Intestinal adaptation to nutritional stress

BY FRANCIS RAUL AND RENE SCHLEIFFER
IRCAD, CJF INSERM 95–09, 1 place de l'hôpital, 67000 Strasbourg, France

Adaptation intestinale au stress nutritionnel

RÉSUMÉ

La muqueuse de l'intestin grêle représente une barrière entre le contenu intraluminal et le milieu intérieur. Elle intervient dans l'hydrolyse des aliments, l'absorption des nutriments et la défense immunitaire. L'ensemble de ces fonctions est assurée par différentes types cellulaires tels que les entérocytes, lymphocytes, macrophages ou fibroblastes. Bien que cette muqueuse soit extrèmement fragile, elle possède un potentiel d'adaptation rapide en réponse aux changements de l'état nutritionnel. Cet article se base essentiellement sur des travaux expérimentaux qui portent sur les réponses adaptatives de la muqueuse accompagnant les modifications de l'état nutritionnel et plus particulièrement celles se produisant lors du sevrage, du jeûne et de la réalimentation, ainsi que lors de la nutrition parentérale exclusive. Au sevrage, le passage de l'alimentation lactée riche en lactose à un régime riche en polysaccharides s'accompagne chez le rongeur, d'une modification importante dans l'expression de deux hydrolases de la bordure en brosse des entérocytes, la lactase (*EC* 3.2.1.23) et la saccharase (*EC* 3.2.1.48). L'activité de la lactase qui reste élevée pendant la période d'allaitement chute au moment du sevrage alors que la saccharase absente de l'intestin pendant l'allaitement apparaît au moment du sevrage et augmente rapidement. L'évolution de ces enzymes est partiellement sous le contrôle des hormones thyroidiennes et corticoides. De plus, les modifications dans l'expression de la lactase peuvent être avancées ou retardées en fonction de la date à laquelle les animaux sont sevrés. Ces modifications sont régulées principalement au niveau post-transcriptionnel. Au cours du sevrage, l'apparition de la saccharase est régulée à la fois au niveau transcriptionnel (par les corticoides) et au niveau post-transcriptionnel (par le saccharose). Chez l'adulte, l'administration orale de sucrose induit rapidement à la fois une augmentation du taux d'ARNm et de la synthèse de la saccharase. En revanche l'administration de lipides conduit à une diminution de l'activité de l'enzyme consécutive à une dégradation plus importante de la molécule enzymatique au niveau de la bordure en brosse par les protéases pancréatiques présents dans la lumière intestinale. Le jeûne, dans les premiers jours, s'accompagne d'une hypoplasie et d'une hypotrophie de la muqueuse intestinale associée à une baisse de l'expression et de la synthèse des protooncogènes c-fos et c-jun, ainsi qu'à une altération fonctionnelle avec réduction de l'activité des hydrolases de la bordure en brosse, à l'exception de la lactase. Ces altérations sont rapidement réversées au cours de la réalimentation. Les capacités d'adaptation de l'intestin à la réalimentation diminuent avec l'âge et intéressent plus particulièrement l'intestin proximal.

La nutrition parentérale totale qui permet de maintenir un apport énergétique normal s'accompagne chez l'animal, d'altérations morphologiques et fonctionnelles importantes: hypoplasie et hypotrophie, chute de l'activité des hydrolases à l'exception de la lactase,

diminution de la motilité et de la réponse immune. L'importance de ces altérations est liée à la composition relative des nutriments présents dans le mélange nutritif. La présence de lipides semble être indispensable à la préservation de la trophicité intestinale. Un certain nombre de nutriments spécifiques tels que la glutamine, les nucléosides et nucléotides, les acides gras à chaîne courte (butyrates) pourraient avoir des effets bénéfiques sur la muqueuse intestinale au cours d'une alimentation parentérale. Cependant l'effet positif de ces nutriments n'est pas démontré lorsqu'ils sont associés à un mélange nutritif contenant des lipides. Les implications cliniques de ces observations sont présentées et les perspectives d'une thérapeutique nutritionnelle sont discutées.

The intestinal mucosa represents a major interface between host and environment. Food is an important stimulus for the growth of the intestinal mucosa. The mucosal cells regulate the entry of ingested nutrients and defend against a multitude of potentially noxious agents present in the lumen. The intestine is unique in its ability to adapt rapidly in response to nutritional stress which is caused by abrupt dietary changes acting either directly or indirectly through diet-regulated systemic factors.

The mucosal epithelium of the small intestine consists of well-organized villi and crypts supported by microvascular, lymphatic, and connective tissues of the lamina propria and submucosa. In addition, other cellular elements, including lymphocytes, macrophages and fibroblasts perform specialized functions in order to preserve mucosal integrity (Williamson, 1978). The adaptive response of the small intestine takes place at multiple levels. The epithelial cells undergo rapid renewal along the crypt–villus axis. Cell division is confined to the crypt. The epithelial cells migrate along the villus axis and during this migration the cells mature morphologically and functionally, with the progressive development of microvilli at the apical surface and the appearance of digestive enzymes. Under normal circumstances there is a balance between the extrusion at the tip of the villus and proliferation in the crypt. In adult rodents, cell migration from the crypt to the villus tip requires 2–3 d; in man, it requires 3–6 d (Lipkin, 1987). This balance is modified by nutritional status and also with ageing.

