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A. R. P. Walker Lecture

Food and the gut

Stephen J. D. O'Keefe

A. R. P. Walker pioneered the research into the association between food, gut function and disease patterns in southern Africa.[1-3] His attention to ways in which dietary differences can explain geographical differences in disease patterns has led to the realisation that civilisation and modern food technology can exert a strong influence on dietary practices, gut function and disease tendencies. Recognition that South African blacks have a very low incidence of colonic problems such as diverticulitis, adenomatous polyps and carcinoma drew attention to the possibility that the traditional African diet, with a high fibre content, may maintain colonic health and prevent disease in old age. This review explores some of the mechanisms that may account for these differences and also examines ways in which malnutrition alters gut function. To quote Walker's conclusions: 'There is a need, indeed a duty, for writers on nutrition to devote a portion of their space to the nutritional lessons to be learned from the past, from war-time experiences and from present day Third-World populations.'[4]

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Nutritional adaptation — lessons from Africa

It must be remembered that the ancestors of modern man were vegetarians. Homo habilis and homo erectus were principally vegetarians, and it was only with the evolution to homo sapiens that the art of making tools and weapons resulted in the transition of man to a hunter-gatherer and, therefore, an omnivore. Very few hunter-gatherers are left in the world, one important exception being the small bands of San (Bushmen) that roam the central Kalahari region of Botswana and Namibia. Hunter-gatherers owe their success partially to the strict segregation of duties, with men being involved in hunting and women in foraging for vegetable foodstuffs; the omnivorous diet is consumed communally. There is, however, considerable variation in the quantity of food taken at different times of the year. For example, during the dry season quantities are low, whereas in the rainy season quantities are high. However, these dietary changes have only a small influence on nutritional status as metabolism has evolved to adapt accordingly. For example, low dietary intake levels are associated with reduced metabolic expenditure, and life continues, but at a slower pace. Health is remarkably well maintained and it is only when major changes in the pattern of life occur that the delicate balance is disturbed and disease results. This is well illustrated by our recent investigations of displaced Bushmen in western Namibia where rapid urbanisation has resulted in dramatic changes in the social behaviour and dietary intake, which now consists chiefly of refined maize meal and excessive quantities of alcohol.[5] The consequence was a dramatic increase in vitamin deficiency states, alcoholic liver disease, protein deficiency and infective disease, such as tuberculosis. The ability of man to adapt to unusual dietary and social changes is great, but there is a threshold level below which the adaptation process breaks down and disease intervenes. This review investigates the level of this threshold.

Another South African illustration of nutritional adaptation is the pattern of female obesity and male slimness in most black African communities, both urban and rural.[6] Our studies indicate that the diet of rural Africans predominantly consists of carbohydrate (approximately 80%), with low intakes of protein (10%) and animal products such as saturated fat and cholesterol.[7] The obesity commonly seen in black women is not associated with increased risk of coronary artery disease but is related to hypertension, diabetes and stroke.[6,8,9] On the other hand, depleted body weight in men was associated with an increased risk of infective disease, particularly tuberculosis.[6] Despite the increased incidence of disease at both ends of the spectrum, it is remarkable how well the health and population growth of most rural African populations are maintained on a diet consisting of refined maize meal and little else. This is a tribute to the adaptability of the physiological processes on which man's survival depends. The abovementioned phenomenon puts into perspective the sometimes fanatical dependence of modern societies on the fortification of common foodstuffs with vitamins and minerals.

Digestive adaptation

One of the best illustrations of physiological adaptation involves the control of digestive enzyme synthesis. Pavlov's group, at the turn of the century, was the first to illustrate the adaptability of digestive enzyme secretion to changes in dietary intake. Their studies on dogs with pancreatic fistulas showed that a diet enriched with meat increased the secretion of protease enzymes, whereas a diet consisting chiefly of carbohydrate reduced protease secretion.[10-12] It was not until the 1940s, when the techniques to measure a wide spectrum of digestive enzymes became available that Grossman and colleagues[13] more clearly described the general adaptation of pancreatic enzyme secretion in rats. Fig. 1 demonstrates the changes in enzyme production in response to either a balanced diet, a high-carbohydrate diet, a high-protein diet or a high-fat diet. In short, a high-carbohydrate diet resulted in induction of amylase secretion, and a high-protein diet in an induction of trypsin secretion. Surprisingly, a high-fat diet did not enhance lipase secretion. However, in further studies, lipase has also been shown to adapt to a high-fat diet. For example, Lavau *et al.*[14] were able to show that rats, given either oral or intravenous feeding for 5 days, responded with an increase in lipase secretion to a diet enriched, either orally or intravenously, with fat. Their studies also showed that amylase and lipase secretion were induced by their products of digestion, in contrast to trypsin secretion which was only induced by the presence of protein in the duodenum. This suggested that trypsin production is stimulated indirectly, probably via CCK and acetylcholine release.[15] Despite a wealth of evidence for enzyme adaptation in animals, remarkably few studies have systematically examined the question of enzyme adaptation in man, possibly because of the difficulty in enforcing dietary change and also because of the difficulty of measuring enzyme synthesis, as opposed to enzyme secretion.[16]

