Progress report

Peptide absorption in man

In this review it is hoped to trace the evolution of our concepts of the absorption of digestion products of dietary protein. Many of the ideas current today were readily accepted by the end of the last century but were ignored by orthodox physiologists during the first half of this century—concepts of sugar absorption suffered a similar fate. Although it has now become clear that brush border hydrolysis and consequent utilization of the sugar pump is the predominant method of sugar absorption it would seem that two major mechanisms are involved in peptide absorption: on the one hand hydrolysis of peptides by brush border enzymes with subsequent uptake of the liberated amino acids by specific amino acid transport systems, and on the other hand, uptake of peptides by mechanisms independent of the specific amino acid entry mechanisms, followed by intracellular hydrolysis.

Historical Background

Nineteenth century physiologists believed that dietary protein was absorbed in the form of polypeptides^{1,2,3}, a view that seemed to be confirmed when Nolf⁴ and Messerli⁵ showed that 'peptones' produced by tryptic hydrolysis of protein disappeared from the lumen of the small intestine more rapidly than equivalent amounts of free amino acids. When Cohnheim demonstrated in 1901⁶ that 'intestinal juice' was capable of hydrolysing peptones to amino acids, some early workers suggested that protein must be hydrolysed to amino acids before absorption took place. This hypothesis began to gain ground when all known free amino acids were detected in intestinal contents obtained during protein absorption *in vivo*^{7,8,9}, and when studies *in vivo* showed that hydrolysates of protein (consisting of amino acids) disappeared rapidly from the lumen of the small intestine^{10,11}. Furthermore, many of the investigators at the time speculated that free amino acids passed into the portal circulation during protein absorption as the non-protein nitrogen values in peripheral and portal plasma increased during absorption of amino acids^{12,14}, protein hydrolysates, and whole protein^{15,16}. When only amino acids were isolated from the portal circulation during protein absorption¹⁷, the idea that protein was completely hydrolysed to amino acids within the intestinal lumen before absorption took place became the classical view of protein absorption (eg, Verzar and MacDougall, 1936¹⁸). This view was held despite later observations that intraluminal peptidase activity was insufficient to account for the absorption of 'peptone' in the form of free amino acids¹⁹.

The concept was questioned by a number of workers who claimed that peptides entered the portal venous circulation during protein absorption^{20,22}. The quantitative significance of their findings was unknown, and later studies, using improved techniques, failed to detect an increase in peptide-bound amino acid levels in portal plasma during protein absorption²³⁻²⁷. The final vindication of the classical view of protein absorption appeared to be provided

by the demonstration, using ion exchange chromatography, that only free amino acids appeared in peripheral plasma after protein was administered to human subjects²⁸.

In 1954 Fisher strongly criticised the classical view of protein absorption²⁹. He pointed out that it had previously been shown that upwards of 200 hours were required for the liberation of 90% of the amino acids from different proteins subjected to successive action of pepsin, trypsin, and erepsin^{30,31}, and made the following statement '... even on the most generous assumption, the time course of liberation of amino nitrogen is too slow to fit with the view that protein must be digested to amino acids before they are absorbed', and he suggested that the idea of absorption of protein in the form of peptides deserved serious consideration²⁹.

Mucosal Uptake of Oligopeptides

Initial experiments *in vitro* with dipeptides showed that small quantities of intact glycyl-glycine and glycyl-L-leucine crossed the intestinal wall³². Similar observations were made when glycyl-glycine was studied *in vitro*³³⁻³⁵ and *in vivo*³⁵ by other workers, and after Newey and Smyth³⁶ demonstrated that dipeptides could be taken up intact by intestinal mucosa they concluded³⁷ that the products of protein digestion could be transported into the mucosal cell in the form of oligopeptides as well as amino acids. The concept of intact peptide uptake as a second mode of protein absorption, although not disputed was not thought to be quantitatively significant³⁸, as it seemed much more likely that absorption of peptides, analogous to disaccharides³⁹⁻⁴², would involve brush border hydrolysis with subsequent absorption of the released amino acids by amino acid transport systems.

