Progress report

Some factors influencing absorption rates of the digestion products of protein and carbohydrate from the proximal jejunum of man and their possible nutritional implications

Ideal requirements of dietary energy (calories) and protein and its amino-acid ratio are difficult to determine¹. At least one essential ingredient is frequently present in an inadequate concentration in the diet of a vast proportion of the world's human population. Ever since the demonstration in the early 1930s by Dr Cecily Williams that kwashiorkor is associated with a low protein intake and a low serum protein concentration, malnutrition in tropical countries has been considered to be entirely dietary in origin. Clearly that is an exaggerated view which has dominated the scene, and other factors, especially malabsorption of dietary constituents, are also important in the pathogenesis of malnutrition. In developing countries energy and protein are often present in low amounts in the average diet. For example, the majority of Zambian Africans live on a carbohydrate diet which contains a marginally adequate amount of protein. The staple diet in most areas is *nshima*, a porridge which is prepared from ground maize or millet². Although childhood malnutrition there is very common, adults are usually moderately well nourished compared with those in many other tropical countries.

Throughout this report, which deals with intestinal absorption of carbohydrates, amino acids and dipeptides, the technique used for measuring the proximal jejunal absorption rate in a 30-cm segment involves a double-lumen tube perfusion system, without proximal occlusion. The infused fluid was introduced into the jejunum at 12.0 ml min⁻¹. Below that rate siphonage is difficult, and higher rates are undoubtedly unphysiological. Polyethylene glycol 4000 was used as a non-absorbable marker. Although the reproducibility of the method for solutes is good^{3,4,5} results for net water transfer are generally less exact. In most of the studies cited, the concentrations of mono- and disaccharides, amino acids and dipeptides in the perfusing fluid were probably greater than are likely to be present at the luminal surface of the enterocyte in the proximal jejunum of man, although there are very few data on that *in vivo*⁶. Whether or not absorption rates in the proximal jejunum bear a significant relationship to total absorption of dietary protein and carbohydrate is not entirely clear. A significant correlation has been demonstrated between the absorption rate of glucose from the proximal jejunum, and the weight of D-xylose excreted after a 25 g oral load⁷. Similarly, a significant correlation has been demonstrated between D-xylose

absorption from a jejunal segment and its excretion after an oral load⁸. There is also very limited information available on the amount of those solutes which can be absorbed further along the intestine if they are not absorbed proximally. Glucose is absorbed rapidly from the proximal jejunum in Zambian African subjects, and there is evidence that only limited absorption can occur further along the small intestine^{9,10,11}. Evidence exists that the amino acid L-methionine is absorbed far more rapidly from the proximal than distal small intestine of man¹². However, glycine seems to be well absorbed further along the small intestine¹³.

Systemic Bacterial Infections

Absorption of several dietary constituents is markedly influenced by intestinal infections¹⁴. The effect of systemic infections on absorption has, however, only recently been explored.

Jejunal absorption rates of glucose have been determined during the perfusion of 56, 139, and 278 mM solutions, all of which were rendered isoosmotic with sodium chloride, in three groups of Zambian Africans. They either had no clinical evidence of an infection, an acute systemic infection (usually pneumococcal lobar pneumonia), or a chronic systemic infection (usually pulmonary tuberculosis)^{7,15}. None of the subjects studied had clinical evidence of malnutrition or of gastrointestinal disease. At glucose concentrations of 139 and 278 mM in the perfusing fluid the subjects with infections had a significantly lower mean rate of glucose absorption ($P < 0.05$ and $P < 0.02$ respectively) than the subjects without infections. In similar groups of subjects, the weight of D-xylose excreted after a 25 g oral load was measured^{15,16}. The mean weight of D-xylose excreted was significantly lower in the groups with pulmonary tuberculosis ($P < 0.001$) and acute bacterial infections ($P < 0.05$) than in the group with no evidence of an infection. Glucose and D-xylose probably share the same transfer mechanism¹⁷.

