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## Gastrointestinal Disease in Malnourished Children<sup>1,2</sup>

by

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### Abstract

*In communities where malnutrition is common, gastrointestinal diseases are prominent and contribute largely to unfavourable morbidity and mortality statistics. Patterns of gastrointestinal disease were studied in two such communities; Aboriginal children in Western Australia and children admitted to the Dr. Cipto Mangunkusumo General Hospital, Jakarta.*

*Two hundred and fifty one (251) young Aborigines were studied. Forty percent of them malnourished, 37% were anaemic and more than 50% had enteric pathogens in their stools. Sugar intolerance was also common (25%). Similar clinical features are seen in the children from Jakarta but more severe forms of malnutrition and gross vitamin deficiency occurred more often.*

*Thirteen of the Aboriginal children died; at necropsy the most remarkable finding was fatty infiltration of the liver which in some cases was extreme. This, of course, is characteristic of protein-calorie malnutrition and has been well documented in other studies. Other pathological findings included severe purulent infections, septic infarcts, haemolysis, acanthocytosis, thrombocytopenia and vascular catastrophes.*

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## Introduction

Malnutrition is one of the main public health problems facing mankind and is one of the main reasons for unsatisfactory morbidity and mortality in infants and children in pre-industrialized countries. Diarrhoeal disease is very common and, often, very serious in malnourished children, yet its pathogenesis is poorly understood.

This paper discusses the pathogenesis of diarrhoea in malnourished children. The information has been obtained from a review of the current literature and from the results of our collaborative research studies being done with members of the Department of Child Health, University of Indonesia. Reference will also be made to studies being done in this laboratory on malnourished Australian aboriginal children.

The factors to be considered include:

- (i) Intestinal infection and infestations
- (ii) Abnormalities in small-intestinal histology
- (iii) Impaired digestive function
- (iv) Poor absorptive function
- (v) Overgrowth in the small intestine by organisms not generally considered 'enteropathogenic'
- (vi) Possible abnormalities of immune function, and
- (vii) Environmental factors

## Pathogenesis of gastrointestinal disease in malnutrition

### 1. Intestinal Infections and Infestations

A high prevalence of infections and infestations of the gut is characteristic of malnutrition (Scrimshaw, et al., 1968). This is in contrast with well-nourished children in whom enteric pathogens are found in only 10 to 25% of patients. In malnourished Australian aboriginal children, for example, enteric pathogens occur in 50% and, in many instances, multiple infections or infestations are common (Gracey, 1973). Often, infections with known enteropathogens can readily be implicated in the causation of diarrhoea as, for example, in patients with gastrointestinal infection with pathogenic strains of *Escherichia coli* or with an infestation by the common intestinal parasite *Giardia lamblia* which has been shown to have deleterious effects on intestinal ultrastructure and function (Barbieri et al., 1970). Quite often, however, pathogenic micro-organisms will not be found in children with diarrhoeal illnesses despite repeated microbiological examinations of specimens of stools.

It has recently been shown that viruses are also an important factor in young children with acute diarrhoea (Bishop et al., 1973) and perhaps are involved in the production

FIG. 1 : Normal steps in digestion of lactose by lactase and absorption of its competent monosaccharides by the small intestine.

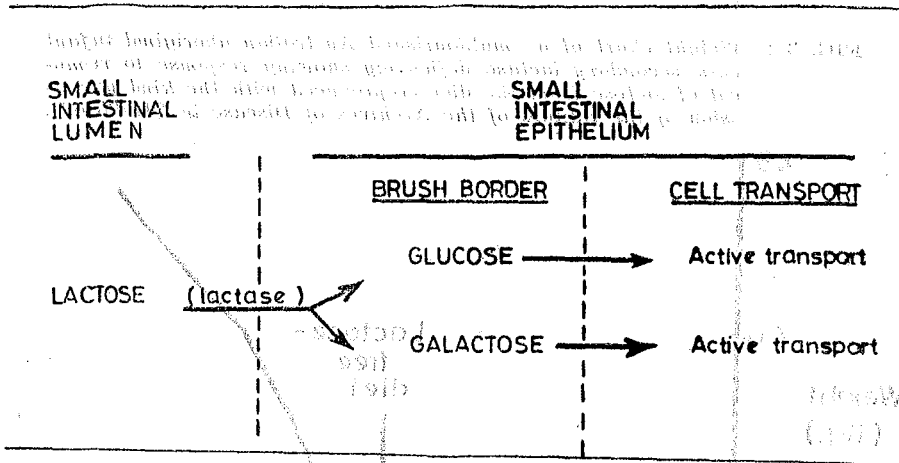


FIG. 2 : Pathogenesis of diarrhoea in patients with sugar malabsorption.