The modern era of our knowledge of peptide absorption stemmed from the results of oral load experiments carried out by Matthews and his colleagues in man^{43,44}. They found that a given quantity of glycine was absorbed faster when administered orally as the dipeptide and tripeptide than in the free form. The authors concluded that the peptides must have been taken up intact by the intestinal mucosa because, if analogous to disaccharide absorption, brush border peptide hydrolysis preceded amino acid transport; when presented initially, the liberated amino acids could not have been absorbed more rapidly than in the free form. Similar findings, subsequently confirmed in the rat⁴⁵, have been demonstrated in man when a perfusion technique was used to study diglycine^{46-48,49} and triglycine absorption⁴⁸.

When the absorption of mixed peptides of glycine and methionine and the corresponding amino acids was studied in the rat^{50,51} it was found that glycine was absorbed at a slower rate from an equivalent mixture of glycine and methionine than from a solution containing only free glycine. This competition for transport between the two amino acids was abolished when glycyl-methionine and methionyl-glycine were presented, and in addition, both amino acids were absorbed faster from the peptides than from the equivalent amino acid mixture. If brush border peptide hydrolysis preceded amino acid uptake, competitive phenomena would not be avoided, and these findings were cited as further evidence in favour of the presence of a specific peptide uptake system. Although not an invariable finding⁵², similar results have been

obtained in man when absorption of a number of other mixed peptides composed of neutral amino acids has been studied (glycyl-leucine⁴⁶, glycyl-alanine^{47,53,54}, and alanyl-glycine⁵³).

Recently a large survey *in vitro* showed that the uptake of one or both constituent amino acids by rat intestine was greater from 18 out of 22 dipeptides containing basic and acidic amino acids than from the equivalent amino acid or amino acid mixtures⁵⁵. These findings have been confirmed in man for glycyl-L-lysine but not for L-lysyl-L-lysine⁵⁶.

After Matthews and his colleagues had implied that oligopeptides are transported intact into the mucosal cell by special peptide uptake systems in normal human subjects^{43,44}, Milne and his colleagues showed that patients with Hartnup absorbed the amino acids histidine, tryptophan, phenylalanine, and tyrosine normally when they were given in the form of the respective dipeptides carnosine⁵², glycyl-tryptophan⁵⁷, phenylalanyl-phenylalanine⁵⁷, and glycyl-tyrosine⁵⁸, but not when they were administered in the free form. In cystinuria the loss of active transport of arginine is also adequately compensated by peptide uptake systems⁵⁹, although loss of active transport of free lysine seems to be compensated by the presence of passive or facilitated diffusion mechanisms⁶⁰, in addition to peptide uptake⁵⁶.

Nutritional Importance of Oligopeptide Uptake in Man

The studies carried out in Hartnup disease^{52,57,58} and cystinuria^{56,60} emphasize the nutritional importance of oligopeptide transport in these two conditions. Although the present experimental data suggest that in normal subjects peptide uptake may play a more important part in protein absorption than had previously been suspected^{61,63}, only 15 oligopeptides have so far been studied in man. In view of the fact that there are about 400 possible dipeptides and 8000 possible tripeptides, it would clearly be impossible to assess the overall nutritional importance of peptide absorption by studying the characteristics of absorption of each one in turn. Nixon and Mawer^{64,65} studied the absorption of small quantities of milk protein and gelatine in man and concluded that although appreciable amounts of the basic amino acids (arginine and lysine) and neutral amino acids (valine, phenylalanine, tyrosine, methionine, and leucine) were released within the intestinal lumen at sufficient rates to account for their absorption in the free form, other amino acids (glycine, proline, hydroxyproline, serine, threonine, aspartic acid, and glutamic acid) were likely to be absorbed in the form of peptides.

Additional evidence has been provided by a recent perfusion study in man to support a concept that mucosal uptake of small peptides has an important or possibly a major role in protein absorption^{66,67}. In agreement with initial studies carried out in the rat⁶⁸⁻⁶⁹ total absorption of α amino nitrogen was greater from a solution containing an enzymic hydrolysate of casein, consisting mainly of oligopeptides of 2-6 amino acid units, than from the corresponding amino acid mixture of identical amino acid composition. In addition, there was less variation in the extent to which individual amino acids were absorbed from the peptide solution compared with that from the amino acid solution. This could result in enhanced protein synthesis, and the authors concluded, as had others^{64,65,70}, that the characteristics of absorption of amino acid mixtures are not representative of absorption of protein digestion products.