In another study¹³ absorption rates of glycine were determined in three groups of subjects, who were similar to those given glucose infusions, from 100, 150, and 250 mM perfusion solutions. In the group with acute systemic bacterial infections (three of the four subjects were afebrile at the time of study) the mean absorption rate was significantly higher than in the group with chronic bacterial infections and the reference group at the concentrations tested. The explanation of that observation is not clear but it seems likely that it represents an adaptive conservation of amino acids in the presence of the high catabolic rate associated with acute bacterial infections.

The dipeptide glycylglycine uses a jejunal transfer mechanism which is different from that used by glycine. That has been demonstrated in man *in vivo*¹⁸. A large amount of evidence is now available suggesting that other amino acids and peptides are also transferred largely by separate mechanisms^{19,20,21,22}. The glycine absorption rate from a 50 mM glycylglycine solution has been studied in three groups of Zambian African subjects; one had no clinical evidence of infection, one had acute bacterial infection, and one had chronic bacterial infection²³. No significant difference in the mean rate of absorption was demonstrated between the three groups. That observation, together with that for glycine absorption rates in similar groups of subjects¹³, is entirely consistent with the presence of separate transfer mechanisms for glycine and glycylglycine, and suggests that the

dipeptide pathway is less influenced by systemic stimulæ than is that for the amino acid.

Most indigenous subjects in tropical countries live very largely on carbohydrate. It is possible therefore that these observations may have a nutritional importance. In a highly developed community, an increased amino acid absorption rate would be possible during an acute infection and would produce the extra energy requirement. However, in an African or Asian community the low amino acid content of the diet would preclude such an adaptive response¹³. Energy intake from carbohydrate would be reduced during the infection due to a reduced rate of glucose absorption⁷. Systemic infections would then be related to the production of malnutrition by way of impaired absorption. In Uganda a close seasonal association has been demonstrated between systemic bacterial and virus infections, as well as acute gastrointestinal infections, and the time of onset of kwashiorkor²⁴. Although much of that association is likely to be mediated by the high catabolic rate associated with the systemic infections, impaired absorption may also be important. Since the rate of glycylglycine absorption is not increased in subjects with bacterial infections, it seems possible that protein supplements should be given to patients with infections in the form of amino acid rather than peptide, even though in normal circumstances the former are absorbed significantly more slowly than the latter.

Serum Globulin and Albumin Concentrations

A significant inverse association has been demonstrated in a group of Zambian African subjects who had no clinical evidence of an infection or of gastrointestinal disease between the glucose absorption rate (from a 200 mM solution) from the proximal jejunum and serum total ($P < 0.02$) and gamma-globulin ($P < 0.01$) concentration¹¹. Raised serum gamma-globulin concentrations in most African subjects are probably largely due to bacterial and parasitic diseases, especially intestinal parasites and malaria. A further study has shown that the impaired glucose absorption rate in those subjects is inversely related to serum IgG concentration but is not significantly related to IgM, IgA, or IgD²⁵. It seems likely therefore that the impairment in glucose absorption rate which has been shown to be associated with systemic infections⁷ is more directly related to a raised serum gamma globulin, and more specifically to a high serum IgG concentration. Whether a high gamma globulin concentration is associated with abnormal membrane transfer at other sites has not been determined. For glycine, a significant positive relationship between jejunal absorption rate (from a 100 mM solution) and serum total ($P < 0.01$) and gamma-globulin ($P < 0.05$) concentration has been demonstrated¹³. That finding implements the demonstration of an increased glycine absorption rate in subjects with acute systemic infections¹³. No significant association could, however, be demonstrated between serum globulin concentrations and glycine absorption rate from a 50 mM glycylglycine solution²³.

In an investigation in Lagos, Nigeria, it has been suggested, on limited evidence, that subclinical malabsorption in Nigerian subjects is directly associated with a low serum albumin concentration²⁶. In Zambian African subjects who had no clinical evidence of infection or gastrointestinal disease no significant associations between absorption rates of glucose^{7,27}, glycine^{13,27},

or glycylglycine^{23,27}, and the serum albumin concentration have been demonstrated.

