Diet and the Human Intestinal Bacterial Flora

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Abstract

In this review, the factors thought to be important in determining the composition of the gut bacterial flora are discussed. In the light of these, the effects of various dietary manipulations on the composition and metabolic activity of the gut flora are described. In general, the main effects of diet would be expected to be manifested in the right colon, whereas the material available for investigation is feces. Consequently, the data that are available tend to underestimate the effects of diet.

Introduction

Most studies of the effect of diet on the human intestinal flora have dealt with the fecal flora; this is reasonable in that feces are readily accessible, but there is no good evidence that the fecal flora is representative of that of the cecum and right colon, and there are some very good reasons for considering that it does not. Consequently, there are no published data on the effect of diet on the human cecal bacterial flora.

This is a serious gap in our knowledge. If bacteria produce metabolites in the colon that are important in the causation of bowel cancer it is probable that they are produced principally in the right colon. There, the population density of bacteria is very high but, whereas the contents are relatively fluid and permit ready interaction between bacterial enzymes and their substrates, as the colonic contents move towards the sigmoid colon they are steadily dehydrated and bacterial enzyme activity is reduced. Further, we have little data on the nutrients which enter the normal human cecum from the small bowel, although some tentative deductions can be drawn from the study of ileostomy patients.

In this review, I will summarize the factors known to affect the composition of mixed populations of bacteria in vivo and in vitro, and then go on to discuss the effect of various dietary changes on the human intestinal flora and on its metabolic activity. It is my opinion that we have still to establish that the animal models of colorectal cancer closely resemble the human situation; therefore I will discuss only human studies.

Factors Affecting the Composition of the Human Intestinal Flora

The factors affecting the composition of the human intestinal flora have yet to be determined, but a number can be deduced from our knowledge of the behavior of mixed populations of bacteria in vitro and from our knowledge of more accessible ecosystems. The factors suggested to be of importance include pH, oxygen tension, nutrient availability, colonic physiology, and bacterial interference.

Bacteria are able to proliferate only when the pH is within a certain range, but this range differs for different organisms.

Effect of Diet on the Fecal Bacterial Flora

The suggestion that diet might influence the composition and/or activity of the gut bacterial flora appears reasonable because of its effect on the supply of nutrients. However, we have no data on the relative contribution of the diet and, e.g., desquamated mucosal cells or biliary conjugates, to the overall nutrition of the flora. Further, because of the crudeness of bacteriological enumeration, only differences more than 3-fold can be detected. Although populations in different parts of the world have different fecal bacterial floras (e.g., Ref. 1), this may not be due to differences in diet since the populations also differ in other respects such as their race and their physical environment.
In short-term studies, volunteers under metabolic ward conditions have undergone changes in all components of their diet and their fecal bacterial flora (Table 1). The normal protocol for this type of study has included a short period on the normal diet of the subject, a period of 3 to 4 weeks on a diet containing a low level of the test component, and then a similar period on a diet rich in the component. All have been short term; perhaps periods of up to 12 months might be needed to bring about changes in the flora detectable by classical bacteriological techniques.

Only one dietary manipulation results in a changed fecal flora. Normal healthy adults fed a chemically defined residue-free diet experience a reduction in their total fecal output, a reduction in the number of anaerobic organisms, and a reduction in some components of the aerobic flora per g of feces (5). The extent of these changes varies somewhat, depending on the nature of the energy source, with glucose-based diets being claimed to result in almost total elimination of the flora; a general feature appears to be the virtual disappearance of enterococci.

This lack of demonstrated effects of the diet on the composition of the fecal flora might lead to doubts about the existence of such effects. These doubts are answered, in part at least, by the results of studies on the metabolic activities of the flora.

Effect of Diet on the Metabolic Activities of the Intestinal Bacterial Flora

In numerous studies, it has been demonstrated that diet affects the metabolic activity of the intestinal bacterial flora. In some of these studies, the enzymic activity of the fecal flora is measured following dietary change and compared to the control value; such studies are a relatively unambiguous demonstration of changes in the flora. In other studies, metabolites of dietary or biliary substrates are measured in the feces or urine; these may indicate an effect of the diet on the composition of the flora, or on the supply of a substrate to the flora, or on the physiology of the intestine.