Mechanisms Involved in the Mucosal Uptake of Oligopeptides

One of the main difficulties in defining the nature of uptake mechanisms is that most peptides are hydrolysed rapidly by mucosal peptidases making it difficult to detect unhydrolysed peptide in the mucosal cell. *In-vitro* studies with the dipeptides glycyl-sarcosine⁷¹ and carnosine⁷², both of which are hydrolysed abnormally slowly by the mucosal cell, indicate that dipeptides may be transported by an active sodium-dependent process.

An important question that arises when considering the details involved in peptide transport is whether peptides are taken up by the same mechanisms that are responsible for the uptake of amino acids or whether independent peptide uptake systems exist as in bacteria^{73,74}. Studies with glycine peptides seemed to indicate that amino acids and dipeptides shared a common entry site into the mucosal cell^{37,44}. Parsons proposed an alternative scheme that dipeptides are taken up by attachment to adjacent amino acid entry sites, attachment and hydrolysis being different aspects of the same process⁷⁵. Both schemes would appear to account for absorption of an 'affected' amino acid presented as a mixed peptide in Hartnup disease^{52,57,58} and cystinuria^{56,60}. Neither scheme, however, can explain the normal uptake of phenylalanyl-phenylalanine in Hartnup disease⁵⁷ or lysyl-lysine uptake in cystinuria⁵⁵. An alternative explanation was thus proposed, that peptides are transported by mechanisms independent of amino acid transport⁵⁷. Many recent *in-vitro* studies support the latter explanation^{71,72,73,77} as uptake of a specific dipeptide is inhibited by the presence of other dipeptides but not by the presence of the constituent amino acids in the free form. Edwards postulated that there may be at least two independent 'dipeptide uptake systems in mammalian gut'⁷⁸. A single report⁷² supports this hypothesis as carnosine uptake was not inhibited by lysyl-lysine or by glutamyl-glutamic acid, and in view of the fact that lysyl-lysine uptake was not inhibited by glutamyl-glutamic acid the authors proposed that independent peptide uptake systems exist for neutral, basic, and acidic dipeptides.

With the possible exception of glycyl-glycine^{46,79} and hydroxyproline peptides⁸⁰, oligopeptides do not pass forward into the portal circulation. The precise site of peptide hydrolysis within the mucosal cell has not yet been defined. Ugolev and his colleagues⁸¹⁻⁸⁴ have proposed that oligopeptides as well as oligosaccharides⁸⁵ are hydrolysed at the external surface of the microvillous membrane by enteric and adsorbed enzymes, a process which is followed by transport of the monomer hydrolytic products across the membrane. In support of this concept Fern *et al* concluded from a kinetic study of uptake *in vitro* of mixed glycine and leucine peptides that hydrolysis of these peptides was entirely superficial⁸⁶, and the detection of free amino acids in the gut lumen during dipeptide absorption in animals^{45,50,51} and man^{46,48,53,54,56} would be readily explained if superficial peptide hydrolysis preceded amino acid uptake. The finding that oligopeptides confer a kinetic advantage on amino acid absorption, and the avoidance of competitive phenomena when oligopeptides are presented, suggests, however, that uptake of intact oligopeptides precedes cellular hydrolysis. The appearance of small quantities of glycyl-glycine in portal blood during absorption of this dipeptide^{35,79}, and the finding of intact dipeptides in the intestinal mucosa *in vitro*^{71,72,88} certainly favours an intracellular hydrolysis site; additional evidence for this hypothesis is provided by cell fractionation studies which show that up to

90% of the total mucosal cell dipeptidase activity is localized to the cytosol fraction⁸⁷⁻⁹⁰.