Competition for Absorption between Amino Acids and Peptides and Glucose

In animal experiments *in vitro*, an interaction during absorption between amino acids and monosaccharides was demonstrated nearly half a century ago^{28,29,30}. However, for glucose the nature of the mutual interference was in some experiments an inhibition and in others a stimulation of absorption. In two groups of Zambian African subjects a mutual inhibition between the rates of glucose and galactose (200 mM) and glycine (100 mM) absorption from the proximal jejunum has been demonstrated³¹. In that study perfusion solutions contained the monosaccharide and the amino acid either alone or together; each subject was therefore perfused with three solutions. The glycine absorption rate was impaired by approximately one third by both glucose and galactose; the degree of impairment of the monosaccharide absorption rate by glycine was less. In a further study⁵ several different concentrations of glucose and glycine were perfused either alone or together. The glycine absorption rate from a 20 mM solution was shown to be decreased by glucose at a concentration of 200 and 280 mM by approximately 30%. However, when a solution containing lower concentrations of glycine (10 mM) and glucose (100 mM) was perfused the degree of impairment of glycine absorption rate was much less and did not reach statistical significance. In that study there was also no significant impairment of the glucose absorption rate by the low glycine concentrations. A similar impairment, but to a lesser degree (19%), of glycine absorption rate from the dipeptide glycylglycine (50 mM) by glucose (200 mM) has also been demonstrated³².

The absorption rate of L-methionine, from a 100 mM solution, has been studied in another group of Zambian African subjects³³. Although the presence of glucose (150 mM) in the perfusion fluid caused a reduction in the absorption rate of L-methionine in six of the subjects, two others showed a marked increase; the overall effect of glucose on the L-methionine absorption rate was therefore not significant.

The mechanism responsible for the mutually inhibitive effect of glucose and galactose on the glycine absorption rate from the jejunum is unknown. That may be related to excessive demands on a common energy supply in the jejunal mucosa³⁴ or to an allosteric interaction at the surface of the brush border³⁵; both hypotheses have been suggested. Whether this observation has a practical value in human nutrition is unknown; many more data are required concerning the concentrations of monosaccharides, amino acids, and peptides which are presented *in vivo* to the luminal surface of the enterocyte. It seems reasonable to suppose that any degree of impairment of amino acid absorption in subjects living on a high carbohydrate diet with a marginally adequate amount of amino acid must assume importance.

Adult Hypolactasia

In northern Europe and north America, most adults maintain a high concentration of brush border lactase in the enterocyte into adult life. In most of the world's adult population, however, hypolactasia is present in most individuals³⁶.

A very high incidence of adult hypolactasia has been reported in Ugandan Africans^{37,38,39} but there are tribal differences in the incidence rates. Adult subjects with a 'Bantu' ethnic origin have been shown to have an incidence of approximately 90% of hypolactasia, whereas most of those with an Hamitic background have high concentrations of lactase and can absorb lactose efficiently. Zambian African subjects belong to a large number of tribal groups, but probably all have a 'Bantu' origin⁴⁰. Adult hypolactasia has been shown to be present in 100% of them⁴¹. In that study brush-border lactase concentrations were determined and were very low, or absent, in the subjects studied.

There is now overwhelming evidence that adult hypolactasia is not an acquired condition, due either to lack of dietary lactose or some other factor³⁶, but is the normal state for all adult mammals, except most northern Europeans and their descendants, and the Hamitic people of Africa, who have consumed milk and milk products for several thousands of years. In a recent study in Finland in which subjects with adult hypolactasia were used as index cases, good evidence has been assembled that that condition is inherited by a single recessive autosomal gene⁴². A suggestion has been made that the high lactase concentration in most northern Europeans has resulted from a selective advantage because it is associated with increased calcium absorption in those population groups, which have been exposed for many centuries to low ultraviolet radiation and a low dietary intake of vitamin D⁴³. However, that observation does not explain the very high incidence of high lactase concentrations in the Hamitic tribes of east Africa^{37,39}. Lactose tolerance may merely be associated with the unspecific nutritional advantage of milk which has been consumed by man in adult life for probably only 4000 to 6000 years³⁶.

