# Diets and Enteropathy in Severe Acute Malnutrition

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# Summary

1. Diarrhoea / malnutrition interactions
2. Intestinal permeability
3. Malabsorption
4. Gut trophic nutrients
5. Diets and enteropathy

# Historical Lessons Learned on Dietary Treatment of SAM (by trial & error)

1. Excess dietary protein resulted in a high mortality
2. High sodium diets (to treat hyponatraemia) led to heart failure
3. Failure to give empirical antibiotics resulted in sudden deaths from sepsis (which is now increasingly resistant to conventional antibiotics)
4. Low potassium diets led to increased deaths, possibly from effect of hypokalaemia on the heart*
5. Lactose-free and low osmolality diets give better outcomes*

*see next slides for evidence

# Potassium Supplementation in Kwashiorkor (Malawi) Manary M, Brewster DR

The case-fatality rate was reduced by 33% in the high potassium intervention group (13/48) compared to controls (21/51). There was a significant reduction in late deaths (13 in controls vs 3 in intervention group; odds ratio 5.3, 95% confidence interval 1.2–31.0) but no difference in early deaths (0–5 days). The intervention group also had significantly fewer presumed septic episodes (3 vs 18, odds ratio 8.9, confidence interval 2.2–50.9), respiratory symptoms, and new skin ulcerations than controls.

**Conclusions:** The high potassium supplementation reduced mortality and significant morbidity in kwashiorkor. This may be due to improved myocardial and immune function from earlier repletion of intracellular potassium. We recommend that the standard potassium supplement for the initial phase of treatment of kwashiorkor be increased from 4 to 8 mmol/kg/day.

# Milk Formula Trial (Darwin)

| MILK FORMULAS | *Carbohydrate* | *Protein* | *Fat* | *Osmolality* |
|---|---|---|---|---|
| **DE-LACT** | Maltodextrin 100% | Casein 100% | Vegetable based 100% (Palm, Coconut, Soy, Canola, Lecithin) | 165mOsm/kg |
| **O-LAC** | Dried glucose syrup 100% | Casein 82% Whey 18% | Vegetable based 100% (Palm Olein, Coconut, Soy Bean, High Oleic Safflower) | 200mOsm/kg |
| **ALFARE** | Maltodextrin 86% Potato starch 12% Lactose 2% | Whey 100% -peptides 80% -free amino-acids 20% | MCT 50% Butter oil 30% Corn oil 20% | 220 mOsm/kg |

# Dietary Trials Conclusions

- *A* whey-based hydrolysed protein formula showed no advantages over the low lactose formulas, indeed had WORSE outcomes (Darwin)
- A milk-based diet was better than an equivalent cereal-based diet (despite lactose intolerance) in kwashiorkor (Malawi)
- Thus, cow's milk protein intolerance did not appear to be prolonging the enteropathy in children in either Darwin or Malawi
- Overall the **lowest osmolality lactose-free formula**, gave the best results with significantly better mucosal recovery and less diarrhoea

# 1. Malnutrition & Diarrhoea: a vicious cycle?

# Effects of Malnutrition on GI System (WHO Manual)

| | |
|---|---|
| Gastrointestinal system | Production of gastric acid is reduced<br>Intestinal motility is reduced<br>Pancreas is atrophied and production of digestive enzymes is reduced<br>Small intestinal mucosa is atrophied; activities of digestive enzymes are reduced<br>Absorption of nutrients is reduced when large amounts of food are eaten |

## Response

| |
|---|
| Give the child small, frequent feeds<br>If absorption is poor, increase the frequency and reduce the size of each feed<br>If there is malabsorption of fat, treatment with pancreatic enzymes may be useful |

## MISSING

**If there is malabsorption of carbohydrates, give a lactose-free milk formula (e.g. De-Lact, LF Nan, Similac LF Advance, etc.**

# Environmental Enteropathy (EE)

**Features**: villous atrophy, crypt hyperplasia, increased permeability, inflammatory cell infiltrate, modest malabsorption

**Causes**: faecal bacteria ingested in large quantities by young children living in conditions of poor sanitation and hygiene

It is difficult to isolate the specific effects of the enteropathy from the consequences of the context of deprivation (malnutrition, neglect, overexposure to pathogens) in which these children live

**Consequences**: poor growth (stunting)

**Prevention**: provision of toilets and promotion of handwashing with soap would reduce or prevent tropical enteropathy and its adverse effects on growth

# PREVENTION OF EE

## Hygiene Systematic Review

**Aim:** What interventions reduce a high incidence of diarrhoeal infections

**Results:** There is **strong evidence of an effect of education and handwashing with soap in preventing diarrhoeal disease among children**. Children living in households that received plain soap and encouragement to wash their hands had a **53% lower incidence of diarrhoea** (CI 35 to 59%). The size of these effects is small and the **quality of the studies generally poor**