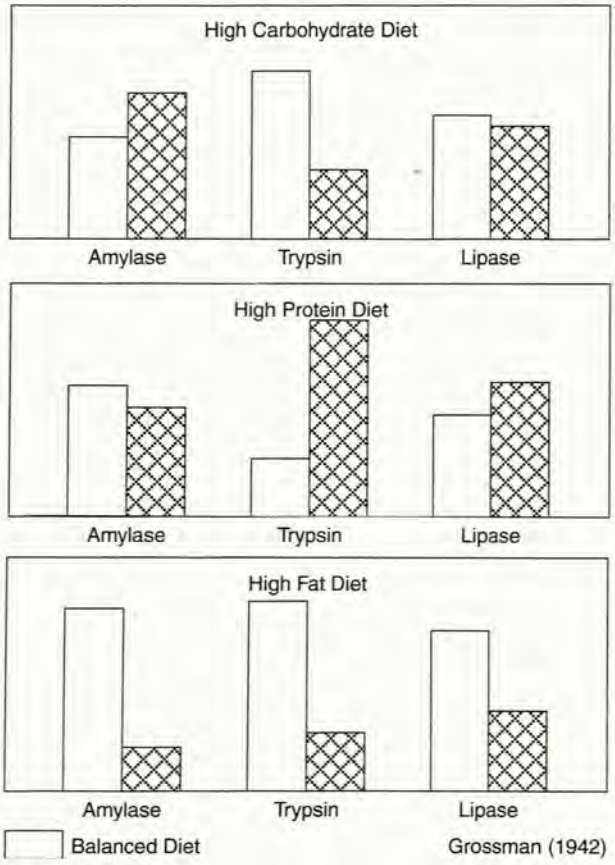

Fig. 1. Illustration of the adaptive response of pancreatic enzyme secretion in rats fed different diets, i.e. a high-protein diet induces trypsin, a high-carbohydrate diet induces amylase.[13]

Nutritional deprivation

The effect of chronic undernutrition on digestive function is summarised in Table I. It is reasonable to conclude that low levels of intake are well tolerated, resulting in conservation through decreased gut function and reduced metabolic expenditure. This may account for the difficulty of international authorities to define 'optimal nutritional requirements'. However, as mentioned above, there is a threshold in extreme starvation where nutritional depletion can result in irreversible damage and threaten survival. Presumably the threshold is related to energy stores which, when completely expended, obligate the cannibalism of structural and functional proteins for energy.

Table I. Some recognised abnormalities of gut function induced by chronic malnutrition

Stomach
Mucosal atrophy
Hypochlorhydria
Barrier function ↓
Bacterial/yeast contamination
Dilatation
Pancreas
Zymogen storage ↓
Enzyme secretion ↓ protein synthesis ↓
Acinar cell atrophy/fibrosis
Small intestine
Atrophy
Brush border ↓
Columnar → cuboidal
Motility ↓
Bacterial overgrowth: anaerobes and yeasts
Disaccharidases ↓
Xylose absorption ↓
Bile salts ↓ micelles ↓
Steatorrhoea

A study performed by Barbezat and Hansen[17] on pancreatic function in children and infants with kwashiorkor and marasmus well illustrates the resilience of pancreatic function to re-feeding. They compared 4 groups of infants, 14 with kwashiorkor (11 of whom were studied again following nutritional repletion), 7 with marasmus and 10 children with what they termed 'chronic malnutrition', who had been treated 5 years previously for protein calorie malnutrition. A fourth group of 7 healthy infants served as controls. Fig. 2 illustrates the changes in pancreatic enzyme secretion in the different groups studied before and after nutritional repletion. It can be seen that both kwashiorkor and marasmus were associated with marked reduction in enzyme secretion. However, refeeding resulted in a rapid increase in secretory capacity to levels equal to, or above, those of controls. In this study they were unable to demonstrate long-lasting changes in pancreatic function