Several factors influence, indirectly or directly, intestinal function and intestinal integrity during food consumption. The intestinal mucosa is affected not only by hormones such as growth hormone, thyroid hormones, glucocorticoids or insulin, but also by a multiplicity of other factors brought into play by the ingestion of food: gastrointestinal peptide release, biliary and pancreatic secretions, changes in intestinal blood flow, innervation, changes in motility etc. The presence of food in the intestinal lumen directly affects villus desquamation and enterocyte metabolism and modulates mucosal growth (Johnson, 1987).

The intralumen chyme contains not insignificant amounts of polyamines (putrescine, spermidine and spermine) which stimulate mucosal growth when absorbed by enterocytes (Osborn & Seidel, 1990). In addition, the nutrients, especially amino acids, resulting from intralumen digestion by pancreatic enzymes activate the endogenous synthesis of polyamines by stimulating the activity of ornithine decarboxylase (ODC; *EC* 4.1.1.17). Intracellular polyamine mobilization through exogenous sources and from endogenous synthesis and catabolism is an important way to maintain intestinal growth (Rajeev *et al.* 1987).

The terminal and limiting step of intralumen digestion is achieved by hydrolase molecules anchored in the brush-border membrane of mature enterocytes by a small hydrophobic sequence. The hydrolase molecule is a glycoprotein carrying one or two active sites floating in the lumen in direct contact with the nutrients and also with bilio-pancreatic secretions (Ahnen *et al.* 1983; Mantei *et al.* 1988).

In addition to its digestive function the intestinal mucosa constitutes a barrier between the non-sterile lumen and the sterile interior of the body. During pathological states such as septic shock or trauma the intestinal mucosal barrier may be impaired or broken down completely after local ischaemic injury. As a consequence the possibility of bacteria and toxins invading the body is greatly enhanced. The response of the defence systems to this invasion may become exacerbated and uncontrolled and may ultimately result in the development of a multiple organ failure syndrome (Haglund, 1994). Lumen nutrients participate in the protection of this barrier under normal nutritional and physiological conditions.

The present review discusses mainly experimental studies that have evaluated the adaptive responses of the small intestine to various changes in the nutritional status. Our particular focus is on the consequences of modifications in diet composition, of starvation periods followed by refeeding and of altering the route of diet delivery (enteral *v.* parenteral) on the digestive and barrier functions of the small intestine. Finally, we address the clinical implications of some experimental data sustaining the concept of nutritional therapy.

ADJUSTMENTS TO CHANGES IN DIET COMPOSITION

Weaning period

The weaning period in rodents shows coordinated changes in behaviour and metabolism in association with modifications of the hormonal and nutritional status (Henning, 1981). Important changes occur in the intestinal mucosa of rodents at the weaning period (3rd week of postnatal life) when the neonates switch from milk to an adult-type diet, from a diet containing lactose to a diet rich in polysaccharides but with no lactose. In parallel with these dietary changes the hydrolase activity of the brush-border membranes of the enterocytes is profoundly modified. Lactase (*EC* 3.2.1.23) activity which is maximum at birth and elevated during the suckling period decreases to low basal adult levels at weaning, whereas sucrase (*EC* 3.2.1.48) which is absent from the intestine during the suckling period appears in the intestinal mucosa at weaning. It is tempting to attribute the control of these enzymic modifications directly to the changes in diet composition. In fact it has been shown that the modifications in enzyme expression at weaning depend on the ontogenetic programme that controls the postnatal development of the small intestine (Kendal *et al.* 1969; Ferguson *et al.* 1973; Montgomery *et al.* 1981). Dietary and hormonal changes may act as regulators of this ontogenetic programme. This is supported by the observation that: (1) the postnatal evolution pattern of circulating thyroxine and cortiscosterone parallels the changes in lactase and sucrase activities (Henning, 1981); (2) exogenous administration of thyroxine causes a precocious decrease in lactase expression in the intestine of suckling rats (Freund *et al.* 1991*a*,*b*), whereas exogenous administration of hydrocortisone leads to a premature appearance of sucrase activity (Doell & Kretchmer, 1964).

By changing the dietary conditions it is possible to modulate the expression pattern of

lactase. Premature weaning by feeding an adult-type diet to suckling rats induces a precocious disappearance of lactase mRNA in the distal small intestine together with an accelerated decrease in lactase activity. Premature weaning leads to the appearance of an adult phenotype in the intestinal epithelial cells (Duluc *et al.* 1992). On the other hand, prolonged nursing of suckling rats delays the decrease in lactase activity and the decay in lactase mRNA in the distal small intestine (Duluc *et al.* 1992). These findings show that the ontogenic decline of lactase can be promoted or delayed by changing the time at which the rats switch over from milk to the adult-type diet; these dietary changes exert a post-transcriptional control on lactase expression.

The appearance of sucrase mRNA and activity can be induced prematurely by isolating the pups from their dam and by food deprivation (Nsi-Emvo *et al.* 1994). This occurs despite the general decline in intestinal protein synthesis caused by food deprivation in pups (Burrin *et al.* 1991*a*). The starvation-evoked expression of sucrase is preceded by changes in the level of endogenous glucocorticoids occurring in parallel with an early transient enhancement of ODC expression, followed by an increase in mucosal polyamine content and by a transient burst of expression of the protooncogene c-fos. The premature induction of sucrase expression, which is regulated at the level of gene transcription, is dependent on changes in polyamine metabolism that can be elicited by endogenous changes in circulating glucocorticoids, which are modulated by the nutritional status of the pups (Nsi-Emvo *et al.* 1996). Precocious and transient expression of sucrase has been obtained also by feeding the pups with polyamines (Georges *et al.* 1990).

