REVIEW OF LITERATURE
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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 (Lofshotz, 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 (1910) Pinbelstein and Meyer advocated the feeding of milk with high protein content "EIWESSMILCH" to infant with gastro-intestinal disturbances. These authors believed that whey 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).

In 1921 Howland 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 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 Dahlquist (1960).

Durand et al (1961) used chromatography to demonstrate sugar in stools. He 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 diarrhoes. They suggested that high protein diet could, in part, compensate for the decrease in dietetic carbohydrate absorption. They noted that changing from milk to carbohydrate free diet resulted in a dramatic decrease in stool weight, in 69% patients.

In 1965 Gray and Ingelfinger reported that there were four or five maltases and at least one of them hydrolyzed isomaltose and another split sucrose. Authors opined that there could be another sucrose, as well.

There were probably 2 lactoses, the major one would reside in the brush border and the second, a non-specific B-galactoside splitting enzyme that was soluble,
presumably remained concentrated in cellular cytoplasm. Authors demonstrated that the concentration of disaccharidase in the intestinal mucosa was the rate limiting step in disaccharide digestion. They opined that hydrolysis probably occurred at the surface of the microvilli or just within its membrane, since portions of the hydrolysis products were released into the intestinal lumen.

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 lactase activity was lower than maltase or sucrase activity and was the most vulnerable end last to recover. Law and Ncole (1966) studied radiographic changes in lactase 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
activities. This was regarded as the most reliable diagnostic means. The technique, difficulties, fallacies and limitations were discussed by Anderson (1966). One such fallacy 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></th>
<th>Lactase</th>
<th>Sucrase</th>
<th>Isomaltase</th>
<th>Maltase</th>
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<tr>
<td>Range</td>
<td>14 - 132</td>
<td>32-228</td>
<td>31 - 177</td>
<td>83 - 615</td>
</tr>
<tr>
<td>Mean</td>
<td>49</td>
<td>95</td>
<td>89</td>
<td>260</td>
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Dahlqrist (1966) described a single step ultramicro 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 syndromes are related to alterations in the functional 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, 1960):

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 lactase 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 (Delmot, 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. Incidence in India is unknown. Most physicians, however, agree that its incidence is less than one in one thousands. 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, (4) Measles virus, (5) Hepatitis virus.

**Bacteria:** Streptococci, shigella, staphylococci, E.coli, Klebsiella, Pseudomonas.
Mycobacteria : Mycobacterium tuberculosis.

Protozoa : Amoeba, giardia (Quinter, 1980).

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

1) Rota virus 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 (Conrad, 1978).

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).

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 carbohydrates (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 lactose 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 reach 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
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 localised in the microsomes by Doell and Kretchmar (1962) while Dehlqrist 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 gastrointestinal 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 infection 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.

i) **Pharmacotoxic agents** - Studies of xylose and saccharic 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 evidences however indicate that pharmacotoxic toxins such as cholera enterotoxin do not affect the
intestinal absorption of sugars and amino acids (Rosenberg, 1978).

ii) **Cytotoxic agents** - They produce damage with or without invasion of mucosa. Shigella toxin contributes 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 maltase or sucrase 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 disturbances (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 differentiated enterocytes in the villi of small intestine. Rota virus 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 diarrheas caused by rotavirus 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 effects 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
There is no evidence that bacterial fermentation of the disaccharide in the colon has an etiological role in the diarrhoea, through inhibition of absorption (Smith, 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 (Meijer, 1982).


Table showing percentage cases of carbohydrate intolerance in different studies (Ashoka, 1989).

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Percentage</th>
</tr>
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<td>1. Chandra, R.K.</td>
<td>1968</td>
<td>54.0</td>
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<td>2. Reddy</td>
<td>1972</td>
<td>37.0</td>
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<td>3. Udani, P.M.</td>
<td>1976</td>
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<td>4. Archer</td>
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<td>5. Ansari</td>
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<td>6. Hirschorn</td>
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<td>7. Ghai, O.P.</td>
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<td>8. Bhave</td>
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<td>9. Clifford</td>
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<td>10. Davidson</td>
<td>1984</td>
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<td>11. Trounce</td>
<td>1985</td>
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Clinical consequences of lactose intolerance

1. Prolongation of diarrhoea: Average duration of rotavirus 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).

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 during diarrhoea may facilitate the colonization 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 mal-function 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 ischaemia or necrosis of the intestinal mucosa. Thus, providing access for the gas into the tissue spaces and resulting in pneumatosis intestinalis (Vazquez and Amador, 1983).

6. **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).
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 gm. of lactose dissolved in 400 ml of water was given 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 mmol/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 technique in the diagnosis of lactose intolerance as opined by Rossi (1970).

4) **Rubner's test**: This test has been used to detect reducing substances in the stool.

According to Singh et al (1985) incidence 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.

5) **Stool chromatography** 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.

Durand et al (1961) used paper chromatography for the first time to identify offending carbohydrate in stool.

Separation and identification of different sugars becomes clear by thin layer chromatography as opined by Joseph (1974).

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 lactase intolerance though it was painstaking and time consuming method.

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 disaccharidases 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 techniques.

8) Breath hydrogen test: Cochet et al (1981) introduced the breath hydrogen test for children with lactose intolerance. After an overnight fast, lactulose 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 in 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 & Stuart (1980).

Larcher et al (1980), Bhan et al (1973) and Bhave et al (1983) have emphasized that there may be
intolerance to low lactose formulas 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.

According to Sandhu et al (1985) aspirin has been used in the treatment of carbohydrate intolerance associated diarrhoea. Loperamide an opioid has shown greater efficacy in clinical trials in controlling diarrhoea. A recent report suggests that prenylamine, a coronary vasodilator reduces symptoms of lactose intolerance. Prenylamine has been shown to have antibacterial effects as it acts by increasing the cell wall permeability.