from severe protein calorie malnutrition, with the possible exception of 1 or 2 children who developed pancreatic fibrosis. We also recently measured pancreatic exocrine function in adult patients with severe malnutrition, i.e. < 70% ideal body weight, due to chronic tuberculosis or calcific pancreatitis with malabsorption. Results (Fig. 3) demonstrated a 75% reduction in enzyme secretion in the tuberculosis patients, in response to intravenous CCK and secretin infusion, with minimal secretion in the pancreatic patients. All patients were then fed intravenously for 3 weeks, which resulted in significant (44%) improvement in enzyme secretion in tuberculosis, but not in pancreatitis patients. This well illustrates the reversibility of pancreatic insufficiency in malnourished patients without pre-existing pancreatic disease.

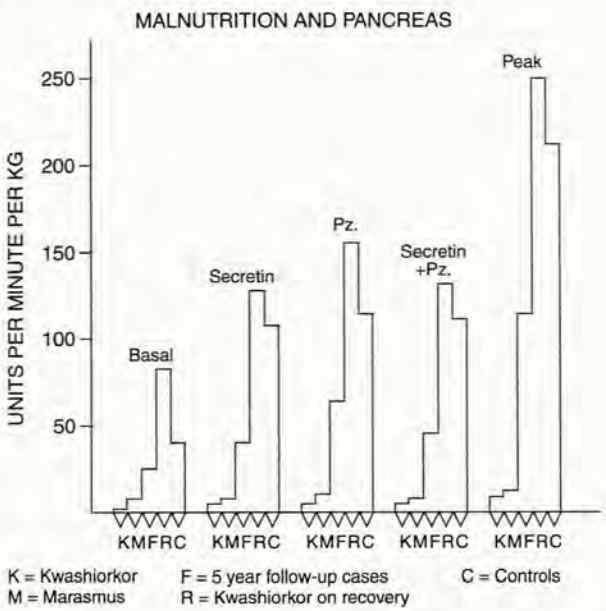

Fig. 2. Comparison of pancreatic chymotrypsin secretion rates in patients with kwashiorkor before (K) and after recovery (R), marasmic patients (M) and patients with chronic malnutrition (F), in comparison with healthy controls (C) (after Barbezat and Hansen[17]).

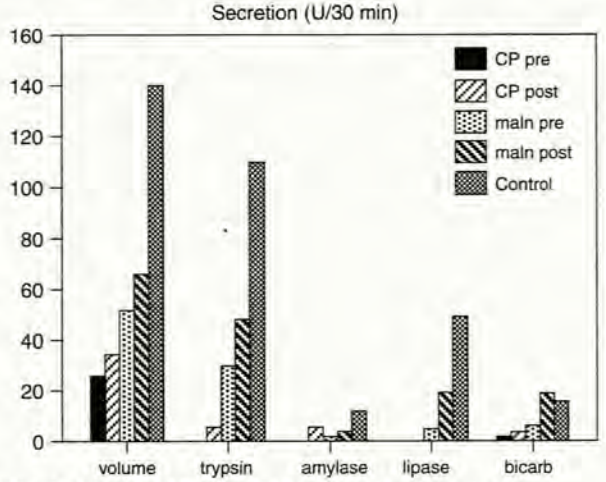

Fig. 3. Stimulated pancreatic enzyme secretion rates in malnourished patients with (CP), and without (MALN), pancreatic disease before (pre) and after (post) 3 weeks of intravenous feeding, in comparison with healthy controls. Provided pancreatic disease is not present, good recovery can be expected.

The question of whether 'nutritional pancreatitis' exists remains unanswered, but a number of workers in India support this view.[18] However, it is virtually impossible to blame malnutrition alone for pancreatic fibrosis, as many other factors in the deprived environment could be responsible. However, the classic study by Veghelyi *et al.*[19] of children who died in the siege of Budapest (1944 - 1945), provided evidence that extreme malnutrition can result in pancreatic atrophy and fibrosis. They observed the following sequence of events: 'the usual parallelism of activities of different enzymes disappeared one by one. The first to be reduced and then disappear was lipase, second the trypsin, amylase never disappeared completely'.[19] Autopsy of the children who died showed that their pancreases were severely atrophic and fibrotic.