In the adult

In the small intestine of the adult rat, a rapid stimulation of sucrase activity can be induced by dietary alteration. Oral administration of sucrose causes an increase in both sucrase mRNA accumulation and sucrase activity, the major response being obtained in the cells located in the lower villus (Raul *et al.* 1980, 1982*b*). Within 3 h of consumption of a sucrose-containing diet, the activity and the amount of sucrase mRNA increase in the jejunum, indicating that this effect is mainly caused by *de novo* synthesis of enzyme molecules (Broyart *et al.* 1990).

On the other hand, animals fed on diets rich in protein (Goda *et al.* 1988) or rich in fat (Takase & Goda, 1990; Goda & Takase, 1994) exhibit lower sucrase activity, resulting from increased lumen degradation of the enzyme molecule by pancreatic proteases. Diets rich in protein or peptides induce both aminopetidase catalytic activity and enzyme synthesis (Reisenauer & Gray, 1985; Raul *et al.* 1987).

INTESTINAL ADAPTATION TO STARVATION–REFEEDING

Intralumen food constitutes the primary stimulus for intestinal growth. When food is withheld an adaptive response rapidly occurs. After a short period of fasting (2–3 d) the observed mucosal alterations are characterized by villus hypoplasia, reduced mucosal mass, DNA synthesis and crypt cell production rate, ODC activity and putrescine content (Brown *et al.* 1963; Clarke, 1975). A reduction in the brush-border-membrane hydrolase activities is observed for all hydrolases within 24 h of starvation, except for lactase which exhibits increased activity (Raul *et al.* 1982*a*). This suggests that systemic

factors exert more control on lactase activity than do the amounts of nutrients. In fact, it has been shown that lactase is under the negative control of thyroid hormones in the rat and that the reduction of circulating thyroxine during fasting may trigger the elevation of lactase activity (Raul *et al.* 1983). Differential changes occur in brush-border amino acid transport during a 3 d period of food deprivation. The transporters for glutamine and arginine decrease, but the transporters for alanine and leucine are maintained. These differences may be related to the need for gluconeogenic precursors during fasting (Sarac *et al.* 1994). Starvation changes the fluidity of the brush-border membrane, which in turn facilitates enhanced D-glucose transport across the intestinal epithelial cell membranes (Gupta & Waheed, 1992).

The alterations induced by the fasting state reverse rapidly when refeeding is initiated (Williamson, 1978). In rats fasted for 4 d and then refed on a standard diet for up to 48 h, the pattern of lactase mRNA expression along the small intestine shows striking differences. Starvation initiates the expression of the transcript in the distal part of the small intestine and also a higher level of expression in the proximal small intestine. Refeeding restores the distribution of lactase mRNA observed in *ad lib.*-nourished rats within 24 h, reflecting a return of the villus phenotype to the normal fed state (Freund *et al.* 1991*a*; Hodin *et al.* 1994). These findings strongly suggest that control at a pre-translational level (transcriptional rates and/or mRNA half-lives) is involved in the changes in lactase mRNA expression induced by starvation–refeeding.

Immediate early genes are induced very rapidly following the growth stimulus, and their expression occurs independently of new protein synthesis. The protooncogenes c-fos and c-jun are among the group of genes which have been found to be part of the immediate early response in various cell types. A 4 d fast causes a dramatic reduction in the amount of c-fos and c-jun mRNA in the intestinal mucosa. Refeeding quickly induces an increase in the expression of both protooncogenes, which is observed within 2 h of refeeding (Hodin *et al.* 1994). This early increase reflects the mitogenic response to refeeding that occurs within the crypt compartment.

The trophic effects of different dietary nutrients on mucosal adaptation have been studied in adult rats subjected to a 4 d fast and refed with an isoenergetic diet containing either protein, starch or lipids (Buts *et al.* 1990). Lipids exert the strongest stimulatory effect on mucosal morphology, the length of the villus is completely normalized within 24 h after refeeding is initiated. Normal lactase activity is also achieved within 24 h, the lipid diet being more efficient than protein or carbohydrates in restoring the normal phenotype of nourished control rats. Stimulation of aminopeptidase and sucrase is observed with their respective substrates (protein and carbohydrate) and refeeding with lipids provokes a decrease in sucrase activity, which corroborates the findings of Goda & Takase (1994) of an accelerated degradation of the enzyme molecule by pancreatic proteases with a high-lipid diet.