Matthews and his colleagues^{51,61}, as a result of kinetic studies *in vitro* with glycine and methionine peptides and the effects of L-amino acid oxidase on peptide uptake, suggested that there may be two modes of uptake of amino acids from oligopeptides: (1) peptide entry into the mucosal cells by a special mechanism, followed by intracellular hydrolysis; (2) surface hydrolysis by mechanisms closely linked to the amino acid entry mechanisms. Silk and his colleagues, who studied absorption of N-terminal glycine and alanine dipeptides in man^{53,91}, reached similar conclusions (see fig). On the one hand,

Fig Postulated mechanisms for peptide uptake in man

(scheme A) they proposed that dipeptides are transported into the mucosal cell by special entry mechanisms followed by intracellular hydrolysis as originally proposed by Newey and Smyth³⁷ which would explain their results with N-terminal glycine dipeptides. On the other hand, the results with N-terminal alanine dipeptides were more readily explained if dipeptide uptake involved both direct peptide entry (scheme A) and absorption of free amino acids, liberated as a result of brush border hydrolysis, by the specific amino acid transport systems (scheme B). They concluded⁵³ that the relative importance of either system was dictated by the affinity of the peptide for the superficial peptide hydrolases, although it is likely that further quantitative and qualitative assessments of enzymes in the human small intestine are needed before further conclusions can be drawn.

Practical Importance of Oligopeptide Transport

The demonstration that dietary protein is absorbed in the form of oligopeptides as well as amino acids explains why patients with Hartnup disease and cystinuria have no clinical signs of protein malnutrition, and the theoretical knowledge gained from investigations into peptide absorption may be expected to have important practical applications, especially in the treatment of protein malnutrition in seriously ill patients who have a reduced absorptive capacity of the small intestine. As it has been found that (a) greater absorption of α amino nitrogen, and (b) more even uptake of individual amino acids occurs from enzymic hydrolysates of protein than from equivalent mixtures of

free amino acids, the oral administration of mixtures of free amino acids in the treatment of such patients is likely to be less satisfactory than the oral administration of enzymic hydrolysates of proteins which consist of oligopeptides as well as free amino acids.