There are only a few studies that examine the effect of severe malnutrition on intestinal function in adults. We were able to study one such individual who was admitted in an extremely marasmic state having lost 60% of his body weight (usually a fatal situation) over a 5-month period.[20] He had been admitted to a number of hospitals but had shown no response to conventional medical therapy, including intravenous fluids and antibiotics. His severe diarrhoea was made worse by eating. On admission he was mentally obtunded, hypokalaemic, had a macrocytic anaemia and decreased lymphocyte function, and had lost 62% of body weight, 55% of muscle mass and 80% of fat stores. Gastro-intestinal investigations revealed a sluggish, dilated small intestine, and secretory testing demonstrated achlorhydria and severely impaired secretion of trypsin, amylase and lipase in response to CCK stimulation (Fig. 4). Duodenal biopsies demonstrated subtotal villous atrophy and immunological staining IgA heavy-chain infiltration; this established the diagnosis of IPSID α-heavy-chain disease. Absorption tests were abnormal for d-xylose (urine excretion < 5 g/5 h) and fat (50% malabsorption). Metabolic rate was reduced by 40% (on indirect calorimetry) and whole-body protein turnover rate was reduced to 70%. As food exacerbated his diarrhoea (> 20 stools/d), intravenous feeding was commenced together with oral tetracycline and, over a period of 7 days, the diarrhoea diminished rapidly to only two semi-formed stools a day. At this stage his appetite returned and a normal ward diet was gradually introduced and well tolerated. Fig. 5 illustrates his rapid progress, with the remarkable achievement of an increase of 45 kg in weight over the following year. We were able to measure his pancreatic secretion at various times during this period as shown in Fig. 4. It can be seen that his initial malabsorption was at least partly caused by failed enzyme secretion, compounded by reduced absorptive cell function. However, nutritional repletion rapidly reversed this trend and, as shown in Barbezat and Hansen's[17] study, enzyme secretion increased to levels higher than normal after 1 year's follow-up. The lesson to be learnt from this case history is that intravenous nutritional supplementation might well be life-saving in that it breaks the vicious cycle induced by protein deficiency, reduced digestive and absorptive function, and impaired dietary utilisation. However, there is clearly a need to perform more studies to determine the exact point at which intravenous nutrition becomes essential.

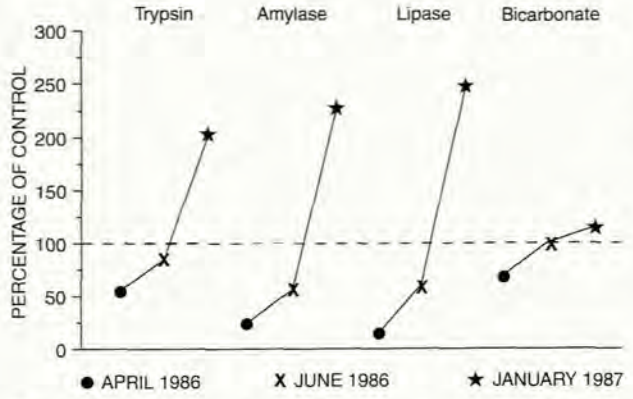

Fig. 4. Pancreatic enzyme secretion rates, stimulated by CCK and secretin, in one extremely malnourished (< 30% ideal weight) patient before (Apr 1986), during (June 1986) and after (Jan 1987) nutritional rehabilitation (body weight, 100% ideal).

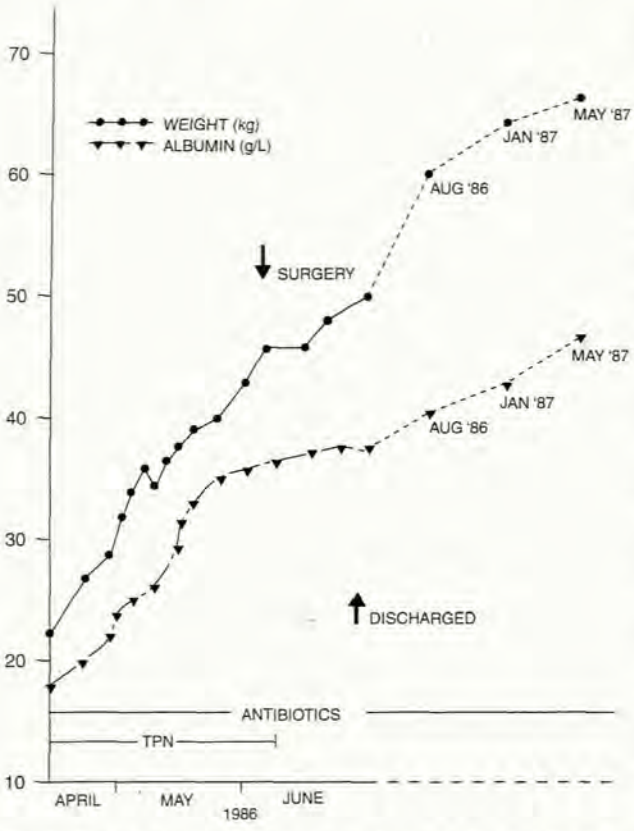

Fig. 5. Clinical progress of the same patient as in Fig. 4, following nutritional and medical treatment of IPSID/α-heavy-chain disease.