In a recent study, kinetic curves for lactose absorption have been constructed in a group of six Zambian African adults, all of whom had hypolactasia⁴⁴. Lactose solutions (50, 125, and 250 mM) were infused into the proximal jejunum. A very 'flat' mean curve was demonstrated, which is shallower than that in European subjects with adult hypolactasia. There is also evidence from that study that some lactose enters the enterocyte intact. Glucose absorption from maltose (100 mM) takes place at a significantly greater rate than from glucose (200 mM) in Zambian African adults⁴⁵; it is possible that that observation also is partly explained by the absorption of some intact disaccharide.

Absence of brush-border lactase in adult life in an individual subject is unlikely to be associated with significant ill health. Intolerance to lactose or milk is nevertheless extremely common in affected African and Asian subjects. After seven to 10 days of regular daily milk intake (0.5 to 1 litre), however, a marked degree of tolerance is acquired despite the fact that the brush-border lactase concentration is not altered. The mechanism of that response is unknown.

In Zambian African infants a high incidence of non-infective diarrhoea has been demonstrated and that responds readily to stopping milk⁴⁶. It seems likely that that is partly due to an early fall of jejunal lactase to the low adult concentration³⁸. How often milk intolerance in those infants is causally related to nutritional marasmus (energy malnutrition) is so far unknown^{36,38,47,48}.

Flat Oral Glucose Tolerance Curves and Impaired D-xylose Excretion Tests in African Subjects

A flat blood-glucose curve after oral glucose (50 or 100g) and a low excretion of D-xylose after a 25g oral load (<5g) are relatively common in African subjects studied in Africa, although there is often no clinical evidence of disease (Cook, G. C., personal observation). It now seems extremely unlikely that the jejunal mucosal morphology of African subjects living in Africa, which differs slightly from English subjects in England⁴⁹, is responsible for those abnormalities, even though the surface area of the jejunum is undoubtedly smaller than that of European subjects living in temperate countries. The mucosa usually consists of broad, leaf-shaped villi with occasional ridges and very rarely finger-shaped villi. In some Zambian African subjects with jejunal morphology which is characteristic for African subjects⁴⁹, the glucose absorption rate⁷ and D-xylose excretion after a 25g oral load¹⁶ are identical to results obtained in European subjects in the United Kingdom. Although the perfusion rate used in the glucose absorption studies presently cited was lower than in a study on English subjects in England³, the mean kinetic curve in the Zambian African subjects without infection was considerably flatter⁷. Many Africans have a high serum gamma globulin which is usually due to an elevated serum IgG. That has been associated with impaired glucose and D-xylose absorption²⁵. It seems likely, therefore, that the frequent occurrence of flat oral glucose tolerance curves and abnormal D-xylose tests in African subjects is associated with that observation.

Further studies are in progress to assess the effect of malnutrition on the absorption rates of glucose, glycine, and glycylglycine and the xylose excretion test in adult Zambian African subjects.