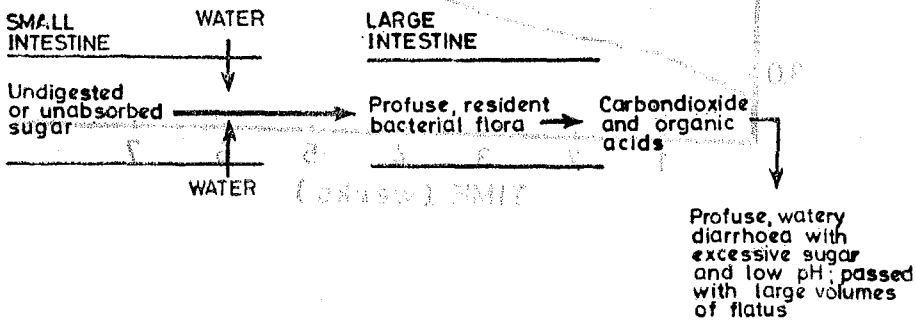
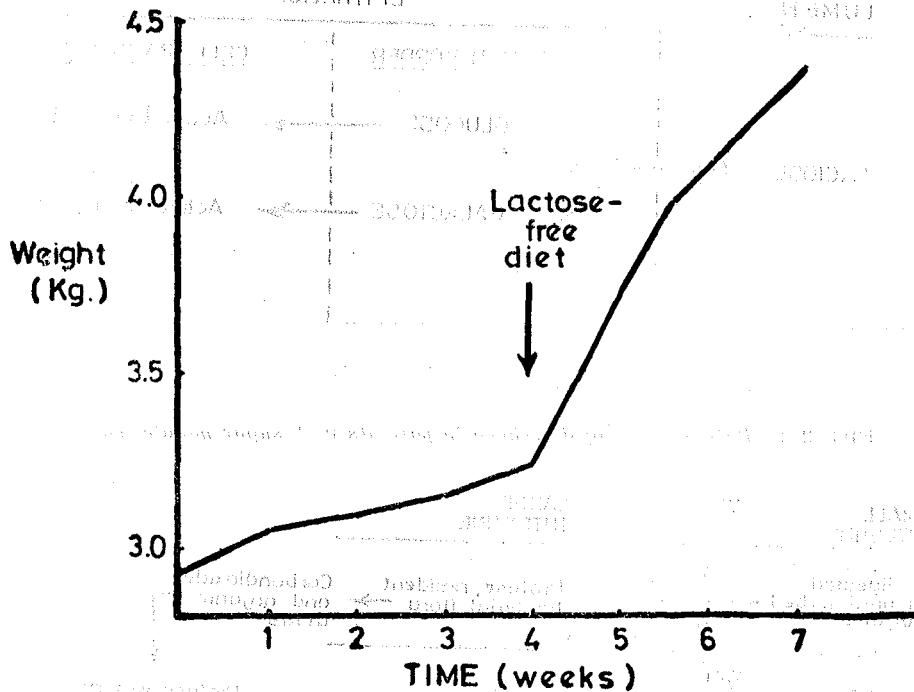


FIG. 3 : *Weight chart of a malnourished Australian aboriginal infant with secondary lactase deficiency showing response to removal of lactose from the diet (reproduced with the kind permission of the Editors of the Archives of Disease in Childhood).*



of gastrointestinal symptoms in malnourished children. Further investigations are needed to confirm this possibility.

## 2. Histological changes in the small bowel epithelium.

Histological abnormalities in the epithelium of the upper small bowel have been reported in malnourished children from many countries including Kenya (Burman, 1965), Uganda (Stanfield et al., 1965) Chile (Brusner et al., 1966) and in Australian aboriginal children (Harris et al., 1970; Walker-Smith and Reye, 1971). These changes appear to be common and may be very severe.