Excessive dietary intake — intestinal adaptation and short-bowel syndrome

It is fair to say that the gut is less adapted to dealing with problems of over-consumption than under-consumption. This occurs because the reserve capacity of the gut is so large that it is difficult for high dietary intakes to overcome absorptive capacity. The increased absorption results in increased protein oxidation, but the capacity to increase energy expenditure is limited and excess calories can only be stored in the form of fat. Obesity results, with all its attendant medical problems.

However, one situation where the adaptation to high nutrient intakes is advantageous, is following massive small-intestinal loss. In order to assess the effects of extensive surgical resection on gut adaptation, it is necessary to study case reports from the time prior to the use of intravenous feeding, given that the response would be masked by parenteral nutrition. Anderson[21] described survival of a 14½-year-old girl who lost all but 6 inches of her small intestine due to volvulus, but survived into adulthood. Initially she had severe diarrhoea, but with time, this gradually reduced to only two semi-formed stools per day. Her initial weight of 44,6 kg decreased rapidly over the first 3 weeks to 30 kg. However, over the next 5 years her weight progressively increased back to 43 kg and then finally 51 kg. She was seen to mature into a fully developed woman. In tandem, her fat absorption was shown to improve dramatically from only 3% to 40%. She was recommended a diet low in fat and high in protein but 'she did not find the diet very palatable and gradually reverted to a normal diet, in fact, she ate what she wanted, when she wanted'.

Dietary restriction has now fallen from favour, rightfully because, although an increased dietary fat intake is associated with an increased amount of fat excreted in the stool, the proportion absorbed remains the same and therefore the quantity of fat absorbed is actually increased.[22] A recent review by McIntyre *et al.*[23] illustrates this point well. Patients generally do what they want when they get home and severe dietary restrictions can only make life more miserable. Furthermore, increased dietary intake may be essential to maximise intestinal adaptation.[24]

Jackson and Linder[25] described a similar problem in a 20-year-old man, who also suffered volvulus of the small intestine, leaving him with only 6 inches of small intestine and an intact colon. His stool frequency was also shown to decrease to approximately 2 stools a day but the volume of the stools remained extremely high. The researchers recorded 1½ gallons at one sitting! His course, however, was completely different to Anderson's patient, with little evidence of adaptation. Fat absorption remained at 3 - 5%, protein at 30%, and no significant weight gain was observed despite a dietary intake of between 3 000 - 5 000 kcal/d. Radiographs also demonstrated a dilated colon but, in contrast to the previous report, measurements of pancreatic function demonstrated 'a very severe deficiency of enzyme secretion'. Unfortunately he died 3½ years later and at autopsy, the pancreas was shown to be severely atrophic. We can only assume that his degree of malnutrition was extreme and similar to that of the children studied in the siege of Budapest.[19]

It is difficult to understand why the outcome was so different in the two case histories described above. Both patients had 6 inches of small intestine remaining and both had colons. The presence of the colon is vitally important, as end-jejunostomy patients will not survive without long-term intravenous feeding. The colon not only reduces fluid and electrolyte loss, but also salvages undigested food by means of symbiotic relationship with bacteria. The bacteria partially metabolise undigested carbohydrate to short-chain fatty acids (SCFAs), which provide most of the colonocyte's fuel requirements.[26]

SCFAs also facilitate the reabsorption of fluid and electrolytes. This probably accounts for our observation that intravenous nutritional requirements are considerably lower in patients who have lost most of their small intestine but still have functional colons (Table II). Did Jackson and Linder's[25] patient also have impaired colonic function?