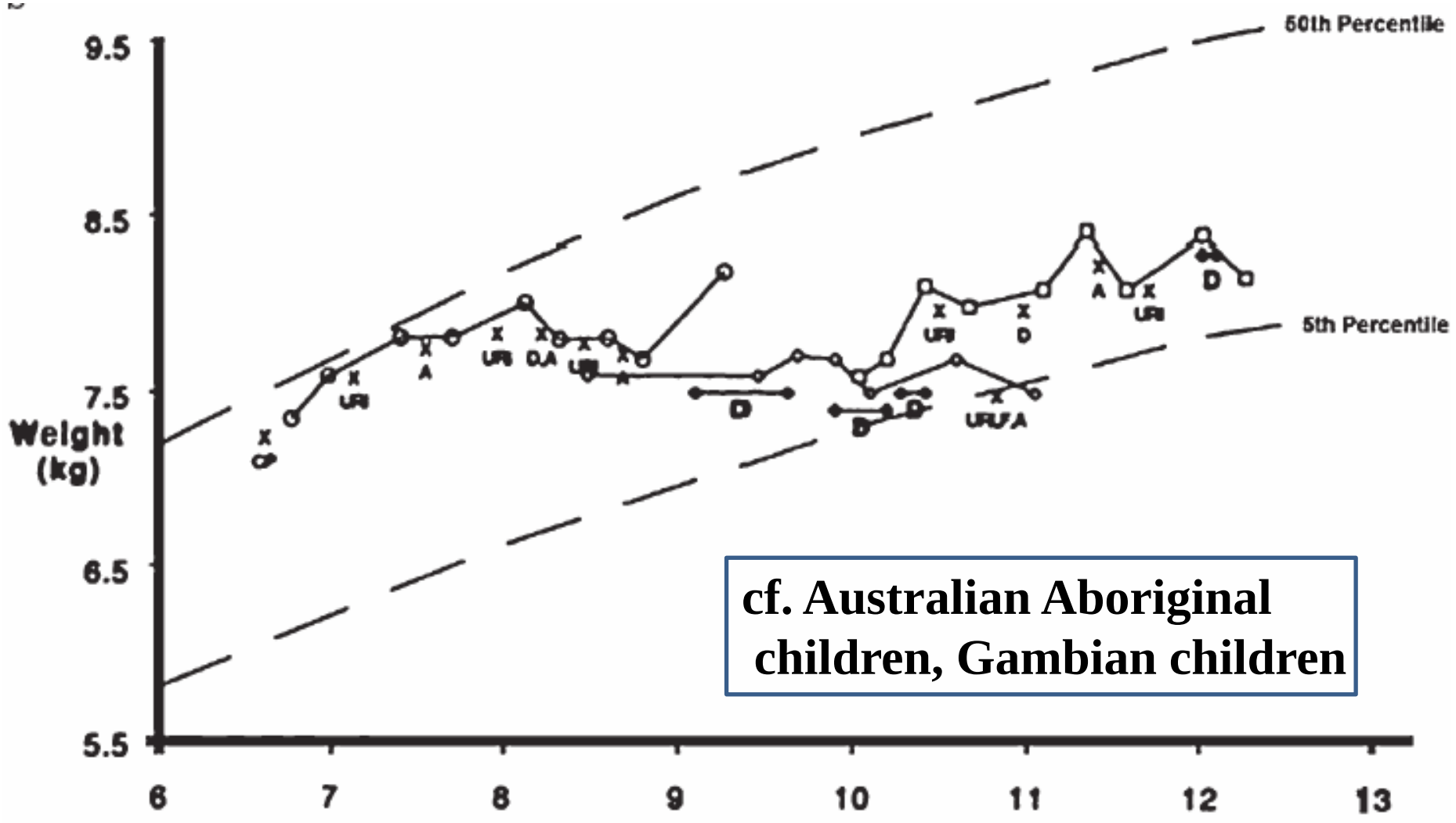
**Conclusion:** Research which measures the effectiveness of hygiene interventions is complex and difficult to implement. Multifaceted **interventions which target handwashing with soap and include water, sanitation and hygiene promotion** are likely to provide the greatest opportunity to improve child health outcomes

# Malnutrition as an enteric infectious disease with long-term effects on child development

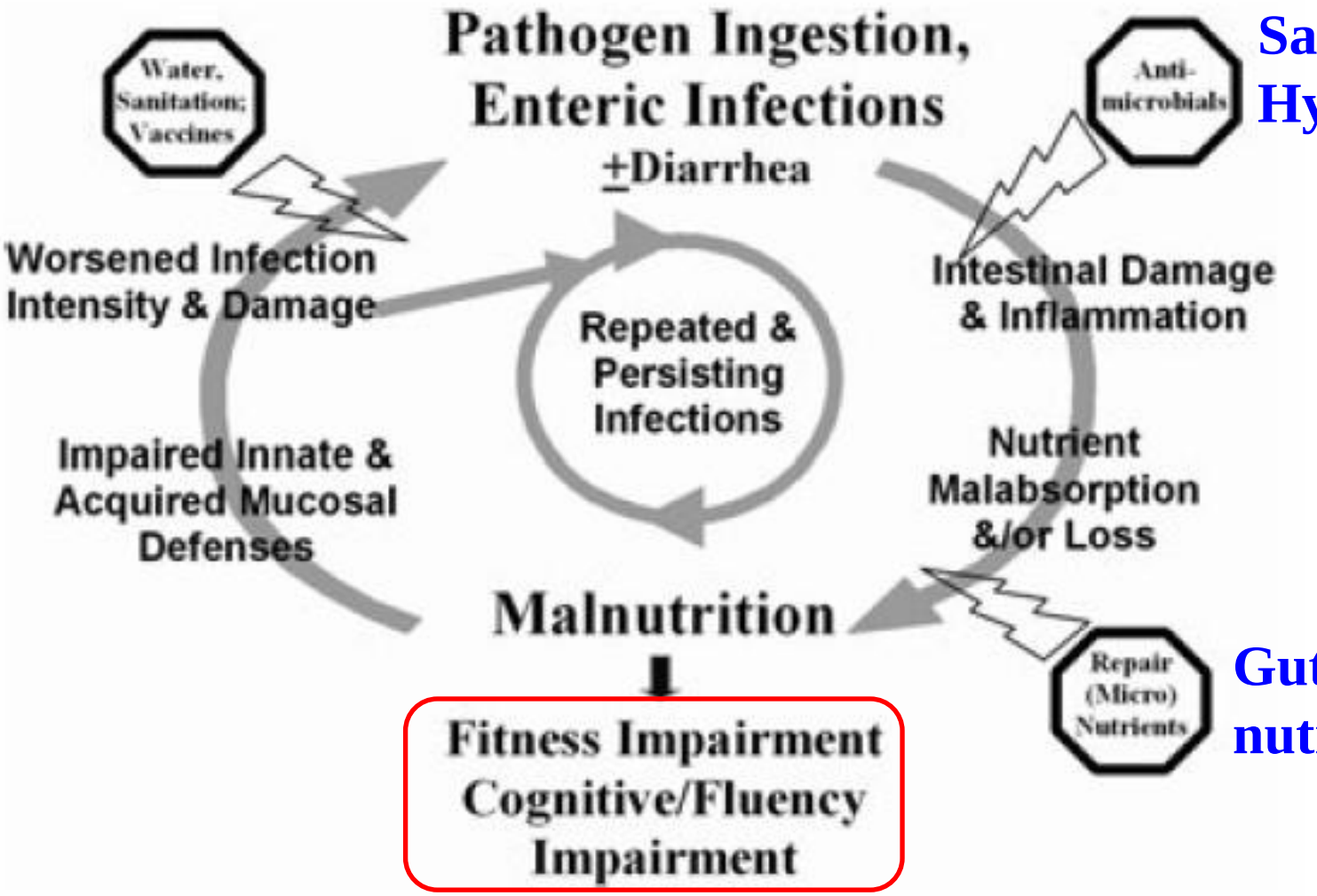
Richard L Guerrant, Reinaldo B Oriá, Sean R Moore, Mônica OB Oriá, and Aldo AM Lima