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References

- ¹Lancet (1973). Leading article. Human energy and protein requirements. *Lancet*, 2, 363-364.
- ²Richards, A. I. (1969). *Land, Labour, and Diet in Northern Rhodesia*. Oxford University Press, London.
- ³Holdsworth, C. D., and Dawson, A. M. (1964). The absorption of monosaccharides in man. *Clin. Sci.*, 27, 371-379.
- ⁴Sladen, G. E., and Dawson, A. M. (1970). Further studies on the perfusion method for measuring intestinal absorption in man: the effects of a proximal occlusive balloon and a mixing segment. *Gut*, 11, 947-954.
- ⁵Cook, G. C. (1972). Effect of intraluminal concentrations on the impairment of glycine absorption by glucose in the human jejunum. *Clin. Sci.*, 42, 525-534.
- ⁶Borgström, B., Dahlqvist, A., Lundh, G., and Sjövall, J. (1957). Studies of intestinal digestion and absorption in the human. *J. clin. Invest.*, 36, 1521-1536.
- ⁷Cook, G. C. (1971). Glucose absorption kinetics in Zambian African patients with and without systemic bacterial infections. *Gut*, 12, 1001-1006.
- ⁸Corcino, J. J., Maldonado, M., and Klipstein, F. A. (1973). Intestinal perfusion studies in tropical sprue. 1. Transport of water, electrolytes, and D-xylose. *Gastroenterology*, 65, 192-198.
- ⁹Cook, G. C. (1972). Localisation of the site of glucose absorption from the small intestine in Zambian African subjects. *East Afr. med. J.*, 49, 840-843.
- ¹⁰Cook, G. C., and Snook, C. R. (1974). Site of glucose absorption from the intestine of Zambian African subjects. *Amer. J. clin. Nutr.*, in the press.
- ¹¹Cook, G. C. (1973). Relation between glucose absorption rate and serum globulin concentration in man. *Nature (Lond.)*, 241, 284-285.
- ¹²Schedl, H. P., Pierce, C. E., Rider, A., and Clifton, J. A. (1968). Absorption of L-methionine from the human small intestine. *J. clin. Invest.*, 47, 417-425.
- ¹³Cook, G. C. (1973). Increased glycine absorption rate associated with acute bacterial infections in man. *Brit. J. Nutr.*, 29, 377-386.
- ¹⁴Montgomery, R. D., Beale, D. J., Sammons, H. G., and Schneider, R. (1973). Postinfective malabsorption: a sprue syndrome. *Brit. med. J.*, 2, 265-267.
- ¹⁵Cook, G. C. (1972). Impairment of glucose and D-xylose absorption by systemic bacterial infections in man. *East Afr. med. J.*, 49, 108-111.
- ¹⁶Cook, G. C. (1972). Impairment of D-xylose absorption in Zambian African patients with systemic bacterial infections. *Amer. J. clin. Nutr.*, 25, 490-493.
- ¹⁷Crane, R. K. (1968). Absorption of sugars. In *Handbook of Physiology*, Sect. 6, *Alimentary Canal*, edited by C. F. Code, Vol. 3, p. 1344. American Physiological Society, Washington, D.C.