Table II. Relative absorption of fat, protein and energy in short-bowel patients with and without remaining colonic function

	Absorption (%)		
Massive intestinal resections (> 90%)	Fat	Protein	Energy
With colon[30]	52	61	67
Without colon[29]	18	22	22

In westernised countries, home parenteral nutrition is now successful in returning patients with almost total loss of small and large intestine to a near-normal state of health, as illustrated by the patient shown in Fig. 6 before and after 1 year of home parenteral nutrition. Surgical resections for severe Crohn's disease left him with 100 cm of small intestine and no colon. His nutrition, as shown in Fig. 6 (above), gradually deteriorated to the degree that it began to interfere with his usual pursuits (for example, hunting!). His dietary intake was shown to be 200% of RDA values but this resulted in an increased stomal loss and exacerbation of fluid and electrolyte deficiencies. After the insertion of a Hickman catheter and cyclic nocturnal infusions of 2 litres of total parenteral nutrition at night, he rapidly regained weight and was able to return to his normal occupation and family life. However, in some patients with end-jejunostomies, it is difficult to keep up with rate of loss of fluid and electrolytes, as the hyperphagic response exacerbates stomal secretory losses.[27] This can lead to ever-increasing fluid intakes as shown in 7 of our permanent jejunostomy patients (Table III), where stomal outputs averaged 9 l/day with 2 patients exceeding 20 l/d! In order to break the cycle, we had to use a hormonal approach, i.e. the long-acting somatostatin analogue, octreotide, which reduced intravenous fluid requirements from over 4 l/day to a more manageable 2,5 l/day.[26,29] However, these short-term benefits need to be balanced against the potential anti-anabolic effects of somatostatin, which might interfere with the adaptation process.[30]

Table III. The effect of the somatostatin analogue, octreotide*, on stomal output in jejunostomy patients

	Daily stomal output rates	
	Before	After
Volume (l)	12,3 ± 8,7	5,8 ± 2,1†
Fat (g)	67 ± 39	64 ± 48
Nitrogen (g)	23 ± 8	15 ± 7†
Sodium (mEq)	605 ± 301	316 ± 109†
Potassium (mEq)	148 ± 92	92 ± 28†
Chloride (mEq)	614 ± 273	363 ± 109†

* 100 µg subcutaneously 3 times a day.
† $P < 0,05$.

Fig. 6. Patient with severe short-bowel syndrome and gut failure due to surgical resection for Crohn's disease: (above) before home parenteral nutrition and (below) after 12 months of HPN.

Nutrition and gastro-intestinal disease

There is a strong inter-relationship between nutrition and gastro-intestinal (GI) disease. Specific dietary components can cause GI dysfunction and, on the other hand, chronic GI disease can be a cause of chronic malnutrition. Examples of the former are food hypersensitivities and coeliac disease/gluten enteropathy. A good example of disease as a cause of chronic malnutrition is Crohn's disease. A number of studies have now demonstrated that the growth failure in adolescents with Crohn's disease can be prevented by increasing nutrient intake.[31] However, this is not as simple as it sounds, because chronic Crohn's disease is associated with chronic anorexia, and nutritional interventional techniques need to be used. One approach is to use nocturnal tube-feeding. In a recent study reported by Aiges *et al.*,[32] a group of 8 adolescents were taught to intubate themselves with small-bore feeding tubes every night in order to supplement their normal diet and achieve an intake of 85 kcal/kg/day for a 12-month period. Their rate of growth was then compared to that of 6 control subjects who had also been selected for study but had failed to tolerate tube-feeding. The researchers were able to demonstrate that, on average, the fed group gained 12 kg in 1 year and grew 7 cm, in comparison to no significant change in the control group. As medical treatment was the same in the 2 groups, it is reasonable to conclude that the growth was simply a result of increased nutrient intake. This is consistent with numerous studies which have shown that the protein and caloric intakes of adolescents with Crohn's disease are decreased.[33] The reason for chronic anorexia has remained unclear but may be related to chronic inflammation or persistent subacute intestinal obstruction. The role of inflammatory mediators is at present favoured following a study by Murch *et al.*[34] which demonstrated that patients both with Crohn's disease and ulcerative colitis in relapse had higher tumour necrosis factor (TNF) α blood levels.[34] It is well recognised that TNF and other cytokines suppress appetite as well as increase protein catabolism and energy expenditure. Recently, antibodies to TNF have been developed and clinical trials are underway to assess whether they will be able to reverse growth failure and chronic undernutrition in inflammatory bowel disease patients.

Gut-specific nutrition

Glutamine, short-chain fatty acids (SCFAs) and lactose malabsorption

There are a number of exciting new developments in the field of intestinal cell metabolism which have opened the possibility of developing 'gut-specific' nutrition. Studies by Windmeuller and Spaeth[35] and Roediger[26] have shown that contrary to previous views, the chief energy supply for the jejunum is the amino acid, glutamine, while that for the colon is butyrate, a SCFA (Table IV). Glutamine supplies are abundant in a normal diet and consequently the normal process of digestion will provide adequate quantities for the enterocyte. The importance of this observation is that part of the 'disuse atrophy' that occurs with 'bowel-rest', may simply reflect a lack of dietary glutamine. It is also important to note that conventional TPN solutions do not contain glutamine because it is relatively unstable in solution. Recent studies have confirmed the importance of glutamine supply, as glutamine supplementation of TPN partially prevents villous atrophy.[36]