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References

- ¹Voit, C., and Bauer, J. (1869). Ueber die Aufsaugung im Dick- und Dunndarme. *Z. Biol.*, 5, 536-563.
- ²Friedländer, G. (1896). Ueber die Resorption gelöster Eiweißstoffe im Dunndarm. *Z. Biol.*, 33, 264-287.
- ³Reid, E. W. (1900). On intestinal absorption, especially on the absorption of serum, peptone and glucose. *Phil. Trans. roy. Soc., Ser. B*, 192, 211-297.
- ⁴Nolf, P. (1907). Les albumoses et peptones sont-elles absorbées par l'épithélium intestinal? *J. Physiol. Path. gén.*, 9, 925-938.
- ⁵Messerli, H. (1913). Ueber die Resorptionsgeschwindigkeit der Eiweiße und ihrer Abbauprodukte im Dünndarm. *Biochem. Z.*, 54, 446-473.
- ⁶Cohnheim, O. (1901). Die Umwandlung des Eiweiß durch die Darmwand. *Hoppe-Seylers Z. physiol. Chem.*, 33, 451-465.
- ⁷Abderhalden, E., and Lampé, A. (1912). Weiterer Beitrag zur Frage nach der Vertretbarkeit von Eiweiß resp. eines vollwertigen Aminosäuregemisches durch Gelatine und Ammonsalze. *Hoppe-Seylers Z. physiol. Chem.*, 80, 160-174.
- ⁸Cohnheim, O. (1912). Zur Frage der Eiweißresorption. III. *Hoppe-Seylers Z. physiol. Chem.*, 76, 293-297.
- ⁹Cohnheim, O. (1913). Die Wirkung vollständig abgebauter Nahrung auf den Verdauungskanal. *Hoppe-Seylers Z. physiol. Chem.*, 84, 419-424.
- ¹⁰Cathcart, E. P., and Leathes, J. B. (1905-1906). On the absorption of proteins from the intestine. *J. Physiol. (Lond.)*, 33, 462-475.
- ¹¹Abderhalden, E., and London, E. S. (1910). Weiterer Beitrag zur Frage nach dem Ab- und Aufbau der Proteine im tierischen Organismus. *Hoppe-Seylers Z. physiol. Chem.*, 65, 251-255.
- ¹²Abderhalden, E., Gigon, A., and London, E. S. (1907). Das Verhalten von d-Alanin im Organismus des Hundes unter verschiedenen Bedingungen. *Hoppe-Seylers Z. physiol. Chem.*, 53, 113-118.
- ¹³Folin, O., and Denis, W. (1912). Protein metabolism from the standpoint of blood and tissue analysis. *J. biol. Chem.*, 11, 87-95.
- ¹⁴Van Slyke, D. D., and Meyer, G. M. (1912). The amino-acid nitrogen of the blood. Preliminary experiments on protein assimilation. *J. biol. Chem.*, 12, 399-410.
- ¹⁵Howell, W. H. (1906). Note upon the presence of amino acids in the blood and lymph as determined by the β -naphthalinsulphochloride reaction. *Amer. J. Physiol.*, 17, 273-279.
- ¹⁶Abderhalden, E., and Lampé, A. E. (1912). Weiterer Beitrag zur Kenntnis des Schicksals von in den Magendarmkanal eingeführten einzelnen Aminosäuren, Aminosäuregemischen, Peptonen und Proteinen. *Hoppe-Seylers Z. physiol. Chem.*, 81, 473-507.
- ¹⁷Abel, J. J., Rowntree, L. G., and Turner, B. B. (1913-1914). On the removal of diffusible substances from the circulating blood of living animals by dialysis. II. Some constituents of the blood. *J. Pharmacol. exp. Ther.*, 5, 611-623.
- ¹⁸Verzár, F., and MacDougall, E. J. (1936). *Absorption from the Intestine*. Longmans, London.
- ¹⁹Cajori, F. A. (1933). The enzyme activity of dogs' intestinal juice and its relation to intestinal digestion. *Amer. J. Physiol.*, 104, 659-668.
- ²⁰Hannaert, L., and Wodon, R. (1923). Contribution à l'étude de L'Hémo-clasie digestive. *C.R. Soc. Biol. (Paris)*, 88, 636-638.
- ²¹Kalmykoff, M. P. (1924). Abbau im Darm und Aufbau in der Leber bei Eiweißresorption. *Arch. ges. Physiol.*, 205, 493-497.
- ²²Kotschneff, N. (1928). Weitere Untersuchungen über das Verhalten verschiedener Eiweißabbauprodukte im Intermediärgebiet nach Versuchen an angiotomierten Hunden. *Pflügers Arch. ges. Physiol.*, 218, 635-646.
- ²³Christensen, H. N., Decker, D. G., Lynch, E. L., Mackenzie, T. M., and Powers, J. H. (1947). The conjugated non protein, amino acids of plasma. V. A study of the clinical significance of peptidemia. *J. clin. Invest.*, 26, 853-859.
- ²⁴Christensen, H. N. (1949). Conjugated amino-acids in portal plasma of dogs after protein feeding. *Biochem. J.*, 44, 333-335.
- ²⁵Dent, C. E., and Schilling, J. A. (1949). Studies on the absorption of proteins: the amino acid pattern in the portal blood. *Biochem. J.*, 44, 318-333.
- ²⁶Denton, A. E., Gershoff, S. N., and Elvehjem, C. A. (1953). A new method for cannulating the portal vein of dogs. *J. biol. Chem.*, 204, 731-735.
- ²⁷Denton, A. E., and Elvehjem, C. A. (1954). Availability of amino acids in vivo. *J. biol. Chem.*, 206, 449-454.
- ²⁸Stein, W. H., and Moore, S. (1954). The free amino acids of human blood plasma. *J. biol. Chem.*, 211, 915-926.
- ²⁹Fisher, R. B. (1954). *Protein Metabolism*. Methuen, London.
- ³⁰Frankel, E. M. (1916). A comparative study of the behavior of purified proteins towards proteolytic enzymes. *J. biol. Chem.*, 26, 31-59.
- ³¹Dunn, M. S., and Lewis, H. B. (1921). A comparative study of the hydrolysis of casein and deaminized casein by proteolytic enzymes. *J. biol. Chem.*, 49, 343-350.
- ³²Agar, W. T., Hird, F. J. R., and Sidhu, G. S. (1954). The uptake of amino acids by the intestine. *Biochim. biophys. Acta (Amst.)*, 14, 80-84.
- ³³Wiggans, D. S., and Johnston, J. M. (1958). Absorptive patterns of peptides through the isolated rat intestine. *Fed. Proc.*, 17, 335.
- ³⁴Wiggans, D. S., and Johnston, J. M. (1959). The absorption of peptides. *Biochim. biophys. Acta (Amst.)*, 32, 69-73.