Recently, Shiner (1973) has shown extensive ultrastructural damage in small bowel biopsies from malnourished children. The pathogenesis of these changes is uncertain. There is no doubt, however, that they have important effects on gastrointestinal function as is outlined below.

## 3. Digestive function

It must be remembered that important digestive enzymes, such as disaccharidases, normally line the luminal surface of the small intestinal epithelium (Miller and Crane, 1961) and are therefore very vulnerable to damage in diseases with abnormalities of small intestinal histology. It is to be expected, then, that deficiencies of these enzymes occur in malnourished children

in whom abnormal histology is common. Secondary disaccharidase deficiency has been reported from various centres (e.g. Bowie et al., 1965; Wharton et al., 1968; Walker and Harry, 1972). This is an important syndrome to recognize since these patients may have very severe, life-threatening diarrhoea which will respond to removal of the offending sugar, usually lactose, from the diet.

It is essential that the pathogenesis of secondary sugar intolerance is thoroughly understood because successful treatment depends on a direct application of this knowledge. As can be seen in Figure 1, lactose is normally digested to its component monosaccharides (glucose and galactose) prior to absorption. In patients with a deficiency of the enzyme lactase, this does not occur and the undigested sugar attracts large volumes of water into the lumen of the gut. When this load of sugar and fluid reaches the large intestine, the large numbers of micro-organisms normally present there produce acidic by-products and large volumes of carbon dioxide which is passed as flatus. (Fig. 2). Excessive amounts of sugar can be detected in the fluid part of the stool by the Clinitest method,\* a simple modification of the method used for detecting glycosuria (Kerry and Anderson, 1964). It must be stressed that this test

\* Clinitest, Ames Company, U.S.A.

must be done on the fluid part of the stool and that the specimen must be fresh; if the specimen is allowed to stand around on a laboratory bench bacteria will rapidly break down any sugar present into organic acids, such as lactic acid, and the test will therefore produce a 'false negative' result. Secondary lactase deficiency will respond rapidly by cessation of diarrhoea and improved weight gain when a lactose-free diet is given (Fig. 3). Feeding formulae containing reduced amounts of lactose are now commercially available.\*\*

Apart from lactase deficiency secondary to mucosal damage, it must be realised that lactase deficiency (possibly genetic in origin) is common in certain ethnic groups including Indonesians (Suharjono et al., 1971). This is important in planning nutritional rehabilitation programmes and foreign aid programmes which often include supplies of milk which may, in fact, be harmful to affected individuals.

#### 4. Absorptive function

Apart from poor digestive function, malnutrition causes poor intestinal absorptive function. The most important clinical result of this is Temporary Monosaccharide Malabsorption (Burke and Danks, 1966). This has been reported from several countries including Australia, (Wal-

ker and Harry, 1972), Uganda (Wharton et al., 1968) and Latin America (Lifshitz et al., 1970). These children are often extremely ill, with severe dehydration and acidosis and their mortality rate is very high. They can be recognized by showing excessive reducing substances in their stools which continues when a lactose-free diet is given because they are unable to tolerate all sugars including glucose, galactose and fructose. They should be treated with a carbohydrate-free feeding formula\* and usually require intravenous fluids. It is likely that these children have malabsorption of other water-soluble nutrients such as amino acids which contributes to their diarrhoea and complicates their management.

#### 5. Overgrowth of micro-organisms

(in the upper gut)

It seems likely that microbial overgrowth in the upper small bowel is a significant feature in malnourished infants and children with diarrhoeal illnesses. In malnourished Australian aborigines we found (Gracey and Stone, 1972) a generalized and marked overgrowth by oral-type and faecal-type micro-organisms in comparison with specimens of upper intestinal contents from well nourished

\*\* e.g. Nutramigen, Mead Johnson; Galactomin, Trufood; Low Lactose Milk Food, Cow and Gate; Eiwit Melk; Almiron-Nutricia, Holland.

