

INTESTINAL MICROFLORA

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Summary

The intestinal bacterial flora forms a complex ecosystem. Its composition, ecology, stability, connection to diseases, and what are its beneficial and harmful effects, these are all still largely unknown. However, the development of diagnostic methodology, especially computerized clustering methods and species specific DNA tests will rapidly change this picture. At present we are unable to grow many of the bacteria living in the gut. Therefore we know little about their physiological role. Even though the normal flora is considered mostly inert, it has components which are clearly pathogenic and there are bacteria which are considered beneficial. At present there is a marked scientific and industrial interest in these beneficial bacterial species—probiotics. The future should show what is the exact role of the intestinal bacteria in diseases and their prevention.

1. Introduction—Composition of the Intestinal Flora

The intestinal bacterial flora is one of the most complex ecosystems known in nature. The human normal bacterial flora consists of 10^{14} bacteria (see Table 1). There are ten times more bacteria in the human body than its own cells, and their metabolic activity is larger than the cells of the body. The amount of bacterial species in the intestine is more than 500. That is the number of species that have been cultured from fecal samples. The new DNA-based methods indicate that the real number of species, including those which cannot be cultured with present methods, is more than double this amount. Most, i.e. 95%, of the species present in the intestine are anaerobic. In general the knowledge

of the composition of the intestinal normal microbial flora is very sparse. There are few studies, which have tried to analyze quantitatively all bacterial species present in the flora. The yield has been around 400-500 species. However, the reproducibility of the bacterial cultures is poor. The use of 16S- ribosomal RNA gene PCR followed by cloning and sequencing of the product has revealed that in environmental samples more than 90% of the species present in the sample are uncultivable and not yet identified. Similar studies have been done from intestinal samples and the result is similar. Most of the species present seem to be “new” and at present uncultivable and unknown.

Location	Amount (cfu/g)
Mouth	10E7 – 10E8
Stomach	0-10E3
Duodenum	<10E3
Jejunum	<10E3 – 10E5
Ileum	<10E5 – 10E7
Colon	10E10 – 10E12
Stool	10E10 – 10E12

Table 1. Presence of bacteria in different parts of the alimentary tract.

2. Microbial Ecology of the Intestinal Flora

The ecology of the human intestinal microflora is poorly understood. This is due to the lack of methods which could be used to study efficiently the differences in the flora between different people. It has been calculated that quantitative bacterial culture of one human fecal sample, where all species are identified and enumerated, takes one man year of work. Thus, because of the lack of suitable methods for efficient study of large numbers of samples, no studies have been done to analyze the ecological changes in the flora in different situations. It is not clearly known how much the flora differs between individuals and how stable is the flora in one individual. Also it is not clear, how much environmental factors such as diet, affect the flora. Similarly it is not clear how the flora behaves in different diseases, and what is the role of the ecology of the flora as a cause of various diseases. Most of the studies, which have been done, deal with the use of antibiotics. These results give some information on the duration of the antimicrobial effect. However, it is not clear whether the flora returns to its initial state or whether there are some permanent changes.

3. Effects of the Intestinal Flora

More is known of the effects of the intestinal flora than its composition. The intestinal microbial flora is probably not essential for life. In this respect, there are differences between different species. Germfree animals, on adequate nutrition, live more than 30% longer than colonized animals. However, the intestinal bacteria are important in the function of the intestine by producing some vitamins and digesting food components, especially some carbohydrates. The results are based on studies with rodents, and it is difficult to make reliable conclusions concerning the function of the human intestinal flora. The most important known function of the flora is to form a colonization barrier

against pathogenic, disease-causing microbes. This role may become in the future even more important and a mode of therapy, if antibiotic resistance increases as predicted.

The harmful effects of the normal flora are seen mostly in situations, where bacteria reach locations and tissues not meant to be colonized by the flora (see Table 2). The ability to cause infections or other diseases varies between the bacterial species. Even though the majority of the species in the normal flora are considered apathogenic, with a low virulence, there are many species in the normal intestinal flora, which are capable of causing even very severe infections. The majority of cells and antibodies of the human immune systems are therefore located in the intestinal mucosa to prevent the invasion of these microbes to other parts of the body. A typical example of situations where the microbes invade other tissues and form a risk of infection, are colonization of the female urinary tract, colonization of the respiratory tract of hospital patients and invasion of the peritoneal cavity after intestinal trauma. Each one of these examples can lead to a very serious infection by the “apathogenic” normal flora of the intestine. Similarly the intestinal anaerobic flora, which is quite avirulent while tissue oxygenation is sufficient, is capable of causing extremely grave infections, if tissue perfusion and oxygen supply diminishes.

<p>Harmful effects of intestinal bacteria (Gibson 1998)</p>	<ul style="list-style-type: none"> • Intestinal infections • diarrhea • toxins • system effects • Production of possible carcinogens • H₂S production
<p>Beneficial effects of intestinal bacteria (Gibson 1998)</p>	<ul style="list-style-type: none"> • Prevention of colonization of harmful microbes • Inhibition of growth of harmful microbes • Lowering the level of cholesterol • Enhancing immunity • Inhibition of allergic reactions • Anti cancerous effect • Digestion of food components • Synthesis of vitamins
<p>Suggested health effects of probiotics (Dugas B. <i>et al</i> 1999)</p>	<ul style="list-style-type: none"> • Increased nutritional value (better digestibility, increased absorption of minerals and vitamins) • Promotion of intestinal lactose digestion • Positive influence on intestinal flora (antibiotics or radiation induced colitis) • Prevention of intestinal tract infections (bacteria or virus induced, <i>Candida</i> enteritis, <i>Helicobacter pylori</i> ulcer/neoplasia) • Regulation of gut motility (constipation, irritable bowel syndrome) • Improvement of immune system • Prevention of cancer • Reduction of catabolic products eliminated

	<p>by kidney and liver</p> <ul style="list-style-type: none"> • Prevention of atherosclerosis (reduction of serum cholesterol) • Prevention of osteoporosis • Better development (growth) • Improved well-being
<p>Mechanisms by which probiotics might inhibit colon cancer (Dugas B. <i>et al</i> 1999)</p>	<ul style="list-style-type: none"> • Suppress the growth of intestinal microflora incriminated in producing putative mutagens/carcinogens and promoters • Produce antimutagenic and antitumorigenic compounds in the colon • Bind potential mutagens and carcinogens • Alter physiological conditions in the colon (lowering the pH) affecting the metabolic activity of the intestinal flora, the action of bile acids and causing quantitative and/or qualitative alterations in the bile acid degrading bacteria • enhance the host's immune system

Table 2. Harmful and beneficial effects of intestinal bacteria and probiotics.

The effects of the changes in the microbial ecology is poorly understood. It is known that changes in the intestinal flora, caused for instance by antibiotic treatment, may cause serious symptoms, and the restoration of the original state may in some cases be extremely difficult. The most common and best understood disturbances of the microbial ecology are the intestinal overgrowth of *Clostridium difficile* causing pseudomembranous colitis, after antimicrobial treatment, and the bacterial vaginosis, the anaerobic overgrowth of female vaginal flora, where the anaerobic mixed growth replaces the lactobacillus dominant normal vaginal flora.

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Biographical Sketches

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