- **Enteric infections and malnutrition: a vicious cycle?**
  - NO - Briend: epidemiological data – catch-up growth
  - YES - Guerrant: high prevalence areas – faltering growth
  - AGREE - Malnutrition does increase risk of diarrhoeal disease
- When challenged by the argument that catch-up growth reverses the growth impairment of isolated diarrhoeal illnesses, analyses of weight gains following a diarrhoeal illness in studies in Brazil revealed that recurrent diarrhoea reduced weight and height gains by 48% and 21%, respectively, when compared with children who did not have recurrent diarrhoea (Cf Leonardo Mata's studies in Guatemala in the 1960s)

# Effects of repeated diarrheal episodes on childhood growth curves (Guerrant)



# Breaking the vicious cycle between malnutrition and diarrhoea by repairing the intestinal mucosa (modified from Guerrant)



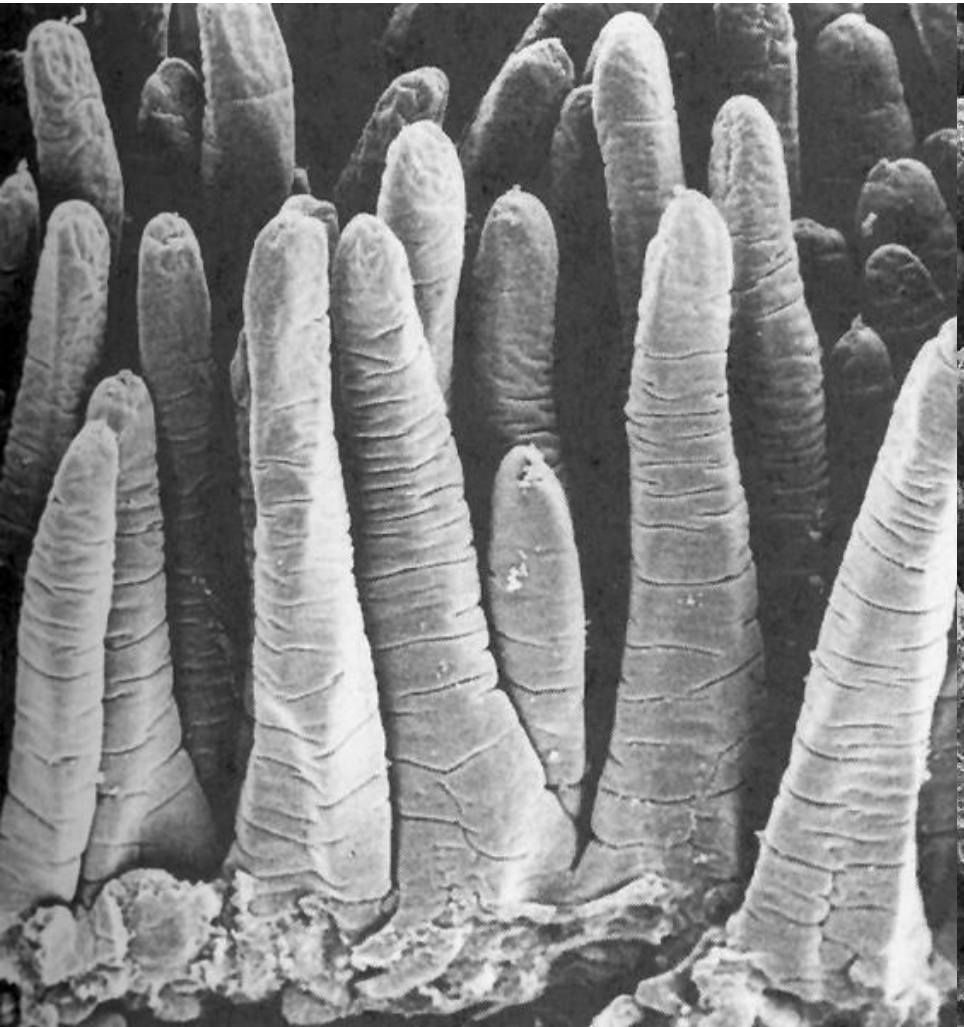
# 2. Intestinal Permeability & Inflammation

