it clear from numerous animal and human studies, that intraluminal food stuffs, carbohydrates and proteins increase intestinal digestive enzyme and cell proliferation in a dose related way. The inductions are somewhat specific. Sucrose induces sucrase formation. Therefore, a mixed carbohydrate diet was most protective against disaccharidase depletion, during diarrhoea.
Mabel et al (1984) has demonstrated that resumption of milk feeding is associated with prompt improvement in nitrogen balance.

Walker et al (1985) postulated that disaccharidases are continuously being synthesised and degraded in the epithelial cells of the small intestine. Decrease in disaccharidases could be explained by either a decline in the rate of synthesis of new enzyme or an increase in the rate of degradation.

A study conducted by Davidson (1984) revealed that antibiotics do not influence the development of either biochemical or chemical malabsorption of lactose.

Brunser and Arya et al (1990) has to be refeed with low lactose products to induce remission of the symptoms. They observed that nutritional parameters were unchanged during and after the diarrhoeal episodes. Their findings suggested that availability of low lactose formula may be advantageous in clinical management of infant with acute diarrhoea and evidence of lactose intolerance.

Bearn and Fontaine et al (1990) suggested that formula based on fermented milk together with oral rehydration can be used to treat malnourished children with sugar intolerance diarrhoea. They observed no difference in mean weight gain between children with sugar intolerance malnourished children and other chronic/acute diarrhoeal cases which had not shown the sugar intolerance.
Sinden and Sutphen (1991) observed that in lactose intolerance children were successfully treated with infant formula, including soya protein and hydrolysate formula in secondary lactase deficiency. He also observed that diet supplemented with lactose can be beneficial in lactose intolerance diarrhoeal patients. The ingestion of milk with food and fibre components in diet had also been shown to improve symptoms of lactose intolerance.

Businco et al (1992) observed that soya based milk was used for different conditions including cow milk protein allergy and lactose intolerance. Feeding soya protein formula to normal term infants is associated with normal growth, normal protein nutritional status and normal bone mineralization. Recent studies of infants fed soya protein formula revealed no immunological abnormalities. He observed that children fed on soya milk protein had allergy with soya protein formula.

A recent Indian study (Bhan and Bhatnagar et al (1992) found no improvement in purge rate, weight gain or overall illness among children with persistent diarrhoea treated with oral gentamycin than with a placebo.

Overall 5% of hospital referred patients required intravenous therapy for few days before full oral feeding is possible. Remaining 80–90% recovered on initial diet and 10% required change of milk free diet. Although the role of antibiotics is achieving recovery from persistent diarrhoea has not been substantiated, systemic antibiotics
may be required in nearly one third of hospitalised persistent diarrhoea cases for associated pneumonia, urinary tract infection or bacteremia as is true for any group of severely malnourished hospitalised cases (Bhan and Bhatnagar, 1993).

Gupta and Gupta et al (1993) observed that soya based milk formula was commonly prescribed for lactose intolerance secondary to infective diarrhoea. They studied two groups of cases, first group of seventy patients was given lactose predigested milk feeding and the second group was treated with soya milk. They observed that refusal of feed was found 30% cases with soya based milk as compared to only 2.8% in lactose predigested milk (lactose group). Vomiting after feed was also found in 10% of babies fed soya based milk as compared to none in lactose group. Motions were controlled in 84.3% cases within 3 days of therapy. They concluded that lactose treated milk was more superior than soya milk for the treatment of lactose intolerance.

Nutritional management plays a vital role in many gastrointestinal problems, most common problem is lactose intolerance. Spollett et al (1994) concluded in their study that lactose free diet was most successful therapy in lactose intolerance diarrhoeal patients.

Thapa et al (1994) studied one hundred twenty infants under one year of age suffering from intractable
diarrhoea. All patients had received prior treatment in the form of antimicrobials and intravenous fluid 33% of cases; antimitility agents 50% cases and stool binding substance in 50% cases, 30% need hospitalization. He observed other symptomatology viz. vomiting 44%, dehydration 23%, fever 33%, paralytic ileus 9%, perianal excoriation 47%, and rectal prolapse 3% of cases, anaemia 70%, vitamin deficiencies 10%, and pedal oedema 3% cases. They reported that besides intractable diarrhoea other associated infection were septicemia 22%, bronchopneumonia 6%, meningitis 4%, and urinary tract infection in 3% of infants. Among them 53% of infants had secondary lactose intolerance.

Pitchumoni (1995) stated that one the diagnosis of lactose intolerance was confirmed, simple dietary management may resolve symptoms completely.

Controlled clinical experience with antibiotics therapy is limited. Hill et al (1984) reported beneficial effects with oral gentamycin therapy in persistent diarrhoea. Their strategy allowed selection mainly of cases of severe high purging diarrhoea of more than 5–7 days.