- ³⁸Newey, H., and Smyth, D. H. (1959). The intestinal absorption of some dipeptides. *J. Physiol. (Lond.)*, **145**, 48-56.
- ³⁹Newey, H., and Smyth, D. H. (1960). Intracellular hydrolysis of dipeptides during intestinal absorption. *J. Physiol. (Lond.)*, **152**, 367-380.
- ⁴⁰Newey, H., and Smyth, D. H. (1962). Cellular mechanisms in intestinal transfer of amino acids. *J. Physiol. (Lond.)*, **164**, 527-551.
- ⁴¹Crane, R. K. (1968). Digestive-absorptive surface of the small bowel mucosa. *Ann. Rev. Med.*, **19**, 57-68.
- ⁴²Crane, R. K. (1962). Hypothesis for mechanisms of intestinal active transport of sugars. *Fed. Proc.*, **21**, 891-895.
- ⁴³Miller, D., and Crane, R. K. (1961). The digestive function of the epithelium of the small intestine. II. Localisation of disaccharide hydrolysis in the isolated brush border portion of intestinal epithelial cells. *Biochim. biophys. Acta (Amst.)*, **52**, 293-298.
- ⁴⁴Gray, G. M., and Ingelfinger, F. J. (1965). Intestinal absorption of sucrose in man: the site of hydrolysis and absorption. *J. clin. Invest.*, **44**, 390-398.
- ⁴⁵Gray, G. M., and Ingelfinger, F. J. (1966). Intestinal absorption of sucrose in man: interrelation of hydrolysis and monosaccharide product absorption. *J. clin. Invest.*, **45**, 388-398.
- ⁴⁶Craft, I. L., and Matthews, D. M. (1968). The absorption of glycine and glycyl-glycine in man, following surgery and in gastro-intestinal disorders. (Abstr.) *Brit. J. Surg.*, **55**, 158.
- ⁴⁷Craft, I. L., Geddes, D., Hyde, C. W., Wise, I. J., and Matthews, D. M. (1968). Absorption and malabsorption of glycine and glycine peptides in man. *Gut*, **9**, 425-437.
- ⁴⁸Matthews, D. M., Craft, I. L., Geddes, D. M., Wise, I. J., and Hyde, C. W. (1968). Absorption of glycine and glycine peptides from the small intestine of the rat. *Clin. Sci.*, **35**, 415-424.
- ⁴⁹Adibi, S. A. (1971). Intestinal transport of dipeptides in man: relative importance of hydrolysis and intact absorption. *J. clin. Invest.*, **50**, 2266-2275.
- ⁵⁰Hellier, M. D., Holdsworth, C. D., McColl, I., and Perrett, D., (1972). Dipeptide absorption in man. *Gut*, **13**, 965-969.
- ⁵¹Silk, D. B. A., Perrett, D., Webb, J. P. W., and Clark, M. L. (1973). Tripeptide absorption in man. (Abstr.) *Gut*, **14**, 427-428.
- ⁵²Cook, G. C. (1973). Independent jejunal mechanisms for glycine and glycylglycine transfer in man *in vivo*. *Brit. J. Nutr.*, **30**, 13-19.
- ⁵³Matthews, D. M., Lis, M. T., Cheng, B., and Crampton R. F. (1969). Observations on the intestinal absorption of some oligopeptides of methionine and glycine in the rat. *Clin. Sci.*, **37**, 751-764.
- ⁵⁴Cheng, B., Navab, F., Lis, M. T., Miller, T. N., and Matthews, D. M. (1971). Mechanisms of dipeptide uptake by rat small intestine *in vitro*. *Clin. Sci.*, **40**, 247-259.
- ⁵⁵Asatoor, A. M., Bandoh, J. K., Lant, A. F., Milne, M. D., and Navab, F. (1970). Intestinal absorption of carnosine and its constituent amino acids in man. *Gut*, **11**, 250-254.
- ⁵⁶Silk, D. B. A., Perrett, D., and Clark, M. L. (1973). Intestinal transport of two dipeptides containing the same two neutral acids in man. *Clin. Sci.*, **45**, 291-299.
- ⁵⁷Silk, D. B. A., Kumar, P. J., Perrett, D., Clark, M. L., and Dawson, A. M. (1974). Amino acid and peptide absorption in patients with coeliac disease and dermatitis herpetiformis. *Gut*, **15**, 1-8.
- ⁵⁸Burston, D., Addison, J. M., and Matthews, D. M. (1972). Uptake of dipeptides containing basic and acidic amino acids by rat small intestine *in vitro*. *Clin. Sci.*, **43**, 823-837.
