Probiotics and colon cancer prevention

Graeme H McIntosh, BSc, PhD (ANU)

CSIRO Division of Human Nutrition

This review examines some of the evidence regarding probiotics bacteria as agents to reduce the risk of colon cancer in humans. While some of the evidence using rodent models of colon cancer is convincing for a reduction in cancer incidence and burden with the introduction orally of such bacteria as Bifidobacterium longum, Lactobacillus acidophilus and gg, convincing evidence in humans is less effective. In epidemiological studies or marker intervention studies using fecal enzymes, fecal bile acids or urinary/ fecal mutagens from microbial activity as measures of cancer risk, following probiotic introduction. Taken together these sources of data provide limited support for the hypothesis that probiotic bacteria are effective in cancer prevention.

Introduction
Colon cancer is a major health problem in Westernised cultures where the lifestyle is considered to be a major factor influencing its prevalence. Diets containing high animal proteins and fat and low dietary fibre have been identified as being associated with greatest risk. Recent research has also focused on the influence that gastrointestinal microflora have on outcome. A large and complex microbiological population inhabiting the colon has been so as being associated earlier in life and relatively unchanged by external factors. However, other research has suggested that it is manipulable by dietary and microbiological means as well as by antibiotic therapy. The side effects of modern antibiotic therapy may include significant disturbances of the gut microflora and have been part of the motivation to find ways of achieving treatment of disease using ‘desirable bacteria’ as an alternative therapy. Insofar as the microflora can influence the immunity and its ability to degrade and detoxify carcinogenic activation mechanisms and thereby the expression of a number of disease processes affecting the bowel, a better knowledge of their contribution to health and disease is warranted.

Probiotics are defined as live microbial food supplements which benefit the host by improving its intestinal microbial balance. Yogurt is a traditional and common vehicle for such probiotics (Lactobacillus and Bifidobacteria species being most often used in this role). They have a significant target, gastrointestinal disturbances and diseases. Wider claims include their value as a life extender, an elixir of life. Elie Metchnikoff, the Russian Nobel Prize biologist, popularised the view that some lactic acid bacteria were capable of increasing length of life, supporting his theory with observations of Bulgarians who ate yoghurt regularly and showed remarkable longevity. At the time, it created a world-wide interest in yoghurt but in the ensuing 70 or so years little attention was given to this claim. However, in the last 20 years, with the upwelling in colon cancer and inflammatory bowel diseases in Westernised countries, it has been given increasing attention by researchers.

Useful reviews by Mizusaka, Adams, Marteau et al., and Batallou, have discussed much of the groundwork research studies, in an area where Japanese and French researchers have made significant contributions.

From North America reviews are provided by Fernandez et al., Fernandez and Shahani, Gorbach and Goldin, and Sanders, while from Scandinavia Lidbeck et al., Saarinen, and Rafter useful reviews have also been provided.

Research with regard to use of probiotics in prevention of colon cancer is reviewed in this paper. It must be appreciated that lack of knowledge of the carcinogenic process, the complexity of colon function, and lack of techniques for adenoma idiomorphology of these bacteria, has held back progress significantly. Nevertheless there have been some impressive advances, which I believe are bringing us nearer to predicting a protective diet and/or probiotic strategy for reducing high rates of colon cancer. The anti-tumour action of probiotics have been proposed as:

1. Reduction of the intestinal pH, thereby altering microbial activity, solubility of bile acids, mucus secretion etc.
2. Alteration of colonic motility and transit time.

Malhotra, a medical officer with the Indian railways, reported on the gastrointestinal cancers in India, and proposed that the much lower incidence of colon cancers in northern people was associated with the significant consumption of dairy (including fermented) foods, cereals and vegetable dietary fibres in the regular diet. Southern diets by contrast were low residue highly digestible diets and tended to create a more alkaline colonic milieu. Similar differences have been noted for rural northern versus urban populations of Sweden, and in Finland versus Denmark. The difference in each case was a reduction to one half to one third the colon cancer incidence and mortality.