Effects of ageing

The digestive capacities of the intestinal mucosa of healthy animals are not significantly altered during ageing (Thompson & Keelan, 1986). However, it has been reported that ageing in Fischer rats is associated with increased crypt-proliferating zones, with higher basal levels of ODC activity and polyamine content (Holt *et al.* 1988; Yoshinaga *et al.* 1993). Young and senescent Fischer rats fasted for 3 d exhibit a substantial drop in

mucosal ODC activity and putrescine content in the proximal small intestine. Reinstating a standard diet increases ODC activity by 17-fold in young rats within 2 h but only by 8-fold in aged rats. Similarly the putrescine content of the mucosa increases much less in aged rats with refeeding (Yoshinaga *et al.* 1993). Functional adaptation to refeeding is also impaired in the ageing animal. In young and aged Wistar rats fasted for 2 d the sucrase and aminopeptidase activities were diminished. The adaptive capacities of the hydrolases to the changes in the diet composition during refeeding are strikingly deficient in the proximal intestine of aged rats. However, these proximal deficiencies are compensated by enhanced ileal functions (Reville *et al.* 1991).

INTESTINAL ADAPTATION TO TOTAL PARENTERAL FEEDING

Total parenteral nutrition (TPN) can be defined as the technique by which all nutrients necessary to sustain life are administered intravenously. This technique is used extensively in patients who are unable to achieve adequate oral intakes of nutrients. The route of nutrient delivery, diet composition and the availability of specific nutrients all have a significant impact on mucosal morphology and physiology. After 3 d, the small intestine of rats fed by TPN exhibits a rapid reduction in villus height, mucosal thickness, N, DNA and RNA contents despite the maintenance of normal energy intake (Johnson *et al.* 1975; Hughes & Dowling, 1980).

Alterations in mucosal function occur simultaneously with changes in intestinal morphology. A decrease in brush-border disaccharidase activity occurs secondary to mucosal atrophy, and intravenously-fed animals have lower total intestinal sucrase activities (Levine *et al.* 1974). However, as in the starved state, the total activity of lactase is not reduced (Czernichow *et al.* 1992). Rats nourished by TPN show reduced intestinal motility and inhibition of hexose absorption, while intestinal absorption of glycine or of the dipeptide glycylglycine is not significantly affected after 2 weeks of TPN (Miura *et al.* 1992).

It has been reported that rats receiving TPN have increased levels of bacterial translocation compared with animals fed orally on a standard diet (Alverdy *et al.* 1988). It is likely that intestinal barrier dysfunction and bacterial translocation during intravenous feeding is related to factors other than the development of gut atrophy (Helton & Garcia, 1993). Enhanced bacterial translocation during TPN in rodents occurs presumably as a result of an increase in the population of caecal anaerobes and of a decreased secretion of intestinal immunoglobulin A (Alverdy *et al.* 1985).

It is noteworthy that one report (Guedon *et al.* 1986) shows there is no clinical evidence that the human gut becomes atrophic during TPN. However, functional alterations characterized by reduced microvillus length and brush-border enzyme activities have been observed also. On the other hand, it has been reported that mucosal atrophy similar to that in animals occurs in human subjects, as shown by gross and microscopic examination of resected segments after a prolonged course of TPN (Inoue *et al.* 1993). Clinically, intestinal atrophy in the human subject is often first recognized during attempts to initiate an enteral diet after a course of TPN, when diarrhoea and malabsorption can be significant problems (Wilmore *et al.* 1988).

The composition of nutrients present in the TPN mixture has a significant influence on intestinal morphology. Administration of a TPN mixture to animals for 1 week, results in a reduction in villus height in the jejunum of 56% when the mixture includes

dextrose, electrolytes and vitamins (Grant & Snyder, 1988). When amino acids are included the reduction in villus height is 35–38% (Hwang *et al.* 1987). When the mixture contains carbohydrates, amino acids and lipids the reduction in the villus height is then limited to 16–22% (Grant & Snyder, 1988; Bark *et al.* 1994).

Specific supplementations

It has been shown that there is no evidence for diminution in the endocrine responses of the adult intestinal tract after prolonged TPN (Greenberg *et al.* 1981), and mucosal atrophy during TPN may be related to the absence of specific energy substrates.

Traditionally, glucose was considered to be the main fuel source for enterocytes, but studies in the 1970s suggested that it was in fact glutamine that provided a major proportion of the energy required by the intestinal mucosa (Windmueller & Spaeth, 1974). Glutamine has been recognized as an important oxidative fuel for enterocytes (Windmueller & Spaeth, 1978). Commercially-available amino acid solutions used in formulations for TPN do not contain glutamine, due to its instability in aqueous solutions and the formation of toxic compounds during sterilization (Adibi, 1989). Glutamine supplementation of TPN solutions leads to apparently contradictory results. When the TPN mixture does not contain lipids, glutamine supplementation produces a positive effect. It has been shown under these conditions that glutamine or branched-chain amino acids (valine, leucine, isoleucine), or the administration of glutamine as the dipeptide, alanyl-glutamine, improve jejunal morphology by reducing the TPN-induced mucosal atrophy in rats (O'Dwyer *et al.* 1989; Tamada *et al.* 1992; Plattell *et al.* 1993). However, when the TPN contains lipids, glutamine supplementation has no influence on intestinal growth and development in infant piglets and no beneficial effects on the intestinal mucosa of adult rats (Burrin *et al.* 1991*b*; Bark *et al.* 1994). Therefore, the effects of glutamine on mucosal atrophy and growth depend on the composition of the TPN mixture (presence or absence of lipids) supplied during parenteral feeding, and the physiological advantages of glutamine supplementation for an otherwise-healthy intestine remain questionable.