- ⁵⁹Hellier, M. D., Holdsworth, C. D., Perrett, D., and Thirumalai, C. (1972). Intestinal dipeptide transport in normal and cystinuric subjects. *Clin. Sci.*, **43**, 659-668.
- ⁶⁰Asatoor, A. M., Cheng, B., Edwards, K. D. G., Lant, A. F., Matthews, D. M., Milne, M. D., Navab, F., and Richards, A. J. (1970). Intestinal absorption of two dipeptides in Hartnup disease. *Gut*, **11**, 380-387.
- ⁶¹Tarlow, M. J., Seakins, J. W. T., Lloyd, J. K., Matthews, D. M., Cheng, B., and Thomas, A. J. (1972). Absorption of amino acids and peptides in a child with a variant of Hartnup disease and coexistent Coeliac disease. *Arch. Dis. Childh.*, **47**, 798-803.
- ⁶²Asatoor, A. M., Harrison, B. D. W., Milne, M. D., and Prosser, D. I. (1972). Intestinal absorption of an arginine-containing peptide in cystinuria. *Gut*, **13**, 95-98.
- ⁶³Asatoor, A. M., Crouchman, M. R., Harrison, A. R., Light, F. W., Loughridge, L. W., Milne, M. D., and Richards, A. J. (1971). Intestinal absorption of oligopeptides in cystinuria. *Clin. Sci.*, **41**, 23-33.
- ⁶⁴Matthews, D. M. (1971). Protein absorption. *J. clin. Path.*, **24**, Suppl. (Roy. Coll. Path.), **5**, 29-46.
- ⁶⁵Matthews, D. M. (1971). Experimental approach in chemical pathology. *Brit. med. J.*, **3**, 659-664.
- ⁶⁶Matthews, D. M. (1972). Rates of peptide uptake by small intestine. In *Peptide Transport in Bacteria and Mammalian Gut* (Ciba Foundation Symposium), edited by K. Elliot and M. O'Connor, pp. 71-92. Associated Scientific Publishers, Amsterdam.
- ⁶⁷Nixon, S. E., and Mawer, G. E. (1970). The digestion and absorption of protein in man. I. The site of absorption. *Brit. J. Nutr.*, **24**, 227-240.
- ⁶⁸Nixon, S. E., and Mawer, G. E. (1970). The digestion and absorption of protein in man. II. The form in which digested protein is absorbed. *Brit. J. Nutr.*, **24**, 241-258.
- ⁶⁹Silk, D. B. A., Marrs, T. C., Burston, D., Addison, J. M., Clark, M. L., and Matthews, D. M. (1973). Rates of absorption of amino acids from an amino acid mixture simulating casein and a tryptic hydrolysate of casein in man. *Clin. Sci.*, **45**, 4P.
- ⁷⁰Silk, D. B. A., Marrs, T. C., Burston, D., Addison, J. M., Clark, M. L., and Matthews, D. M. (1973). Absorption of amino acids from an amino acid mixture simulating casein and a tryptic hydrolysate of casein in man. *Clin. Sci.*, **45**, 715-719.
- ⁷¹Crampton, R. F., Gangolli, S. D., Matthews, D. M., and Simson, P. (1971). Rates of absorption from tryptic hydrolysates of proteins and the corresponding acid hydrolysates or amino acid mixtures. *J. Physiol. (Lond.)*, **213**, 43-44P.
- ⁷²Crampton, R. F., Gangolli, S. D., Simson, P., and Matthews, D. M. (1971). Rates of absorption by rat intestine of pancreatic hydrolysates of proteins and their corresponding amino acid mixtures. *Clin. Sci.*, **41**, 409-417.
- ⁷³Nasset, E. S. (1965). Role of the digestive system in protein metabolism. *Fed. Proc.*, **24**, 953-958.
- ⁷⁴Addison, J. M., Burston, D., and Matthews, D. M. (1972). Evidence for active transport of the dipeptide glycyl-sarcosine by hamster jejunum *in vitro*. *Clin. Sci.*, **43**, 907-911.
- ⁷⁵Addison, J. M., Burston, D., and Matthews, D. M. (1973). Carnosine transport by hamster jejunum *in vivo* and its inhibition by other di- and tripeptides. *Clin. Sci.*, **45**, 3-4P.
- ⁷⁶Payne, J. W. (1968). Oligopeptide transport in *Escherichia coli*. specificity with respect to side chain and distinction from dipeptide transport. *J. biol. Chem.*, **243**, 3395-3403.
- ⁷⁷Payne, J. W., and Gilvarg, C. (1971). Peptide transport. *Advanc. Enzymol.*, **35**, 187-244.