Table 1. Chemical colon cancer studies in rats and mice

<table>
<thead>
<tr>
<th>Tumours</th>
<th>% rats with colon cancer</th>
<th>% rats with colon tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMH (SC)</td>
<td>20%</td>
<td>100%</td>
</tr>
<tr>
<td>L. bulgaricus</td>
<td>14%</td>
<td>70%</td>
</tr>
<tr>
<td>L. acidophilus</td>
<td>12%</td>
<td>60%</td>
</tr>
<tr>
<td>C. butyricum</td>
<td>10%</td>
<td>50%</td>
</tr>
</tbody>
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Some recent animal studies have been paralysed by human and animal faecal enzyme studies, assessing nitro- reducata, β-glucuronidase, azoreductase and/or urease activity to predict risk of colon cancer. The hypothesis relies on the assumption that modulation of deconjugating and/or dehydrorylating enzymes found in certain colon bacteria but not in others will alter risk of carcinogens being generated from procarcinogenic agents or released from bound faecal components, as they traverse the large intestine. Displacement by probiotic bacteria (of undesirable bacteria) will effect significant change. Significant results (Table 2) have been achieved with this approach to assessment of risk.

Table 2. The effects of oral consumption of lactic cultures on faecal enzyme activity

<table>
<thead>
<tr>
<th>Reference</th>
<th>Bacteria used</th>
<th>Reduction of enzyme activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldin et al. (18)</td>
<td>L. acidophilus (7 subjects)</td>
<td>+ nitroreductase, - azoreductase</td>
</tr>
<tr>
<td>Gorbach (20)</td>
<td>L. acidophilus (7 subjects)</td>
<td>+ nitroreductase, - azoreductase</td>
</tr>
<tr>
<td>Marteau et al. (30)</td>
<td>L. acidophilus B bifidum, and mesophilic cultures (9 subjects)</td>
<td>+ nitroreductase, - azoreductase</td>
</tr>
<tr>
<td>Goldin et al. (21)</td>
<td>Lactobacillus GF (frozen concentrate (8 subjects)</td>
<td>+ nitroreductase, - azoreductase</td>
</tr>
<tr>
<td>Lidbeck (12)</td>
<td>L. acidophilus N-2 (12 subjects)</td>
<td>+ nitroreductase, - azoreductase</td>
</tr>
<tr>
<td>Ling et al. (32)</td>
<td>L. GG (64 subjects)</td>
<td>+ nitroreductase, - azoreductase</td>
</tr>
<tr>
<td>Kullkani and Roddy (29)</td>
<td>L. acidophilus (33 rats)</td>
<td>+ nitroreductase, - azoreductase</td>
</tr>
</tbody>
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* = statistically significant positive, results; ** = negative results; † = results not definitive.
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Introduction

Colon cancer is a major health problem in Westernised cultures. Risk factor is considered to be a major factor influencing its prevalence. Diets containing high animal proteins and fat and low dietary fibre have been identified as being associated with greatest risk. Recent research has also focused on the influence that gastrointestinal microflora have on outcome. A large and complex microbiological population inhabiting the colon has been shown to be established early in life and relatively unchangeable by external factors. However, other research has suggested that it is manipulable by dietary and microbiological means as well as by antibiotic therapy. The side effects of modern antibiotic therapy may include significant disturbances of the gut microflora and have been part of the motivation to find ways of achieving treatment of disease using ‘desirable bacteria’ as an alternative therapy. Insofar as the microflora can influence the immune system and other local processes, the detoxification and carcinogen activation mechanisms and thereby the expression of a number of disease processes affecting the bowel, a better knowledge of their contribution to health and disease is warranted.

Probiotics are defined as live microbial food supplements which benefit the host by improving its intestinal microbial balance. Yogurt is a traditional and common vehicle for such probiotics (Lactobacilli and Bifidobacteria species being most often used in this role). They have a significant target, gastrointestinal disturbances and diseases. Wider claims include their value as a life extender, an elixir of life. Elie Metchnikoff, the Russian Nobel Prize biologist, popularised the view that some lactic acid bacteria were capable of increasing length of life, supporting his theory with observations of Bulgarians who ate yoghurt regularly and showed remarkable longevity. At the time, it created a world-wide interest in yoghurt but in the ensuing 70 or so years little attention was given to this claim. However, in the last 20 years, with the upswing in colon cancer and inflammatory bowel diseases in Westernised countries, it has been given increasing attention by researchers.