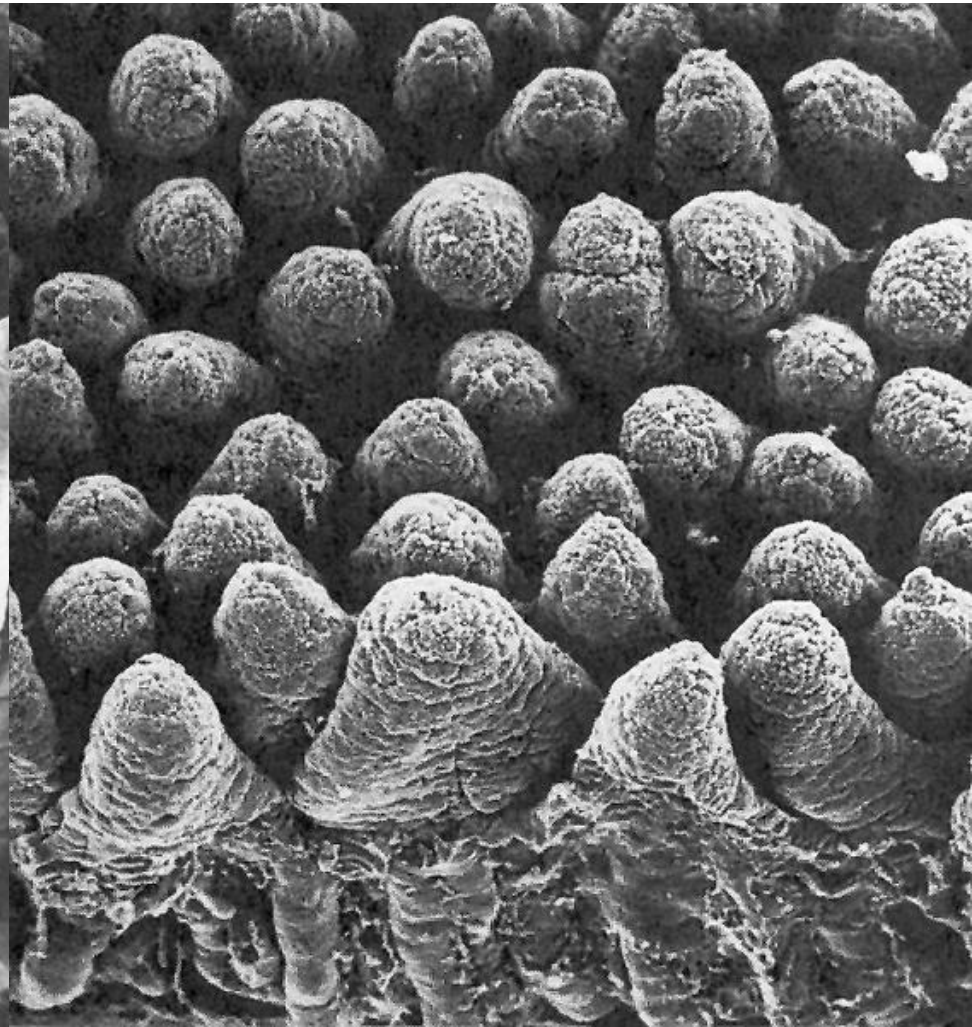
# Scanning Electron Microscopy

Normal brush border

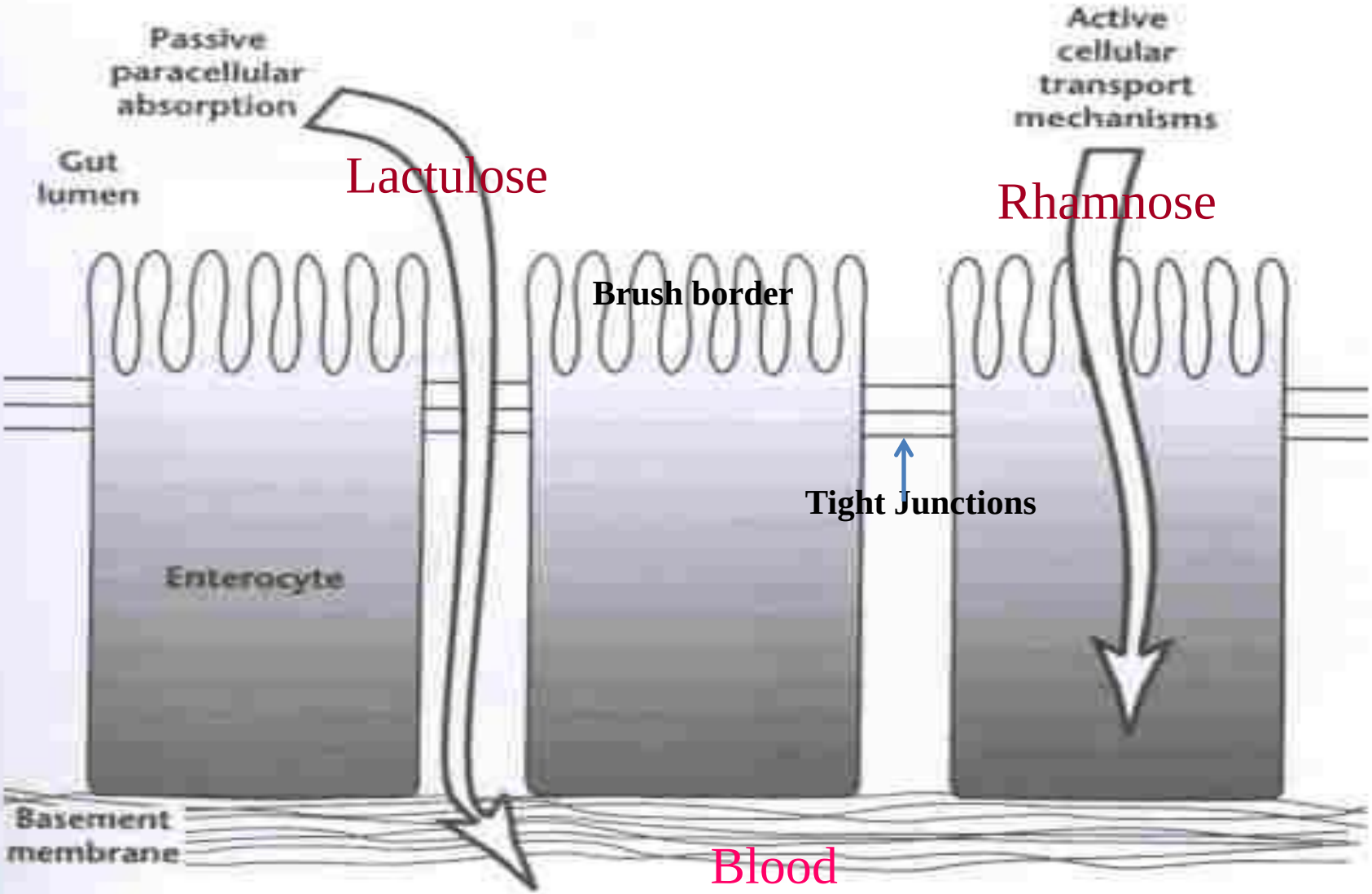
Villous atrophy (Rotavirus-infected)