Dietary nucleosides contribute to mucosal growth and to maturation of the developing gut in the rat (Uauy *et al.* 1990). Dietary nucleotides enhance intestinal repair in rats with chronic diarrhoea (Nunez *et al.* 1990). Positive effects on the intestinal mucosa of supplementation of TPN solutions with nucleosides and nucleotides have been reported only in the absence of lipids. Under those conditions it has been shown that supplementation with a source of purines and pyrimidines exerts a more trophic effect on the mucosa than glutamine (Iijima *et al.* 1993) and stimulates the proliferative activity of crypt cells, improving mucosal maturity and integrity during TPN (Tsunjinaka *et al.* 1993).

From studies reported previously, lipids seem to be an essential component of the TPN mixture in order to maintain mucosal growth. Changing the lipid composition of the TPN mixture may be one approach in order to reduce the hypotrophic effects of TPN on the mucosa. In this regard, medium-chain triacylglycerols (MCT) have physiological advantages over long-chain triacylglycerol (LCT); they represent a high-energy fuel rapidly transported and oxidized in tissues that is less likely to be deposited (Bach *et al.* 1982).

Enteral or parenteral administration to rats of the same nutritive mixture differing in the lipid composition, MCT:LCT (50:50, w/w) or LCT, for 7 d shows that there is no

prevention of the villus hypotrophy and the functional deficit observed during TPN with the diet containing MCT. However, enteral infusion of the diet containing MCT stimulates the epithelial cell renewal specifically in the proximal intestine where the MCT are preferentially absorbed (Galluser *et al.* 1993).

CLINICAL IMPLICATIONS: NUTRITIONAL THERAPY

Artificial nutrition is essentially used in patients in order to restore a balanced nutritional state. It appears that nutrition can be used as a primary therapy for the disease process itself. In such a way, specific nutrients delivered by either the enteral or parenteral route may have several beneficial effects on intestinal structure and function in pathological states. TPN has been used as a primary therapy for inflammatory bowel disease (Steiger *et al.* 1969). It has been shown that therapy with an elemental diet is comparable with steroid therapy in Crohn's disease (Hunt *et al.* 1989).

Among the short-chain fatty acids, the butyrates are the preferred substrates for colonic epithelial metabolism (Roediger, 1980), and nutritional therapy using fermentable fibres as the lumen source of butyrates has shown accelerated healing of inflamed colonic mucosa (Rolandelli *et al.* 1988).

In other pathological states, dietary supplementations with specific amino acids showed beneficial effects. Arginine given to patients by either enteral or parenteral routes acts by improving N balance, accelerating wound healing and restoring depressed immunity (Cynober, 1994). Enteral administration of arginine in an experimental model of intestinal ischaemia does not prevent the ischaemic damage but strikingly accelerates the recovery of the mucosa through enhanced production of endogenous polyamines and NO. The arginine-derived NO appears as an important mediator in the restitution of intestinal mucosa after ischaemia by minimizing cell injury during re-perfusion (Raul *et al.* 1995).

CONCLUSIONS

The development and use of nutritional formulas in pathological states and abnormal gastrointestinal function has led to the availability of diets which do not maintain normal gut physiology or function. Those diets are absorbed better, but at the expense of maintaining vital mucosal function such as epithelial integrity and immune activation. The role of supplementing elemental diets with specific nutrients such as arginine, glutamine, ornithine, polyunsaturated fatty acids or short-chain fatty acids, needs to be better defined. Research into the mechanisms by which these nutrients modulate the functional adaptation and the neuro-endocrine immune function of the gastrointestinal tract is needed. Future research efforts will probably result in the formulation of diets administered enterally or parenterally in which some defined nutrients are used as specific 'drugs' in order to promote protection and healing of the mucosa, and/or to modulate the immune responses.

REFERENCES

Adibi, S. A. (1989). Intravenous use of glutamine in peptide form: clinical application of old and new observations. *Metabolism* **38,** 89–92.

Ahnen, D. J., Mircheff, A. K., Santiago, N. A., Yoshioka, C. & Gray, G. M. (1983). Intestinal surface aminooligopeptidase. Distinct molecular forms during assembly on intracellular membranes in vivo. *Journal of Biological Chemistry* **258,** 5960–5966.

Alverdy, J. C., Aoyes, E. & Moss, G. S. (1988). Total parenteral nutrition promotes bacterial translocation from the gut. *Surgery* **104,** 185–190.

Alverdy, J. C., Chi, H. S. & Sheldon, G. F. (1985). The effect of parenteral nutrition on gastrointestinal immunity: the importance of enteral stimulation. *Annals of Surgery* **202,** 681–684.

Bach, A. C. & Babayan, V. K. (1982). Medium chain triglycerides: an update. *American Journal of Clinical Nutrition* **36,** 950–962.

Bark, T., Svenberg, T., Theodorsson, E., Uribe, A. & Wennberg, A. (1994). Glutamine supplementation does not prevent small bowel mucosal atrophy after total parenteral nutrition in rat. *Clinical Nutrition* **13,** 79–84.

Brown, H. O., Levine, M. L. & Lipkin, M. (1963). Inhibition of intestinal epithelial cell renewal and migration induced by starvation. *American Journal of Physiology* **205,** 868–872.