Intestinal bacteria produce a range of glycosidases, the activity of the enzyme differing between genera, between species within a genus, and between strains within a species (9). The same is undoubtedly true of other bacterial enzymes. Thus, changes in the composition of the gut flora will be reflected in a change in the mean enzymic activity of that flora. Effects of diet on the fecal enzymic activity have been demonstrated in this way by a number of groups.

A number of metabolites are produced from dietary or biliary substrates by bacteria and excreted in the feces or urine. In one respect, this is a more attractive method of investigating the effects of diet since the enzymic activity measured is likely to be that of the flora of the cecum and ascending colon; the activity probably will be relevant in colon carcinogenesis. However, there are a number of pitfalls which make such measurements difficult to interpret. Lactulose is known to suppress the metabolism of cholesterol to coprostanol and to reduce the extent of dehydroxylation of the bile acids during colonic transit; however, this is more likely to be due to the traumatic effect of lactulose on the cecal pH than to a change in the intestinal flora (11). Similarly, increased dietary fiber leads to a reduction in the amount of urinary volatile phenols (produced by the colonic bacterial flora from the phenolic amino acids tyrosine and phenylalanine) which can be correlated with a reduction in the transit time of the intestinal contents (7). In contrast, the effect of elemental diets on the cholesterol and bile acid metabolism by the gut flora and on the production of urinary volatile phenols is undoubtedly due, at least in part, to the massive reduction in the numbers of bacteria in the gut.

Potentially, measurement of fecal bacterial enzymes provides the best method for demonstrating effects of diet on the fecal flora. The enzymes must be carefully chosen, with constitutive enzymes being preferable to inducible ones. Organisms which produce a key marker enzyme rarely produced by other organisms are, of course, the easiest to monitor. We have monitored a particular group of organisms, the NDH clostridia (i.e. those able to dehydrogenate the steroid nucleus), in order to test the possible role of unsaturated bile acids in the causation of bowel cancer (10, 11). Using a deliberately crude assay which allows us to separate people into “carriers” or “noncarriers” of NDH clostridia, we find that 30 to 40% of normal English persons are carriers, compared with more than 80% of patients with large-bowel cancer (a finding confirmed in Ref. 3). Interestingly, only a small proportion of persons with small adenomas carry NDH clostridia (Table 2), compared with a high proportion of persons with large adenomas, supporting our postulate (12) that an unsaturated bile acid metabolite causes small adenomas to grow. NDH clostridia are monitored in all of our current prospective studies into the causation of bowel cancer (11). To date, we have been unable to alter the NDH status of any person by dietary manipulation.

Conclusions

It is clear that the bacterial flora produces carcinogens or promoters of carcinogenesis in the normal human gut (11); it

<table>
<thead>
<tr>
<th>Dietary change</th>
<th>Period of diet (wk)</th>
<th>Effect on fecal bacterial flora</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>Increase dietary fat</td>
<td>4</td>
<td>None</td>
<td>13</td>
</tr>
<tr>
<td>Increase dietary meat</td>
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<td>None</td>
<td>2</td>
</tr>
<tr>
<td>Wheat bran supplement (39 g)</td>
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<td>None</td>
<td>6</td>
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<tr>
<td>Wheat bran supplement (100 g)</td>
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<td>None</td>
<td>2</td>
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<tr>
<td>Bagasse supplement (105 g)</td>
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<td>None</td>
<td>Unpublished results</td>
</tr>
<tr>
<td>Pectin supplement (36 g)</td>
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<td>None</td>
<td>Unpublished results</td>
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<td>Guar gum supplement (36 g)</td>
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<td>Lactulose supplement</td>
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<td>5</td>
</tr>
<tr>
<td>Elemental, soluble diet</td>
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<td>Reduced anaerobes, enterococci eliminated</td>
<td></td>
</tr>
</tbody>
</table>
must still be demonstrated that these have any relevance in human carcinogenesis. If we are to investigate this, then it must be recognized that: (a) the region of the intestine where carcinogens-promoters are most likely to be produced is the right colon (in which the numbers of organisms per g of contents are maximal and the contents are still fluid); (b) we know very little about the factors determining the composition and activity of the bacterial flora of this region of the gut; (c) we do not have good techniques to detect changes in the intestinal bacterial flora. We certainly have no techniques for answering the problems posed in b. Until we have solved these problems and answered the questions raised by them, the role of bacteria in human carcinogenesis remains a matter of conjecture. I believe that bacteria have such a role, but it will be many years before there is any solid evidence either for or against this belief.

References

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