**The equivalent surface area of a doubles tennis court which regenerates every 3 days**

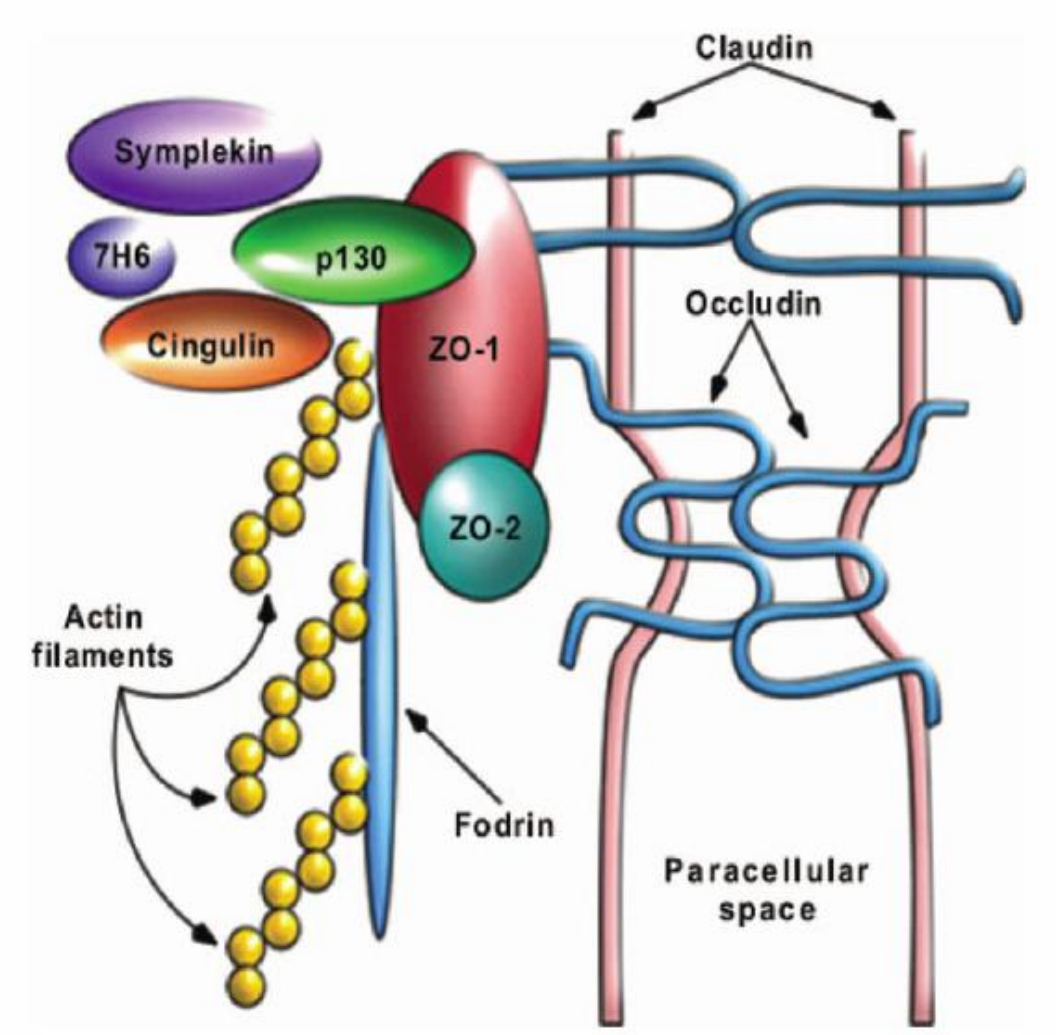




# Intestinal Permeability Pathways



# Tight Junction Complex



# Functional Significance of Abnormal Permeability

- Gambian study: abnormal permeability ratios explained 40% of growth faltering in weight and 46% in height in children 2-15 months
- Severe lactose malabsorption occurred in 26% of breast fed children aged 12-15 months
- Lactose malabsorption and high permeability ratios **explained 48% of growth faltering**

# Causes of Persistent Diarrhoea in Brazil

*Table 2* **Emerging causes of persisting diarrhea in shantytowns in Fortaleza northeastern Brazil.**

| Pathogen | Cases (%) ($n = 127$) | Controls (%) ($n = 331$) |
|---|---|---|
| Enteroaggregative *E. coli* | | |
| AA probe + | 32* | 14 |
| AA probe – | 36* | 17 |
| *Cryptosporidium* | 25** | 0 5 |
| *Giardia lamblia* | 21** | 0 8 |

* $p < 0.05$
** $p < 0.02$

# Key Associations in Darwin

1. prolonged gut damage:
   *Cryptosporidium*
2. severe diarrhoea and dehydration:
   *Cryptosporidium* & Rotavirus
3. hypokalaemia and wasting:
   *Strongyloides*
4. metabolic acidosis & lactose intolerance:
   Rotavirus
5. Enteroaggregative *E. coli* was commonest

# HIV Infection

- HIV is commonly associated with persistent diarrhoea
- Malnutrition in HIV is associated with a rapid decrease in the CD4+ cell number and an increased risk of opportunistic infections
- Lactose malabsorption is particularly common, even in exposed uninfected infants
  - Several cellular mechanisms are directly affected by HIV infection
    - As an example, Tat protein released by the virus can interact directly with enterocytes functioning both as a viral cytotoxin and an enterotoxin
    - This protein-cell interaction impairs cell growth and proliferation, and inhibits ion transport
    - In the setting of immunosuppression, opportunistic agents (e.g. cryptosporidium, blastocystic hominis, candida albicans) contribute to the diarrhoea and mucosal injury