Table IV. The relative contribution of glutamine, butyrate and glucose to energy consumption by small and large intestine

Preferred gut fuels (% utilisation)	Jejunum[35]	Colon[26]	
		Ascending	Descending
Glutamine	35		
3-hydroxybutyrate	26		
Aceto-acetate	24		
Glucose	7	41	16
Butyrate		59	72

On the other hand, SCFAs are volatile, unstable and do not form part of the normal diet. They are produced in the colon by bacterial fermentation of malabsorbed nutrients. It was previously assumed that bacterial metabolism depended upon the malabsorption of 'resistant starches' and dietary fibre. However, more recent studies have demonstrated that malabsorption of 'digestible' carbohydrate can also be normal in human subjects. For example, studies by Stephen *et al.*,[37] using techniques of small intestinal intubation and caecal collection, have demonstrated that between 2% and 22% of digestible starch in a normal westernised diet was malabsorbed by the small intestine. This would represent a colonic caloric intake of between 10 and 75 g carbohydrate per day. Furthermore, estimates of the metabolic requirements for colonic bacteria have suggested that 70 g/day are required to maintain the bacterial population.[38] It is clear that the normal quantity of fibre in the diet is well below this level and that therefore the difference has to be made up of unabsorbed digestible starch. One would assume that the quantity of starch malabsorbed would increase in populations such as rural Africans who exist on high-carbohydrate diets that result in an increased colonic bacterial load and an increased fermentive capacity. Some evidence for this was gained from our studies which demonstrated that the fasting breath H_2 levels of Africans were higher than those of Americans and that only 10% of lactose-malabsorbing Africans developed abdominal symptoms after drinking a glass of milk.[39] Furthermore, some individuals, tolerated up to 150 g of lactose in a milk diet given over a 24-hour period.[40] This brings into question the clinical relevance of adult 'lactose-intolerance' and also suggests a mechanism for the low incidence of colonic diseases, such as diverticulitis, adenomatosis, polyps and cancer in black Africans.[1-3] Perhaps the higher fermentative metabolism maintains colonic health?

The importance of SCFAs in the maintenance of colonic function is well illustrated by the entity 'diversion colitis'. In situations where the ileal stream is diverted from the colon post-surgically, it has been recognised for years that a colitis can occur in the excluded colonic segment; this resolves on restoration of intestinal continuity. Examination of the colon reveals changes remarkably similar to those of ulcerative colitis. Harig and colleagues[41] recently reported a SCFA

deficiency in the colonic mucosa of patients with diversion colitis that responded to 2 - 3 week irrigations with SCFAs (acetate 60 mmol/l, proprionate 30 mmol/l and butyrate 40 mmol/l). They demonstrated both macroscopic and histological resolution of inflammation. Prompted by these results, Scheppach *et al.*[42] have recently described the beneficial use of butyrate enemas (100 mmol twice daily) in patients with distal colitis. In comparison to patients given placebo, there was reduced stool frequency, reduced bleeding and histological and endoscopic improvement. In addition, they measured *in vitro* tritiated thymidine incorporation into rectal biopsies and noted a significant reduction. The importance of this observation is that it is now generally accepted that the characteristics of tritiated thymidine incorporation provide a marker for the susceptibility to cancer; and it is well recognised that patients with ulcerative colitis are at increased risk of developing colon cancer.

Immunonutrition

Fascinating reports recently illustrated the strong influence that diet can have on inflammation and immunity. For many years clinicians have suspected that certain dietary items may play a role in triggering acute relapses in patients with Crohn's disease and ulcerative colitis. Support for these points of view has been obtained from studies that demonstrated that exclusion diets delay the relapse rate in Crohn's disease.[43] Further support has been obtained from the detection of antibodies to dietary proteins in patients with inflammatory bowel disease.[44,45] This has led to the hypothesis that certain dietary proteins are instrumental in exacerbating inflammatory activity in such patients. Consequently it is common practice to manage patients with acute attacks with 'bowel-rest' and intravenous feeding. Alternatively, elemental diets, in which dietary proteins are broken down to individual amino acids which are not antigenic, may be used. Controlled trials have, indeed, shown that elemental diets are as effective as corticosteroids in inducing a remission from an acute attack of Crohn's disease,[46] but bowel-rest on its own appears to have little therapeutic value.[47] For the malnourished patient, the option of a trial of elemental diet may be preferable to corticosteroids as the former maintains nutritional status, whereas the latter can exacerbate protein deficiency through increased protein catabolism.[48] Recent studies also show that elemental diets, by reducing inflammation, can also reduce hypermetabolism and therefore basic caloric needs.[49]