\* e.g. CF1, Nestlé, Australia.

children. More recently we have found significant microbial contamination of aspirates from the upper gastrointestinal tract in 21 malnourished Indonesian patients (Gracey et al., 1973). A wide variety of organisms were found including Staphylococci, *E. coli*, *Pseudomonas* sp., Streptococci, Anaerobic bacteria and *Candida* sp. (Gracey et al, in press) The possible contribution of these microbiological abnormalities to the symptoms occurring in such patients has not yet been elucidated although it is known that bacterial contamination of the upper small bowel results in various metabolic sequelae including malabsorption of fat, proteins and carbohydrates (Gracey, 1971).

Preliminary results from this laboratory (unpublished data) suggest that several organisms not generally considered to be 'enteropathogenic', including non-pathogenic varieties of *E. coli*, may cause impaired intestinal absorption of water-soluble nutrients. Our traditional ideas about enteropathogenicity may need considerable revision in the near future.

#### 6. Immunological function

The gut is a major organ of immune defence and has a high rate of exposure to foreign antigens. It is important, therefore, to consider what circumstances allow gross overgrowth of this organ to occur in malnourished children. Is it, for example, due to a break-down in

the immune defence mechanisms allowing bacteria and yeasts to proliferate uncontrolled? Studies done in malnourished Australian aboriginal and Indonesian children show that these individuals do not have decreased levels of serum and intestinal immunoglobulins (Bell et al., 1973). In fact, their levels of immunoglobulins were significantly increased indicating that their immunoglobulin responses seem adequate. Cellular mediated immunity is known, however, to be impaired in malnutrition (Chandra, 1973) and it seems important that local intestinal cell-mediated immune responses should be investigated in infants and children with malnutrition.

#### 7. Environmental factors

In communities where malnutrition is endemic, living conditions are overcrowded and unhygienic (Jelliffe, 1970). This is due to a combination of poverty, ignorance and unsatisfactory habits in nutrition and hygiene. In a recent study, we found a high rate of isolation of significant numbers of faecal organisms not normally encountered in oro-pharyngeal secretions in malnourished children (Gracey et al., 1973). This emphasizes the importance of the faecal-oral route of transmission of infections and infestations in malnourished children living in unsatisfactory circumstances. It also re-emphasizes the importance of adequate

educational and public health measures in preventive health programmes. Repeated hospital treatment is not only expensive but it will be ineffective if children return to living in a grossly contaminated environment.

### The future

It should be clear from the foregoing discussion that the production of gastrointestinal disease in malnourished children is a very complex process which, as yet, is not fully understood. One would seem justified in asking 'what is the point of undertaking sophisticated research investigations in children with malnutrition when the solution to their problem would seem simple - more food?'. There are at least a couple of reasons why such studies are necessary. We have a grave responsibility as professionals to indicate to those responsible for administering Government funds that malnutrition and intestinal disease are major problems in certain communities. Politicians

and Government officials are not easily convinced by emotional pleas or poorly substantiated arguments.

They can, however be convinced by facts and figures. The financial costs involved in current therapeutic health measures in hospitals would, in many instances, be more usefully employed in preventive programmes.

And, of course, we must convince these people that the future prosperity of any nation depends ultimately on the health of its children. Furthermore, results of research studies should be applied in clinical practice; one example is the useful place modified milk formulae, which were introduced only recently, now have in the management of children with sugar intolerance. Continued research into gastrointestinal disease in malnourished children will lead to better management of our patients and to a better understanding of gastrointestinal disorders which will, eventually, benefit many children.

### REFERENCES

1. BARBIERI, D., DE BRITO, T., HOS. HIMO, S., NASCIMENTO F.O.B., MARTINS CAMPOS, J.V., QUARENTEL, G. and MARCONDES, E.: Giardiasis in childhood, absorption tests and biochemistry. histochemistry, light and electron microscopy of jejunal mucosa. Arch. Dis Child. 45:466 (1970).
2. BELL, R.G., TURNER, K.J. and GRACEY, M.: Serum and intestinal immunoglobulins in malnourished children Proc. aust. Soc. med. Res. 3: 140 (1973).
3. BISHOP, R.F. DAVIDSON, G.P., HOLMES, I.H. and RUCK, B.J.: Virus particles in epithelial cells of duodenal mucosae from children with non-bacterial gastroenteritis. Lancet ii: 1281 (1973).
4. BOWIE, M.D., BRINKMAN, G.L. and HANSEN, J.D.: Acquired disaccharide intolerance in malnutrition. J. Pediatr. 66: 1083 (1965).