**HIV infection both directly and indirectly induces intestinal dysfunction, malnutrition and immune impairment**

# 3. Malabsorption:

a) Protein

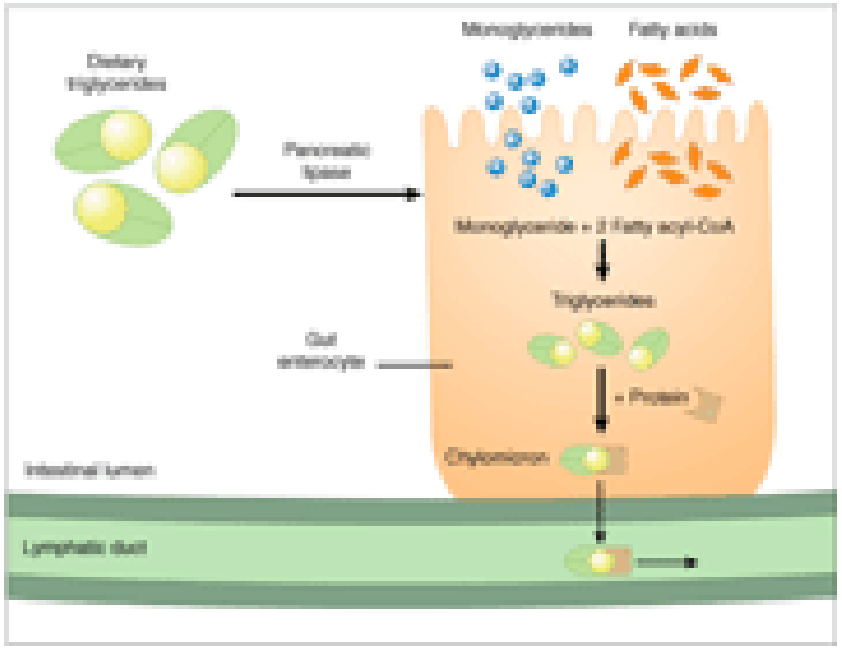
b) Fat

c) Sugars

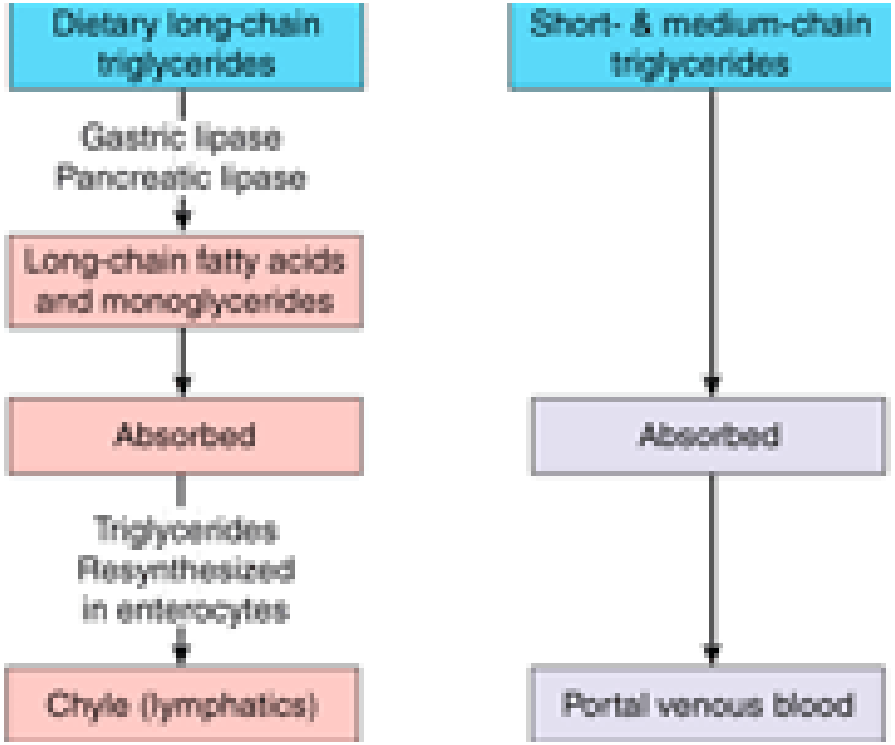
# Protein Loss

- Protein-losing enteropathy (PLE) is a **rare** condition characterised by protein loss through the gastrointestinal tract, leading to reduced serum protein levels
- Other causes of hypoproteinaemia such as malnutrition, impaired synthesis, or protein loss through the kidney have to be excluded
- The disorders causing PLE can be divided into those due to:
  - 1. protein loss from intestinal lymphatics, like primary intestinal lymphangiectasia or congenital heart disease and those with
  - 2. protein loss due to an inflamed or abnormal mucosal surface
- The diagnosis is confirmed by increased **faecal alpha-1-antitrypsin**