Specific nutrients may also have anti-inflammatory properties. The majority of fatty acids contained in a westernised diet are either of plant or animal origin and belong to the ω6 variety. All of these fatty acids have, in addition to their energy supply potential, important effects upon prostaglandin synthesis. They stimulate cyclo-oxygenase and the synthesis of arachidonic acid, PGE_2 and leucotriene B_4, all of which are inflammatory mediators. On the other hand, fish oils belong to the different class of ω3 fatty acids, and consist chiefly of eicosapentanoic acid (EPA) and docosahexanoic acid (DHA). These compounds have been shown to inhibit cyclo-oxygenase, arachidonic acid, PGE_2 and leucokotriene B_4 synthesis and thereby inhibit interleukin-1 and TNF-α production. Their metabolism is by an alternative pathway which forms PGE_3 and leucotriene B_5, which are considerably less potent. Many experimental studies have now demonstrated that fish oils have a specific anti-inflammatory potential, as well as the ability to inhibit tumour development and growth,[50] and can also reduce diarrhoea.[51] This combination of actions could theoretically prove useful in the treatment of patients with ulcerative colitis, where there is evidence of increased PGE_2 activity in association with colonic inflammation. The first controlled study has recently been published by Aslan and Triadafilopoulos[52] in which 17 patients with resistant chronic ulcerative colitis were randomised to receive either fish oil supplements in the form of 2,7 g of EPA and 1,8 DHA, or placebo for 3 weeks followed by a washout period and then crossover. The results leave room for optimism as disease activity was reduced by 56% in those on fish oil, compared with 4% in those on placebo. In addition, there was a reduced need for anti-inflammatory drugs in three-quarters of the patients. It should be noted that the conventional management for chronic ulcerative colitis is 5 amino salicylic acid — a potent prostaglandin inhibitor.

The potential use of fish oil as an anti-tumour agent is also exciting. Cell culture studies demonstrating the inhibitory effect of ω3 fatty acids on cell proliferation, have been backed up by epidemiological evidence of a low incidence of colon cancer in fish eaters (e.g. Alaskan Eskimos, Greenlanders).[53] In order to test this hypothesis prospectively, Anti *et al.*[50] recently described a trial where they randomised 24 patients with adenomatous colonic polyps, a precancerous condition, to receive either 3 capsules (4,1 g EPA 3,6g DHA and vitamin E carrier) 3 times a day, or placebo, in order to assess the effect upon cell proliferation. After 2 weeks of therapy they were indeed able to demonstrate a decrease in the S-phase cells in the upper parts of the colonic crypts obtained from mucosal biopsy samples. This change is claimed to represent a decrease in risk of neoplastic transformation.

Finally, industry has been quick to exploit the possible development of 'immuno-nutrition'. Recently, a liquid formula diet has been designed for tube-feeding hospital patients; it is rich in ω3 fatty acids, glutamine and RNA nucleotides. In experimental studies, RNA nucleotides and the amino acid arginine have both been shown to have immunoregulatory properties: nucleotides enhance the maturation and expression of T lymphocytes, while arginine is thymotrophic, increasing killer T- and helper T-cell production as well as the synthesis of interleukin-2, a cytokine with antitumour properties (Table V). The clinical efficacy of this formula has yet to be proven but a preliminary communication from Daly and colleages[54] reported reduced wound infections, reduced pneumonias, reduced hospitalisation time and reduced mortality in a group of patients following surgical procedures.

Many of the recent advances on which the above findings are based originated from research on cell biology and cellular nutrition. As the development of cell biology as a research tool is relatively new, we can expect major advances in gut-specific and disease-specific nutrition in the coming years.

Table V. Enrichment of a nutritional formula with specific nutrients known to be immunostimulatory

1. ω3 fatty acids	Anti-inflammatory
2. Arginine	Immunostimulatory, thymotrophic Killer cells ↑, helper T cells ↑ Interleukin-2 (anti-tumour) ↑
3. RNA nucleotides	Immunostimulatory Maturation and expression of T lymphocytes
4. Glutamine	Increased host-defence Trophic to small intestine Bacterial translocation ↓
5. Enteral nutrients	→ Hepatic protein synthesis ↑ Acute phase reactions ↑ Albumin synthesis, Ig synthesis ↑ Mucosal synthesis

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