Useful reviews by Mitsuoka, Adachi, Marteau et al., and Balliong3, have discussed much of the groundwork research studies, in an area where Japanese and French researchers have made significant contributions. From North America reviews are provided by Fernandes et al., Fernandes and Shahani, Gorbach and Goldin, 4, while from Scandinavia Lidbeck at et al., Salminen, Rafter useful reviews have also been provided.

Research with regard to use of probiotics in prevention of colon cancer is reviewed in this paper. It must be appreciated that lack of knowledge of the carcinogenic process, the complexity of colon function, and lack of techniques for adenoma or early stages of these bacteria, has held back progress significantly. Nevertheless there have been some impressive advances, which I believe are bringing us nearer to protecting a predictive diet and/ or probiotic strategy for reducing high rates of colon cancer. The anti-tumour action of probiotics have been proposed as:

- Reduction of the intestinal pH, thereby altering microbial activity, solubility of bile acids, mucus secretion etc.

- Alteration of colonic motility and transit time.

Malhotra5, a medical officer with the Indian railways, reported on the gastrointestinal cancers in India, and proposed that the much lower incidence of colon cancers in northern people was associated with the significant consumption of dairy (including fermented) foods, cereals and vegetable dietary fibres in the regular diet. Southern diets by contrast were low residue highly digestible diets and tended to create a more alkaline colonic milieu. Similar differences have been noted for rural northern versus southern urban populations of Sweden,6 and in Finland versus Denmark.7 The difference in each case was a reduction to one half to one third the colon cancer incidence and mortality.

Table 1. Chemical colon cancer studies in rats and mice

<table>
<thead>
<tr>
<th>% rats with colon carcinoma</th>
<th>% dead at 26 wks (colon carcinoma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldin and Gorbach (17)</td>
<td></td>
</tr>
<tr>
<td>n=22 L. acidophilus</td>
<td></td>
</tr>
<tr>
<td>DMM</td>
<td>77%</td>
</tr>
<tr>
<td>Beef +</td>
<td>49%</td>
</tr>
</tbody>
</table>


| n=25 L. bulgaricus          |                                   |
| DMM                          | 28%                              |
| Sm +                         | 7%                               |
| 344 rats                     |                                   |
| S. thermophilus              |                                   |


| DMM (S/C)                   |                                   |
| n=9 L. helvetica + C. utilis |                                   |
| Control rats                |                                   |
| n=15 & = 10%                |                                   |

Tumours Tumours

| DMM (S/C)                   |                                   |
| n=9 C. utilis               |                                   |
| C. thermophilus             |                                   |
| n=21 + 5% myosage           |                                   |

Research up to the mid 1980s was mainly concerned with the direct or indirect anti-tumour action of streptococci, lactobacilli, and bifidobacteria studied in animals and to a lesser extent in man.8,9 To induce the effect, bacteria were often injected systemically and/ or cancers were transplanted into mice. Bifidobacterium longum had a direct inhibitory effect on liver tumours in the mouse. In the BALB/C mouse, B. infantis and B. adolescentis injected subcutaneously or intraperitoneally had an antitumour effect. The number of tumours developed by mice with an intestinal flora including Escherichia coli, Entercoccus faecalis, and Clostridium paraputrificum was considerably reduced if B. longum was present.9,10 Feeding fermented milks or cultures containing Lactobacillus acidophilus, L. bulgaricus and L. casei inhibited Ehrlich ascites tumour cell growth or growth of Sarcoma 180 in mice.10,11 Gorbach and Gorbach used the dimethyl-hydrazine (DMH) rat model to help assess the impact of lactobacilli on intestinal tumours and their studies and others are presented in Table 1. It was shown that the high incidence of DMH induced colon carcinomas in rats fed beef could be lowered from 77 to 40%, while L. acidophilus was fed simultaneously with the beef diet.