# Fat Digestion

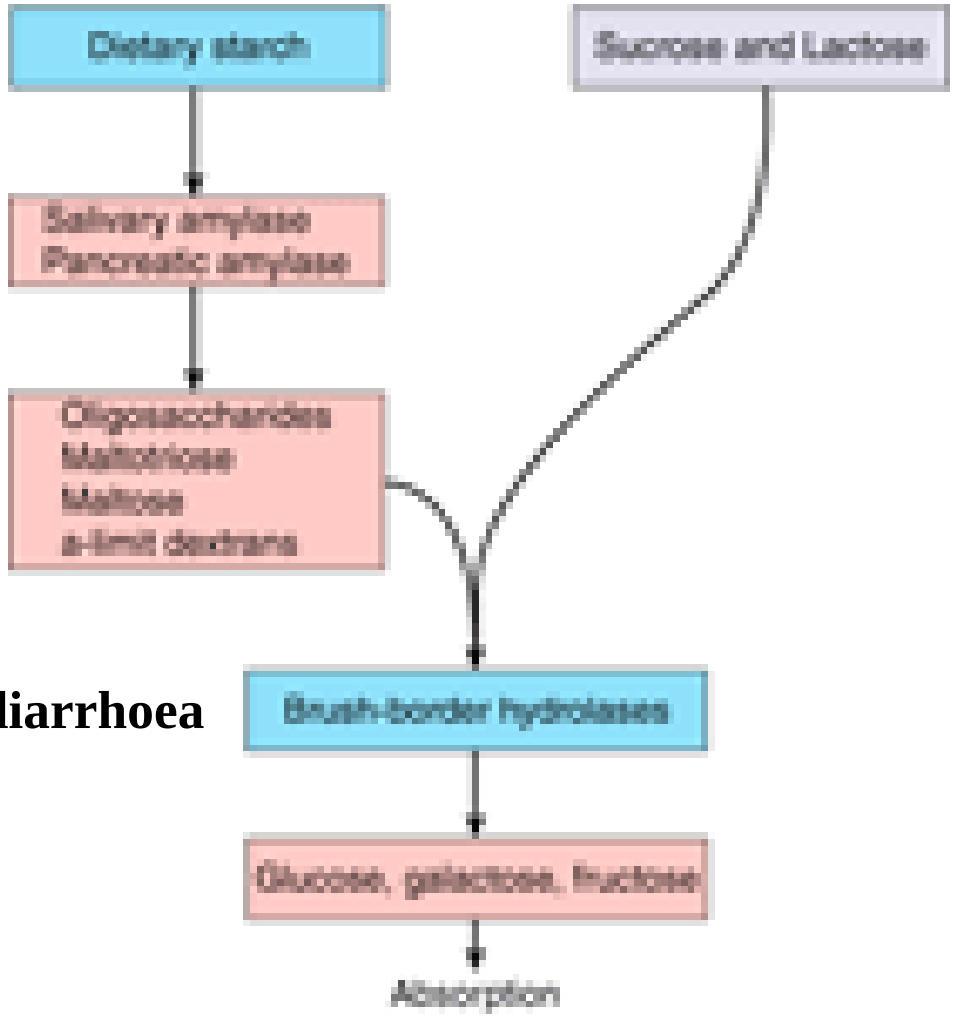



**Pancreatic lipase in small intestinal brush borders hydrolyses triglycerides**



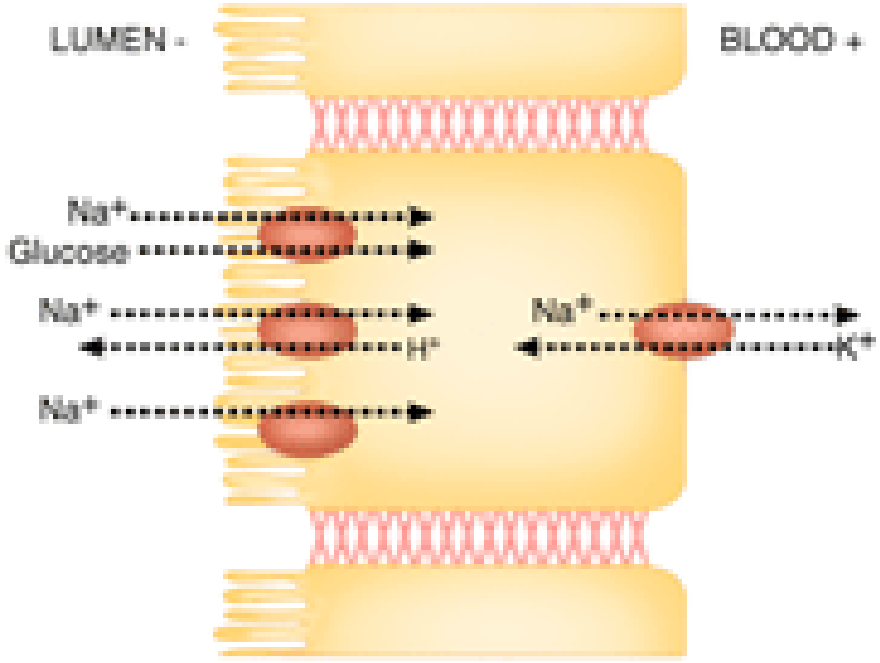

**Absorption of long *vs* medium-chain triglycerides**

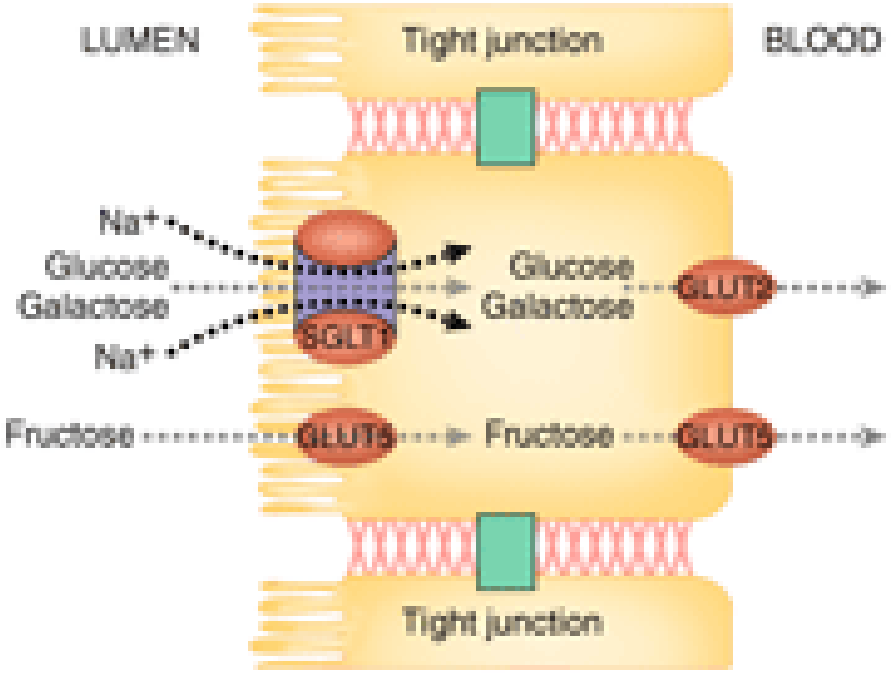
# Sugar Digestion




**Deficiency leads to osmotic diarrhoea**

# Transcellular Monosaccharide Absorption



# 4. Gut Trophic Nutrients

a) Probiotics
b) Prebiotics
c) Zinc
d) Vitamin A
e) Glutamine
f) Arginine

# Gut Trophic Nutrients

- Gut trophic nutrients - such as **zinc**, **vitamin A** (retinol, carotenoids), **glutamine** derivatives and **arginine** - are involved in the:

1. regulation of intestinal epithelial proliferation
2. migration, differentiation, apoptosis, and necrosis
3. intestinal epithelium transcellular and paracellular transport
4. enterocyte turnover,
5. Enhancement of immune responses
6. rehabilitate the intestinal mucosal barrier following mucosal injury
7. offer the potential of breaking the vicious cycle of malnutrition and enteric infections with mucosal damage