Broyart, J. P., Hugot, J. P., Perret, C. & Porteu, A. (1990). Molecular cloning and characterization of a rat intestinal sucrase-isomaltase cDNA: regulation of sucrase-isomaltase gene expression by sucrose feeding. *Biochimica et Biophysica Acta* **1097,** 61–67.

Burrin, D. G., Davis, T. A., Fiorotto, M. L. & Reeds, P. J. (1991*a*). Stage of development and fasting affect protein synthetic activity in the gastrointestinal tissues of suckling rats. *Journal of Nutrition* **121,** 1099–1108.

Burrin, D. G., Shulman, R. J., Storm, M. C. & Reeds, P. J. (1991*b*). Glutamine or glutamic acid effects on intestinal growth and disaccharidase activity in infant piglets receiving total parenteral nutrition. *Journal of Parenteral and Enteral Nutrition* **15,** 262–266.

Buts, J. P., Vivjerman, V., Barudi, C., De Keyser, N., Maldague, P. & Dive, C. (1990). Refeeding after starvation in the rat: comparative effects of lipids, proteins and carbohydrates on jejunal and ileal mucosal adaptation. *European Journal of Clinical Investigation* **20,** 441–452.

Clarke, R. M. (1975). The time course changes in mucosal architecture and epithelial cell production and cell shedding in the small intestine of the rat fed after fasting. *Journal of Anatomy* **120,** 321–327.

Cynober, L. (1994). Can arginine and ornithine support gut functions. *Gut*, Suppl. 1, S42–S45.

Czernichow, B., Galluser, M., Hasselmann, M., Doffoel, M. & Raul, F. (1992). Effects of aminoacids in mixtures given by enteral or parenteral route on intestinal morphology and hydrolases in rats. *Journal of Enteral and Parenteral Nutrition* **16,** 259–263.

Doell, R. & Kretchmer, N. (1964). Intestinal invertase: precocious development of activity after injection of hydrocortisone. *Science* **143,** 42–44.

Duluc, I., Galluser, M., Raul, F. & Freund, J. N. (1992). Dietary control of the lactase mRNA distribution along the rat small intestine. *American Journal of Physiology* **262,** G954–G961.

Ferguson, A., Gerskowitch, V. P. & Russel, R. I. (1973). Pre- and postweaning disaccharidase patterns in isografts of fetal mouse intestine. *Gastroenterology* **64,** 292–297.

Freund, J. N., Duluc, I. & Raul, F. (1991*a*). Lactase expression is controlled differently in the jejunum and ileum during development in rats. *Gastroenterology* **100,** 388–394.

Freund, J. N., Foltzer-Jourdainne, C., Duluc, I., Galluser, M., Gossé, F. & Raul, F. (1991*b*). Rat lactase activity and mRNA expression in relation to the thyroid and corticoid status. *Cellular and Molecular Biology* **37,** 463–468.

Galluser, M., Czernichow, B., Dreyfus, H., Gossé, F., Guérold, B., Kachelhoffer, J., Doffoel, M. & Raul, F. (1993). Comparison of different lipid substrates on intestinal adaptation in the rat. *Gut* **34,** 1069–1074.

Georges, P., Dandrifosse, G., Vermesse, P., Forget, P., Deloyer, P. & Romain, N. (1990). Reversibility of spermine-induced intestinal maturation in the rat. *Digestive Diseases and Sciences* **35,** 1528–1536.

Goda, T., Raul, F., Gossé, F. & Koldovsky, O. (1988). Effects of a high protein, low-carbohydrate diet on degradation of sucrase-isomaltase in rat jejunum. *American Journal of Physiology* **254,** G907–G912.

Goda, T. & Takase, S. (1994). Dietary carbohydrate and fat independently modulate disaccharidase activities in rat jejunum. *Journal of Nutrition* **124,** 2233–2239.

Grant, J. P. & Snyder, J. P. (1988). Use of L-glutamine in total parenteral nutrition. *Journal of Surgical Research* **44,** 506–513.

Greenberg, G. R., Wolman, S. L., Chritofides, N. D., Bloom, S. R. & Jeejeebhoy, K. N. (1981). Effect of total parenteral nutrition on gut hormone release in humans. *Gastroenterology* **80,** 988–993.

Guedon, C., Schmitz, J., Lerebours, E., Metayer, J., Audran, E., Hemet, J. & Colin, R. (1986). Decreased brush border hydrolases without gross morphologic changes in human intestinal mucosa after prolonged total parenteral nutrition of adults. *Gastroenterology* **90,** 373–378.

Gupta, P. D. & Waheed, A. A. (1992). Effect of starvation on glucose transport and membrane fluidity in rat epithelial cells. *FEBS Letters* **300,** 263–267.

Haglund, U. (1994). Gut ischemia. *Gut*, Suppl. 1, S73–S76.

Helton, W. S. & Garcia, R. (1993). Oral prostaglandin E2 prevents gut atrophy during intravenous feeding but not bacterial translocation. *Archives of Surgery* **128,** 178–184.

Henning, S. (1981). Postnatal development: coordination of feeding, digestion and metabolism. *American Journal of Physiology* **241,** G199–G214.

Hodin, R. A., Graham, J. R., Meng, S. & Upton, M. P. (1994). Temporal pattern of rat small intestinal gene expression with refeeding. *American Journal of Physiology* **266,** G83–G89.