- ¹⁸Cook, G. C. (1973). Independent jejunal mechanisms for glycine and glycylglycine transfer in man *in vivo*. *Brit. J. Nutr.*, **30**, 13-19.
- ¹⁹Newey, H., and Smyth, D. H. (1959). The intestinal absorption of some dipeptides. *J. Physiol. (Lond.)*, **145**, 48-56.
- ²⁰Matthews, D. M. (1971). Protein absorption. *J. clin. Path.*, **24**, Suppl. (Roy. Coll. Path.), **5**, 29-40.
- ²¹Matthews, D. M. (1972). Rates of peptide uptake by small intestine. In *Peptide Transport in Bacteria and Mammalian Gut: A Ciba Foundation Symposium*, edited by K. Elliott and M. O'Connor, pp. 71-92. Associated Scientific Publishers, Amsterdam.
- ²²Cook, G. C. (1974). Effect of glycylglycine and glycine on jejunal absorption rate of L-histidine in man *in vivo*. *J. Physiol. (Lond.)*, in press.
- ²³Cook, G. C. (1974). Effect of systemic infections on glycylglycine absorption rate from the human jejunum *in vivo*. *Brit. J. Nutr.*, in press.
- ²⁴Poskitt, E. M. E. (1972). Seasonal variation in infection and malnutrition at a rural paediatric clinic in Uganda. *Trans. Roy. Soc. trop. Med. Hyg.*, **66**, 931-936.
- ²⁵Cook, G. C. (1973). Inverse relationship between glucose and D-xylose absorption and serum IgG concentration in man *in vivo*. (Awaiting publication).
- ²⁶Falaye, J. M. (1971). Present status of subclinical intestinal malabsorption in the tropics. *Brit. med. J.*, **4**, 454-458.
- ²⁷Cook, G. C. (1974). Relation of absorption rates of glucose, glycine and glycylglycine to serum globulin concentrations in man *in vivo*. *East Afr. med. J.*, in the press.
- ²⁸Cori, C. F. (1926). The absorption of glycine and d, l-alanine. *Proc. Soc. exp. Biol. (N.Y.)*, **24**, 125-126.
- ²⁹Newey, H., and Smyth, D. H. (1964). Effect of sugars on intestinal transfer of amino-acids. *Nature (Lond.)*, **202**, 400-401.
- ³⁰Saunders, S. J., and Isselbacher, K. J. (1965). Inhibition of intestinal amino-acid transport by hexoses. *Biochim. biophys. Acta (Amst.)*, **102**, 397-409.
- ³¹Cook, G. C. (1971). Impairment of glycine absorption by glucose and galactose in man. *J. Physiol. (Lond.)*, **217**, 61-70.
- ³²Cook, G. C. (1972). Comparison of intestinal absorption rates of glycine and glycylglycine in man and the effect of glucose in the perfusing fluid. *Clin. Sci.*, **43**, 443-453.
- ³³Cook, G. C. (1972). Intestinal absorption rate of L-methionine in man and the effect of glucose in the perfusing fluid. *J. Physiol. (Lond.)*, **221**, 707-714.
- ³⁴Bingham, J. K., Newey, H., and Smyth, D. H. (1966). Interaction of sugars and amino acids in intestinal transfer. *Biochim. biophys. Acta (Amst.)*, **130**, 281-284.
- ³⁵Robinson, J. W. L., and Alvarado, F. (1971). Interaction between the sugar and amino-acid transport systems at the small intestinal brush-border; a comparative study. *Pflügers. Arch. ges. Physiol.*, **326**, 48-75.
- ³⁶Cook, G. C. (1973). Incidence and clinical features of specific hypolactasia in adult man. In *Intestinal Enzyme Deficiencies and Their Nutritional Implications*, edited by B. Borgström, A. Dahlqvist, and L. Hambræus, pp. 52-73. Almqvist and Wiksells, Uppsala.
- ³⁷Cook, G. C., and Kajubi, S. K. (1966). Tribal incidence of lactase deficiency in Uganda. *Lancet*, **1**, 725-730.
- ³⁸Cook, G. C. (1967). Lactase activity in newborn and infant Baganda. *Brit. med. J.*, **1**, 527-530.
- ³⁹Cook, G. C., and Dahlqvist, A. (1968). Jejunal hetero- β -galactosidase activities in Ugandans with lactase deficiency. *Gastroenterology*, **55**, 328-332.
- ⁴⁰Brelsford, W. V. (1965). *The Tribes of Zambia*, 2nd ed. Government Printer, Lusaka.
- ⁴¹Cook, G. C., Asp, N. G., and Dahlqvist, A. (1973). Activities of brush-border lactase, acid β -galactosidase and hetero β -galactosidase in the jejunum of the Zambian African. *Gastroenterology*, **64**, 405-410.
- ⁴²Sahi, T., Isokoski, M., Jussila, J., Launiala, K., and Pyörälä, K. (1973). Recessive inheritance of adult-type lactose malabsorption. *Lancet*, **2**, 823-826.
- ⁴³Flatz, G., and Rothauwe, H. W. (1973). Lactose nutrition and natural selection. *Lancet*, **2**, 76-77.
- ⁴⁴Cook, G. C., Asp, N. G., and Dahlqvist, A. (1973). Lactose absorption kinetics in Zambian African subjects. *Brit. J. Nutr.*, **30**, 519-527.
- ⁴⁵Cook, G. C. (1973). Comparison of absorption rates of glucose and maltose in man *in vivo*. *Clin. Sci.*, **44**, 425-428.
- ⁴⁶King, F. (1972). Intolerance to lactose in mother's milk? *Lancet*, **2**, 335.
- ⁴⁷Cook, G. C. (1967). The practical significance of lactase deficiency in childhood. *J. trop. Pediatr.*, **13**, 85-86.
- ⁴⁸Cook, G. C. (1968). Some observations on racial lactase deficiency. *Proc. Roy. Soc. Med.*, **61**, 1102-1104.
- ⁴⁹Cook, G. C., Kajubi, S. K., and Lee, F. D. (1969). Jejunal morphology of the African in Uganda. *J. Path.*, **98**, 157-169.

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