Other studies using the same or similar experimental cancer models have largely confirmed this early observation, although as can be seen there have been differences in results. These animal studies have been paralleled by human and animal faecal enzyme studies, assessing nitro-reductase, B-glucuronidase, azoreductase and/ or uroselect activity to predict risk of colon cancer. The hypothesis relies on the assumption that modulation of deconjugating and/ or dehydroylating enzymes found in certain colonic bacteria but not in others will alter risk of carcinogens being generated from procarcinogenic agents or released from bound end-products, as they traverse the large intestine. Displacement by probiotic bacteria (of undesirable bacteria) will effect significant change. Significant results (Table 2) have been achieved with this approach to assessment of risk.
For example, Lidbeck et al.4 produced a significant increase in lactobacilli and dietary calcium by feeding L. acidophilus fermented milk to colon cancer patients for 6 weeks. Faecal enzyme activity was reduced 14% and soluble faecal bile acids were both results not significant. They attributed this result to small number (n=12) of patients and the large variability in enzyme activity between patients. Ling et al.5 also showed a greater reduction of faecal enzyme activity by feeding 4 weeks of lyophilised lactobacillus GG and dietary fibre as cereal rye, related to controls. Urinary paracresol, a mutagenic metabolite of protein, was also significantly reduced by 56% (P<0.05). Both Ling et al.5 showed they could increase the fecal excretion of B. longum with oral supplements of the bacteria via yogurt(>10^6 cfu/L) and lactulose, and that breath hydrogen increased and mouth-cum transit time increased, but no other changes (such as bile acids, pH, SCFA, pH) were observed. They attributed this to significant microbial flora stability.

It is apparent from the above studies that there are differences of opinion as to which bacteria offer most potential for human health and cancer prevention, as well as considerable variation in background diets which could significantly influence outcome of such studies. This could account for some of the large differences in results, and present a possible reason for further studies. To help sort out the bacteria most likely to be effective against colon cancer cells Barcud and co-workers7 introduced the use of an in vitro cultured colon cancer cell (HT-29) assay. The test relied on inhibition of cells to grow into a confluent layer, or to differentiate under the influence of inhibitory bacteria. In an examination of a number of the probiotic bacteria being currently used they identified Lactobacillus helveticus (a species not named) as being effective, whereas Lactobacillus acidophilus was not.

Study of the growth requirements of Lactobacilli and an optimal healthy dietary habits led to the recognition of some desirable substrates for fermentative bacteria in vivo, when fed alter significantly the proportion of beneficial bacteria present in the colon. Without the need to orally administer cultures, it could be argued that this aspect of diet may have a bigger impact on health objectives than the provision of probiotic bacteria orally. Ecological studies of faecal microflora support this well.6 These 2 points very clearly to the impact of diet on colonic microflora and colon cancer risk but come to opposite conclusions regarding the relevance of bifidobacteria species to colon cancer risk. In a workshop summary report Roberfroid et al.9 referred to the circumstantial evidence of colonic microflora on cancer risk, and proposed the absorption and metabolism of mutagens and carcinogens as the primary role in prevention, while SCFA production from carbohydrate fermentation as seen secondary in its influence.

Studies in my laboratory have identified the potential of whey proteins to significantly reduce cancer incidence (to one half) relative to red meat and soybean protein in the DMMI a cancer model. This raises the possibility that dairy foods may offer, apart from any probiotic influence, high quality proteins which protect the gut from chemical carcinogenesis by an as yet undefined mechanism. It also highlights undesirable characteristics shared by two disparate sources of protein, soybean and meat. Several of the % of the reviewed, grilled or dried beef is used as a background diet to enable a significant improvement to be achieved with probiotics. A recent study by Reddy and Rivenson10 is of interest in this regard. They have used their well characterized strain L. casei (4-5) df-qulinole to induce cancers in male and female rats. It is capable of producing breast, liver and colon tumours in rats and mice. When B. longum was fed at 0.5% as a lyophilised culture or to rats was significantly suppressed of colon tumours, this suppression of liver tumours and in females 50% suppression of mammary tumours. Whatever the mechanism for this inhibitory influence, it is an impressive demonstration of a probiotic effect.

A number of studies have reported the use of specific agents to improve the growth of desirable gut microflora such as Bifidus growth factors. They fall into the category of dietary fibre or fibre like components (such as resistant starch, oligosaccharides) which have the attribute of passing undigested through the small intestine to supply a substrate for the colonic bifidobacteria.11 A list of some of the agents reported to be beneficial is shown in Table 3. In general their presence in the diet significantly increases the total counts of bifidobacteria in faeces. For example, with 9g/day gluconic acid, 10 healthy volunteers showed a significant increase (p<0.001) of the desirable bacteria like C. perfringens fell in number and Enterobacteriaceae stayed constant.