Holt, P. R., Yeh, K. Y. & Kotler, D. P. (1988). Altered control of proliferation in proximal small intestine of senescent rat. *Proceedings of the National Academy of Sciences, USA* **85,** 2771–2775.

Hughes, C. A. & Dowling, R. H. (1980). Speed of onset of adaptive mucosal hypoplasia and hypofunction in the intestine of parenterally fed rats. *Clinical Science* **59,** 317–322.

Hunt, J. B., Payne-James, J. J. & Palmer, K. R. (1989). A randomized controlled trial of elemental diet and prednisone as primary therapy in acute exacerbations of Crohn's disease. *Gastroenterology* **96,** A244 Abstr.

Hwang, T. L., O'Dwyer, T. & Smith, R. J. (1987). Preservation of small bowel mucosa using glutamine-enriched parenteral nutrition. *Surgical Forum* **38,** 56–58.

Iijima, S., Tsunjinaka, T., Kido, Y., Hayashida, Y., Ishida, Y., Homma, T., Yokoyama, H. & Mri, T. (1993). Intravenous administration of nucleosides and a nucleotide mixture diminishes intestinal mucosal atrophy induced by parenteral nutrition. *Journal of Enteral and Parenteral Nutrition* **17,** 265–270.

Inoue, Y., Grant, J. P. & Snyder, P. J. (1993). Effect of glutamine-supplemented total parenteral nutrition on recovery of the small intestine after starvation atrophy. *Journal of Enteral and Parenteral Nutrition* **17,** 165–170.

Johnson, L. R. (1987). Regulation of gastrointestinal growth. In *Physiology of the Gastrointestinal Tract*, pp. 301–309 [L. R. Johnson, editor]. New York: Raven Press.

Johnson, L. R., Copeland, E. M., Dudrick, S. J., Lichtenberger, L. M. & Castro, G. A. (1975). Structural and hormonal alterations in the gastrointestinal tract of parenterally fed rats. *Gastroenterology* **58,** 1177–1183.

Kendal, K., Jumawan, J. & Koldovsky, O. (1969). Development of jejunoileal differences of activity of lactase, sucrase and acid betagalactosidase in isografts of fetal rat intestine. *Pediatric Research* **36,** 206–214.

Levine, G. M., Deren, J. J., Steiger, E. & Zinno, R. (1974). Role of oral intake in maintenance of gut mass and disaccharidase activity. *Gastroenterology* **67,** 975–982.

Lipkin, M. (1987). Proliferation and differentiation of normal and diseased gastrointestinal cells. In *Physiology of the Gastrointestinal Tract*, pp. 255–284 [L. R. Johnson, editor]. New York: Raven Press.

Mantei, N., Villa, M., Enzler, T., Wacker, H., Boll, W., James, P., Hunzinker, W. & Semenza, G. (1988). Complete structure of human and rabbit lactase-phlorizin hydrolase. Implication for biosynthesis, membrane anchoring and evolution of the enzyme. *EMBO Journal* **7,** 2705–2713.

Miura, S., Tanaka, S., Yoshioka, M., Serizawa, H., Tashiro, H., Shiozaki, H., Imaeda, H. & Tsuchiya, M. (1992). Changes in intestinal absorption of nutrients and brush border glycoproteins after total parenteral nutrition in rats. *Gut* **33,** 484–489.

Montgomery, R. K., Sybicki, M. A. & Grand, R. J. (1981). Autonomous biochemical and morphological differentiation in fetal rat intestine transplanted at 17 and 20 days of gestation. *Developmental Biology* **87,** 76–84.

Nsi-Emvo, E., Chaton, B., Foltzer-Jourdainne, C., Gossé, F. & Raul, F. (1996). Premature expression of sucrase-isomaltase triggered by corticoid-dependent changes in polyamine metabolism. *American Journal of Physiology* (In the Press).

Nsi-Emvo, E., Foltzer-Jourdainne, C., Raul, F., Gossé, F., Duluc, I., Koch, B. & Freund, J. N. (1994). Precocious and reversible expression of sucrase-isomaltase unrelated to intestinal cell turnover. *American Journal of Physiology* **266,** G568–G575.

Nunez, M. C., Ayudarte, M. V., Morales, D., Suarez, M. D. & Gil, A. (1990). Effect of dietary nucleotides on intestinal repair in rats with experimental chronic diarrhoea. *Journal of Enteral and Parenteral Nutrition* **14,** 598–604.

O'Dwyer, S. T., Smith, R. J., Hwang, T. L. & Wilmore, D. W. (1989). Maintenance of small bowel mucosa with glutamine-enriched parenteral nutrition. *Journal of Enteral and Parenteral Nutrition* **13,** 579–585.

Osborn, D. L. & Seidel, E. R. (1990). Gastrointestinal luminal polyamines: cellular accumulation and enterohepatic circulation. *American Journal of Physiology* **258,** G576–G584.

Plattell, C., McCauley, R., McCulloch, R. & Hall, J. (1993). The influence of parenteral glutamine and branched-chain amino acids on total parenteral nutrition-induced atrophy of the gut. *Journal of Enteral and Parenteral Nutrition* **17,** 348–354.

Rajeev, J., Eikenburg, B. E. & Johnson, L. R. (1987). Stimulation of ornithine decarboxylase activity in digestive tract mucosa. *American Journal of Physiology* **253,** G303–G307.