# Nutrients inducing intestinal growth and mucosal repair

- New strategies to ameliorate the impact of enteric diseases through nutrients which:
  1) **promote intestinal barrier repair**
  2) **treat mucositis**
  3) **repair intestinal absorptive function**
  4) expand the **surface absorptive area**
- **Glutamine** inhibits toxin-induced damage to tight junctions essential to the integrity of intestinal epithelial monolayers
- Targeted therapies for the nutritional consequences of enteric infections and inflammation

# e) Glutamine

- An important precursor for nucleotide synthesis
- An important fuel source for rapidly dividing cells such as gastrointestinal epithelia
- Helps the gastrointestinal mucosa heal more promptly after damage

# Glutamine Supplementation

Systematic Review

- Two trials with a total of 100 infants
- These studies were generally of good methodological quality but were underpowered to detect clinically important effects of glutamine supplementation
- Meta-analysis did not reveal a statistically significant difference in either the risk of death before hospital discharge, or in the rate of invasive infection

Authors' conclusions

- The available data from randomised controlled trials are **not sufficient to determine whether glutamine supplementation confers clinically significant benefits** for infants with severe gastrointestinal disease

# Glutamine Studies

1. A significant decrease was observed in the permeability ratio after 10 days of glutamine (2.75 g/kg/day) compared to a similar dose of glycine (placebo)
2. Prospective double-blind clinical trial in **Brazil**, 10-day administration of glutamine *vs* glycine significantly improved intestinal paracellular barrier function and there were long-term beneficial effects on growth, consistent with another the double-blind intervention trial with a glutamine derivative, alanyl-glutamine, as compared to glycine control
3. A double-blind clinical trial in growth-faltering **Gambian** infants using glutamine (0.25 g/kg body weight/day) or an isonitrogenous, isoenergetic mix of nonessential amino acids administered daily per mouth for 5 months did not improve growth or intestinal barrier function, but the dose of glutamine was tenfold lower than in the other two studies

# f) Arginine

- An amino acid with important roles in nitrogen and ammonia metabolism, and in the generation of nitric oxide
- Animals subjected to wounds or fractures have improved rates of wound-healing, nitrogen retention, and growth when supplemented with dietary arginine
- Rats receiving arginine-supplemented parenteral nutrition show an increased ability to synthesize acute phase proteins when challenged with sepsis

# Arginine Supplementation

- Decreased concentration of nitric oxide is proposed as one of the possible cellular mechanisms for **necrotising enterocolitis (NEC)**
- Arginine can act as a substrate for the production of nitric oxide in the tissues and arginine supplementation may help in preventing NEC
- Only one eligible study was identified of good methodological quality
- There was a statistically significant **reduction in the risk of developing NEC in the arginine group** compared with the placebo group (RR 0.24; CI 0.1-0.6)
- No significant side effects directly attributable to arginine were observed

# Glutamine & Arginine

- Glutamine and arginine are essential for nucleic acid biosynthesis and for key intermediates of cellular replication
- Glutamine oxidation by intestinal cells provides a **major energy source for the mucosa**
- Its major limitations as an oral therapy are its poor solubility and tendency to hydrolyse to potentially toxic glutamate
- Linking glutamine to alanine solves both drawbacks, as alanyl-glutamine is stable, highly soluble, well tolerated, and at least as effective as glutamine alone in driving sodium co-transport and intestinal injury repair

# 5. Dietary Management of SAM

# What are the treatment implications for practice?

- Zinc and vitamin A should be given routinely to SAM cases after 6 months of age
- Before 6 months, use a humanised infant formula rather than F75 milk
- Have a high index of suspicion for osmotic diarrhoea; test reducing substances in stool, change to low lactose milk formula (or Lactaid with breastfeeding)

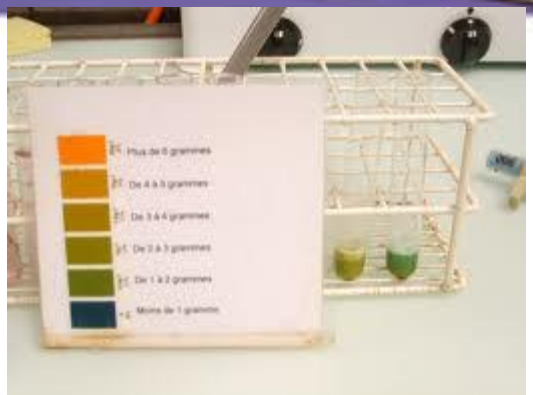
# WHO DIETS

***Table 8. Composition of F-75 and F-100 diets***

| Constituent | Amount per 100 ml | |
|---|---|---|
| | F-75 | F-100 |
| Energy | 75 $kcal_{th}$ (315 kJ) | 100 $kcal_{th}$ (420 kJ) |
| Protein | 0.9 g | 2.9 g |
| Lactose | 1.3 g | 4.2 g |
| Potassium | 3.6 mmol | 5.9 mmol |
| Sodium | 0.6 mmol | 1.9 mmol |
| Magnesium | 0.43 mmol | 0.73 mmol |
| Zinc | 2.0 mg | 2.3 mg |
| Copper | 0.25 mg | 0.25 mg |
| Percentage of energy from: | | |
| protein | 5% | 12% |
| fat | 32% | 53% |
| Osmolarity | 333 mOsmol/l | 419 mOsmol/l |

# Lactose intolerance

## Testing for stool sugars

## Treating with Lactase

# Lactose-free Formulas



**OSMOLALITY**

**PediaSure 345**

**De-Lact 165**

# Finally, pay attention to details

1. Check how F75 & F100 formulas are actually mixed
2. Are 8-12 feeds actually given per day initially?
3. Dose of potassium in milk & supplement
4. Check osmolality of milk formula
5. Stool water for hot & cold reducing substances
6. Correct procedure for tube-feeding, when necessary

# Conclusions

1. Why is protein deficiency still given as the cause of kwashiorkor?
2. Is the interaction between malnutrition and diarrhoea a vicious cycle?
3. What is intestinal permeability?
4. Malabsorption of protein, fat or sugars in SAM?
5. What are gut trophic nutrients?
6. How can we improve the dietary management of SAM with diarrhoea? (in view of our new understanding of enteropathy)

# END