Table 3. Some oligosaccharides used to promote bifidobacteria in vivo

| Lactulose, Lactitol, Lactobionic Acid | Neosugar P* |
| Transgalactosylated oligosaccharides | Galactooligosaccharide oligosaccharides* |
| Glucosidic Acid | Xylooligosaccharides |
| Fructooligosaccharides | Maltooligosaccharides |
| Stachyose, Raffinose |

Provided that increasing bifidobacteria can be identified with reducing risk of cancer, these types of studies support a view that such perturbation of gut flora is in a desirable direction. Finally there has been considerable research investigating the health benefits of consuming fermented yoghurt (peptidoglycans, β-glucans and other polysaccharides) for their influence as an anticancer-stress in stimulating the immune system via the gut associated lymphoid tissue. This represents a relatively new and challenging area for future research.

Conclusion

There is a promising future for research into probiotic bacteria, this exciting area of research is expected to provide contribution to health of well constructed balanced microflora in the large intestine. Its potential for prevention of colon cancer is currently under active investigation, with both animal and human studies contributing. Both approaches appear to be valid and necessary, albeit several of the reported studies are exercised in extrapolating animal results directly to humans.

While some of the data supports the view that probiotics as freeze dried powder capsules or as yoghurts provide a genuine cancer benefit, the nature of the diet and/or components provided by the yoghurt vehicle must also be taken into account.

This means carefully controlled experiments are needed to provide reliable interpretation.

Acknowledgements

I wish to acknowledge the assistance of Leanne Griffiths, Librarian, CSIRO Division of Human Food Science, Dr Martin Phayne of the CSIRO Division of Food Science and Technology, Higheh Veryan, the CSIRO for the feeding for the Dairy Research and Development Corporation for its research grant support.

References

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It is apparent from the above studies that there are different opinions as to which bacteria offer most potential for human health and cancer prevention, as well as considerable variation in background diets which could significantly influence outcome of studies. This could account for some of the large differences in results, and present a possible barrier to progress. To help sort out the bacteria most likely to be effective against colon cancer cells Barcault and co-workers introduced the use of an in vitro cultured colon cancer cell (HT-29) assay. The test relied on inhibition of cells to grow into a confluent layer, or to differentiate under the influence of inhibitory bacteria. In an examination of a number of the probiotic bacteria being currently identified they Lactobacillus helveticus and Bifidobacterium (species not named) were being effective, whereas Lactobacillus acidophilus was not.

The study of growth requirements of Lactobacillus and of optimal dietary heating conditions did not lead to the identification of some desirable substrates for fermentative bacteria in vivo, which fed altered significantly the proportion of beneficial bacteria present in the colon. The colon can be affected by diet, but it was argued that this could be a bigger impact on health objectives than the provision of probiotic bacteria orally. Ecological studies of faecal microflora support this well. These 2 points very clearly to the impact of diet on colonic microflora and colon cancer risk but come to opposite conclusions regarding the relevance of Bifidobacteria species to colon cancer risk. In a workshop summary report Roberfroid et al. referred to the "certainly substantial evidence of colonic microflora on cancer risk, and proposed the absorption and metabolism of mutagens and carcinogens as the primary role in prevention, while SCFA production from carbohydrate fermentation as secondary in its influence.

Studies in my laboratory have identified the potential of whey proteins to significantly reduce cancer incidence (to 30%). They showed to reduce cancer incidence (to 30% of the control) significantly. This finding suggests that feeding the rat gut from chemical carcinogenesis by an as yet undefined mechanism. It also highlights undesirable characteristics shared by two disparate sources of protein, soybean and dairy. Several of the experiments reviewed, alluded to Validation of the protein food as a background diet to achieve a significant improvement in the quality of the diet influenced by probiotics. A recent study by Reddy and Rivenson is of interest in this regard. They have used a low-cholesterol diet to inhibit various plant sterols in an animal model. The diet used is a low-fat diet that is rich in dietary fiber and plant sterols. The diet was effective in reducing cholesterol levels and in improving the ratio of HDL to LDL cholesterol.