Raul, F., Galluser, M., Schleiffer, R., Gossé, F., Hasselmann, M. & Seiler, N. (1995). Beneficial effects of L-arginine on intestinal epithelial restitution after ischemic damage in rats. *Digestion* **56,** 400–405.

Raul, F., Goda, T., Gossé, F. & Koldovsky, O. (1987). Short term effect of a high protein, low-carbohydrate diet on aminopeptidase in adult rat jejunoileum: site of aminopeptidase response. *Biochemical Journal* **247,** 401–405.

Raul, F., Noriega, R., Doffoel, M., Grenier, J. F. & Haffen, K. (1982*a*). Modifications of brush border enzyme activities during starvation in the jejunum and ileum of adult rats. *Enzyme* **28,** 328–335.

Raul, F., Noriega, R., Nsi-Emvo, E., Doffoel, M. & Grenier, J. F. (1983). Lactase activity is under hormonal control in the intestine of adult rat. *Gut* **24,** 648–652.

Raul, F., Pousse, A. & Grenier, J. F. (1982*b*). La stimulation de l'activité de la saccharase par le saccharose est-elle sous la dépendance d'une synthèse d'acides ribonucléiques dans l'intestin de rat adulte. *Gastroenterologie Clinique Biologique* **6,** 424–429.

Raul, F., Simon, P., Kedinger, M., Grenier, J. F. & Haffen, K. (1980). Effect of sucrose refeeding on disaccharidase and aminopeptidase activities of intestinal villus and crypt cells in adult rats. *Biochimica et Biophysica Acta* **630,** 1–9.

Reisenauer, A. M. & Gray, G. M. (1985). Abrupt induction of a membrane digestive enzyme by its intraintestinal substrate. *Science* **227,** 70–72.

Reville, M., Gossé, F., Kachelhoffer, J., Doffoel, M. & Raul, F. (1991). Ileal compensation for age-dependent loss of jejunal function. *Journal of Nutrition* **121,** 498–503.

Roediger, W. E. (1980). Role of anaerobic bacteria in the metabolic welfare of the colonic mucosa in man. *Gut* **21,** 793–798.

Rolandelli, R. H., Saul, S. H., Settle, R. G., Jacobs, D. O., Trerotola, S. U. & Rombeau, J. L. (1988). Comparison of parenteral nutrition and enteral feeding with pectin in experimental colitis in the rat. *American Journal of Clinical Nutrition* **47,** 715–721.

Sarac, T. P., Souba, W. W., Miller, J. H., Ryan, C. K., Koch, M., Bessey, P. Q. & Sax, H. C. (1994). Starvation induces differential small bowl luminal amino acid transport. *Surgery* **116,** 679–686.

Steiger, E., Wilmore, D. W. & Dudrick, S. J. (1969). Total intravenous nutrition in the management of inflammatory disease of the intestinal tract. *Federation Proceedings* **28,** 808 Abstr.

Takase, S. & Goda, T. (1990). Effects of medium-chain triglycerides on brush border membrane-bound enzyme activity in rat small intestine. *Journal of Nutrition* **120,** 969–976.

Tamada, H., Nezu, R., Imamura, I., Matsuo, Y., Tkagi, Y., Kamata, S. & Okada, A. (1992). The dipeptide alanyl-glutamine prevents intestinal mucosal atrophy in parenterally fed rats. *Journal of Parenteral and Enteral Nutrition* **16,** 110–116.

Thompson, A. B. R. & Keelan, M. (1986). The aging gut. *Canadian Journal of Physiology and Pharmacology* **64,** 30–38.

Tsunjinaka, T., Iijima, S., Kido, Y., Homma, T., Ebisui, C., Kan, K., Imamura, I., Fukui, H. & Mori, T. (1993). Role of nucleosides and nucleotide mixture in intestinal mucosal growth under total parenteral nutrition. *Nutrition* **9,** 532–535.

Uauy, R., Stringel, G., Thomas, R. & Quan, R. (1990). Effect of dietary nucleosides on growth and maturation of the developing gut in the rat. *Journal of Pediatric Gastroenterology and Nutrition* **10,** 497–503.

Williamson, R. C. N. (1978). Intestinal adaptation. Structural, functional and cytokinetic changes. *New England Journal of Medicine* **298,** 1444–1452.

Wilmore, D. W., Smith, R. J., O'Dwyer, S. T., Jacobs, D. O., Ziegler, T. R. & Wang, X. D. (1988). The gut: A central organ after surgical stress. *Surgery* **104,** 917–923.

Windmueller, H. G. & Spaeth, A. E. (1974). Uptake and metabolism of plasma glutamine by the small intestine. *Journal of Biological Chemistry* **249,** 5070–5079.

Windmueller, H. G. & Spaeth, A. E. (1978). Identification of ketone bodies and glutamine as the major respiratory fuels in vivo for postoperative rat small intestine. *Journal of Biological Chemistry* **253,** 69–76.

Yoshinaga, K., Ishizuka, J., Evers, B. M., Townsend, C. & Thompson, J. C. (1993). Age-related changes in polyamine biosynthesis after fasting and refeeding. *Experimental Gerontology* **28,** 565–572.

Printed in Great Britain