5. BRUSNER, O., REID, A., MONCKEBERG, F., MACCIONI, A. and CONTRERAS, I.: Jejunal biopsies in infant malnutrition: with special reference to mitotic index. *Pediatrics* 38: 605 (1966).
6. BURKE, V. and DANKS, D.M.: Monosaccharide malabsorption in young infants. *Lancet* i: 1177 (1966).
7. BURMAN, D.: The jejunal mucosa in kwashiorkor. *Arch. Dis Child.* 40: 526 (1965).
8. CHANDRA, R.K.: Immunocompetence in undernutrition. *J. Pediatr.* 81: 1194 (1972).
9. GRACEY, M.: Intestinal absorption in the "contaminated small-bowel syndrome", *Gut* 12: 403 (1971). Enteric disease in young Australian Aborigines. *Aust. N.Z.J. Med.* 3: 576 (1973).
10. GRACEY, M., SUHARJONO, SUNOTO and STONE, D.E.: Microbial contamination of the gut; Another feature of malnutrition. *Am. J. clin. Nutr.* 26: 1170 (1973).
11. GRACEY, M. and STONE, D.E.: Small-intestinal microflora in Australian aboriginal children with chronic diarrhoea. *Aust. N.Z.J. Med.* 3: 215 (1973).
12. GRACEY, M., STONE, D.E., SUHARJONO and SUNOTO: Oro-pharyngeal microflora in malnourished children. *Aust. Paediatr. J.* 9: 260 (1973). Isolation of *Candida* species from the gastrointestinal tract in malnourished children. *Am. J. clin. Nutr.* (in press)
13. HARRIS, M.J., DUFFY, B.J. and BEVERIDGE, J.: Studies on the small bowel of a group of New South Wales Aboriginal Children. *Med. J. Aust.* 1: 356 (1970).
14. JELLIFFEE, D.B.: Diarrhoeal disease of early childhood in Woodruff's *Alimentary and Haematological Aspects of Tropical Disease* pp. 145-181 (Edward Arnold, London 1970).
15. KERRY, K.R. and ANDERSON C.M.: A ward test for sugar in faeces. *Lancet* i: 981 (1964).
16. LIFSHITZ, F., COELLO RAMIREZ, P. and GUTIERRES-TOPETE, G.: Monosaccharide intolerance and hypoglycaemia in infant with diarrhoea. I. Clinical course of 23 infants. *J. Pediatr.* 77: 595 (1970).
17. MILLER, D. and CRANE, R.K.: The digestive function of the epithelium of the small intestine. II. Localization of disaccharide hydrolysis in the isolated brush border portion of intestinal epithelial cells. *Biochem. biophys. Acta* 52: 293 (1961).
18. SCRIMSAW, N.S., TAYLOR C.E. and GORDON J.E.: Interactions of Nutrition and Infection. WHO Monogr. Ser. No. 57, Geneva (1968).
19. SHINER, M.: A comparison of ultrastructural appearances of Reticulin, Endothelium and Inflammatory cells of the jejunal mucosa in children with normal mucosae, untreated Coeliac Disease and Protein-Energy Malnutrition. in Proc. 6th annu. Meet. eur. Soc. paediatr. Gastroenterol. Helsinki, August, 1973, p. 12 (1973).
20. STANFIELD, J.P., HUTT, M.S.R. and TUNNICLIFFE, R.: Intestinal biopsy in kwashiorkor. *Lancet* ii: 519 (1965).
21. SUHARJONO, SUNOTO, ASWITHA BUDIARSO and SUTEJO: Lactose malabsorption in healthy Indonesian pre-school children. *Paediatr. Indones.* 11: 251 (1971).
22. WALKER, A.C. and HARRY, J.G.: A survey of diarrhoeal disease in malnourished Aboriginal children. *Med. J. Aust.* 1: 904 (1972).
23. WALKER-SMITH, J.A. and REYE, R.D.K.: Small Intestinal Morphology in Aboriginal Children. *Aust. N.Z.J. Med.* 1: 377 (1971).
24. WHARTON, B.A. HOWELLS, G. and PHILLIPS, I.: Diarrhoea in kwashiorkor. *Br. med. J.* 4: 608 (1968).