A number of studies have reported the use of specific agents to improve the growth of desirable gut microflora like Bifidobacterium. They die as the category of dietary fibre or fibre like components (such as resistant starch, oligosaccharides) which have the attribute of passing undisggested through the small intestine to provide a substrate for the colon bacilli. A list of a number of the agents reported to be beneficial is shown in Table 3. In general their presence in the diet significantly influences the total counts of bifidobacteria in faeces. For example, with 5g/day gluconic acid, 10 healthy volunteers showed a significant increase in the desirable bacteria like C. perfringens fell in number and Entobacteriaceae stayed constant.

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| Stachyose, Raffinose | Provided that increasing bifidobacteria can be identified with reducing risk of cancer, these types of studies support a view that such perturbation of gut flora is a desirable direction.

Finally there has been considerable research investigating the host and the cancer cell (epithelial/lymphocytes, B-glucans and other polysaccharides) for their influence as an anti-cancer-stimulating in the immune system via the gut associated lymphoid tissue. This represents a relatively new and challenging area for future research.

**References**


Probiotics and stabilisation of the gut mucosal barrier

Salminen S1, Isolauri E2, Salminen E1

1 Dept of Biochemistry and Food Chemistry, University of Turku, and Key Centre for Applied and Nutritional Toxicology, RMIT, Melbourne, Australia 2 Dept of Medicine, University of Tampere, Finland 3 Dept of Oncology and Radiotherapy, Turku University Hospital, Turku, Finland

Probiotic bacteria are used to treat disturbed intestinal microflora and altered gut permeability which are characteristic to many intestinal disorders. Examples include children with acute infectious diarrhea, subjects with food allergy and patients undergoing pelvic radiotherapy. Altered intestinal microflora has been treated by oral intake of probiotic bacteria which are able to survive gastric conditions, colonise the intestines, at least temporarily, by adhering to the intestinal epithelium. Such probiotic microorganisms appear to be promising candidates for the treatment of clinical conditions with abnormal gut microflora and altered gut mucosal barrier functions.

Introduction

The intestinal epithelium and the normal intestinal microflora represent a barrier to the movement of pathogenic bacteria, antigens and other noxious substances from the gut lumen. Under normal circumstances this barrier is intact and provides normal intestinal function. When either the epithelial cells or the normal microflora are disturbed altered permeability facilitates the invasion of pathogens, foreign antigens and other harmful substances. For future clinical applications and the interfering with the adherence of antigens and the development of new probiotic bacteria understanding of the mechanisms of this barrier system are essential.

Mucosal and microflora defects and disease

Intestinal barrier

The intestinal mucosa is an important organ of defence providing a barrier against the antigens encountered by the enteric route, and most foreign antigens are excluded by the intestine’s mucosal barrier. Apart from the barrier function, the intestinal mucosa is efficient in assimilating antigens. For this purpose, there are specialised antigen transport mechanisms in the villous epithelium and particularly in Peyer’s patches, essential for evoking specific immune responses.

Even in physiological conditions, a quantitatively nonimportant but immunologically important fraction of antigens bypasses the defence barrier. They are absorbed across the epithelial layer by transcytosis along two functional pathways. The main degenerative pathway entails lysosomal processing of the protein to smaller peptide fragments which reduces immunogenicity of the protein and is important in host-defense in diminishing the antigen load. More than 90% of the protein internalised passes in this way. A minor pathway allows the transport of intact proteins which results in antigen-specific immune responses. In health paracellular leakage of macromolecules is not allowed due to intact intercellular tight junctions maintaining the macromolecular barrier. The integrity of the defence barrier is necessary to prevent inappropriate and uncontrolled antigen transport.

Intestinal antigen handling determines subsequent immune response to the antigen. These include immune exclusion of antigens encountered by the enteric route by the interfering with the adherence of antigens, immune elimination of substances that have penetrated the mucosa, and immune regulation of the systemic immune response to antigen-specific systemic hyporesponsiveness. There is evidence that during the absorption process across the intestinal mucosa, antigens are altered into tolerogenic form.

Immune gut defence barrier

The barrier functions are incompletely developed in early infancy. Intestinal permeability can be transiently increased postnatally, particularly in premature infants.

The binding of antigens to immature gut microvilli membrane is increased compared to the mature mucosa, which has been shown to correlate with the increased uptake of intact macromolecules. An increased antigen load may evoke aberrant immune responses and lead to sensitisation.

Intestinal inflammation

As a result of local intestinal inflammation, a greater amount of antigens may traverse the mucosal barrier and induce a systemic immune response.