- ⁷⁶Parsons, D. S. (1971). Black box models of intestinal mucosal function. In *Intestinal Transport of Electrolytes, Amino Acids, and Sugars* (An International Symposium, Indianapolis, 1968), edited by W. M. Armstrong and A. S. Nunn Jr., pp. 24-51. Thomas, Springfield, Illinois.
- ⁷⁸Rubino, A., Field, M., and Shwachman, P. (1971). Intestinal transport of amino acid residues of dipeptides. I. Influx of the glycine residue of glycyl-L-proline across mucosal border. *J. biol. Chem.*, **246**, 3542-3548.
- ⁷⁷Cheeseman, C. I., and Smyth, D. H. (1973). Specific transfer process for intestinal absorption of peptides. *J. Physiol. (Lond.)*, **229**, 45-46P.
- ⁷⁸Edwards, K. D. G. (1970). Intestinal absorption of oligopeptides. (Letter). *Med. J. Aust.*, **2**, 1213.
- ⁷⁹Peters, T. J., and MacMahon, M. T. (1970). The absorption of glycine and glycine oligopeptides by the rat. *Clin. Sci.*, **39**, 811-821.
- ⁸⁰Prockop, D. J., Keiser, H. R., and Sjoerdsma, A. (1962). Gastrointestinal absorption and renal excretion of hydroxyproline peptides. *Lancet*, **2**, 527-528.
- ⁸¹Ugolev, A. M., Iesuitova, N. N., Timofeeva, N. M., and Fediushina, I. N. (1964). Location of hydrolysis of certain disaccharides and peptides in the small intestine. *Nature (Lond.)*, **202**, 807-809.
- ⁸²Ugolev, A. M. (1965). Membrane (contact) digestion. *Physiol. Rev.*, **45**, 555-595.
- ⁸³Ugolev, A. M. (1968). Some properties and functions of hydrolytic enzymes of the surface of intestinal cells. *Protides biol. Fluids*, **15**, 149-155.
- ⁸⁴Ugolev, A. M. (1972). Membrane digestion. *Gut*, **13**, 735-747.
- ⁸⁵Crane, R. K. (1968). Absorption of sugars. In *Handbook of Physiology*, Section 6, *Alimentary Canal*, Vol. 3 edited by C. F. Code, pp. 1323-1351. American Physiological Society, Washington, D.C.
- ⁸⁶Fern, E. B., Hider, R. C., and London, D. R. (1969). The sites of hydrolysis of dipeptides containing leucine and glycine by rat jejunum *in vitro*. *Biochem J.*, **114**, 855-861.
- ⁸⁷Robinson, G. B. (1963). The distribution of peptidases in subcellular fractions from the mucosa of the small intestine of the rat. *Biochem. J.*, **88**, 162-168.
- ⁸⁸Josefsson, L., and Sjöström, H. (1966). Intestinal dipeptidases. IV. Studies on the release and subcellular distribution of intestinal dipeptidases of the mucosal cells of the pig. *Acta. physiol. scand.*, **67**, 27-33.
- ⁸⁹Peters, T. J. (1970). The subcellular localisation of di- and tri-peptide hydrolase activity in guinea-pig small intestine. *Biochem. J.*, **120**, 195-203.
- ⁹⁰Kim, Y. S., Birtwhistle, W., and Kim, Y. W. (1972). Peptide hydrolases in the brush border and soluble fractions of small intestinal mucosa of rat and man. *J. clin. Invest.*, **51**, 1419-1430.
- ⁹¹Silk, D. B. A. M.D. Thesis in preparation.