For creatures your size I offer
a free choice of habitat,
so settle yourselves in the zone
that suits you best, in the pools
of my pores or the tropical
forests of arm-pit and crotch,
in the deserts of my fore-arms,
or the cool woods of my scalp.

Wystan Hugh Auden

Chapter 10
Man and his microbes

Without the bacteria in our tummies, we would be one kilogram (2.2 pounds) lighter.

Are you serious? Do you really mean that the bacteria living in our bodies weigh that much?

Correct. This weight corresponds to a bacterial dry weight of approximately 100 grams. Bacteria not only reside in your tummy but also in your nose, mouth, and throat, and on your skin. It is hard to believe, but a healthy human body consists of approximately 10^{13} cells as well as nearly 10^{14} bacterial and archaeal cells. Archaea don't play a big role, but two species of methanoarchaea are usually found in our intestines, where they effectively produce biogas. An overview of our microflora is presented in Figure 22.

Let's begin with our skin, which is densely populated by bacteria. There are nearly 10^5 bacterial cells per cm^2, so a penny on the back of your hand would cover about 100 000 bacterial cells. They are especially dense between adjacent skin cells. Bacterial proliferation on our skin is limited because skin is relatively dry. Nevertheless, more than 20 different bacterial species have been detected on our skin; two of these are *Staphylococcus epidermidis* and *Propionibacterium acnes*.

Doesn't the second one cause acne?

Yes and no. We are covered with cells of this bacterium, but acne does not occur on all parts of our body nor occur at every age. Several factors have to coincide, such as the hormonal changes during puberty and the clogging of hair follicles with sebum, a wax-like substance. This results in the formation of a favorable habitat for *P. acnes*. For a more detailed description of acne, let us turn to Holger Brueggemann (Goettingen/Berlin, Germany), who was involved in the total sequencing of the genome of *P. acnes*:

Discover the World of Microbes: Bacteria, Archaea, and Viruses, First Edition. Gerhard Gottschalk.

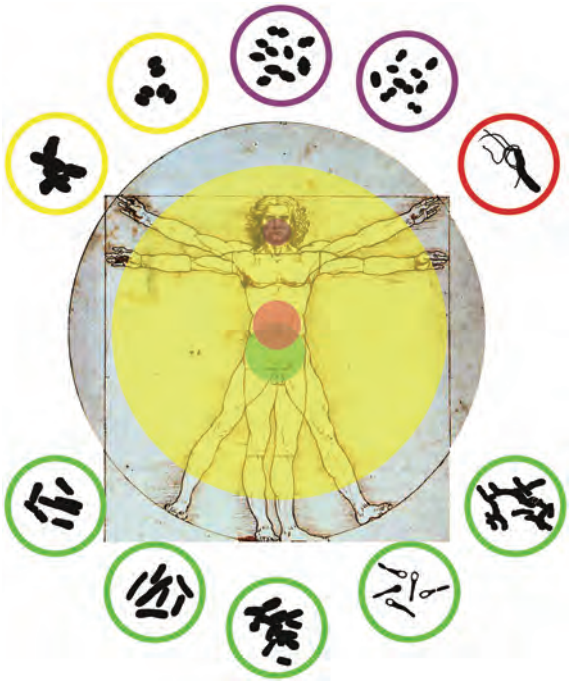

Figure 22 Microbes and men. Locations of microflora are: skin (yellow): *Propionibacterium acnes*, *Staphylococcus epidermidis*; mouth (purple): *Streptococcus salivarius*, *Streptococcus mutans*; stomach (red): *Helicobacter pylori*; intestine (green): *Bifidobacterium*, *Clostridium difficile*, *Escherichia coli*, *Eubacterium rectale*, *Bacteroides fragilis*. (Diagram: Anne Kemmling, Goettingen, Germany.)

> "The importance of *P. acnes* for the formation of inflammatory skin acne cannot be recognized by simply applying the Henle-Koch postulate because the presence of this bacterium does not inevitably lead to acne. The pronounced response of the immune system to rapidly proliferating *P. acnes* suggests an opportunistic-pathogenic character of this organism. Especially the deciphered sequence of the genome of *P. acnes* provided new insights into the (pathogenic) lifestyle and the survival strategies of *P. acnes* on the human skin. The genome sequence provided information on the potential of this bacterium for the enzymic breakdown of constituents of dermal tissue, the development of the virulence traits as well as the interaction with the immune system, which contributes to the inflammatory efflorescence (skin proliferation). Currently, new therapy forms for acne are discussed on the basis of these findings. These are vaccine-based strategies, e.g., against dominant markers on the bacterial surface as well as the use of specific growth inhibitors that could replace the application of broadband antibiotics. Incidentally, it is now investigated if *P. acnes* is the causative agent of another disease. This bacterium is frequently detected in diseased prostate tissues. Like *Helicobacter pylori* in the stomach, *P. acnes* could contribute to the development of prostate cancer."

A few explanatory remarks may prove helpful. The Henle-Koch postulate will be discussed in Chapter 22. Opportunistic-pathogenic refers to a microorganism that

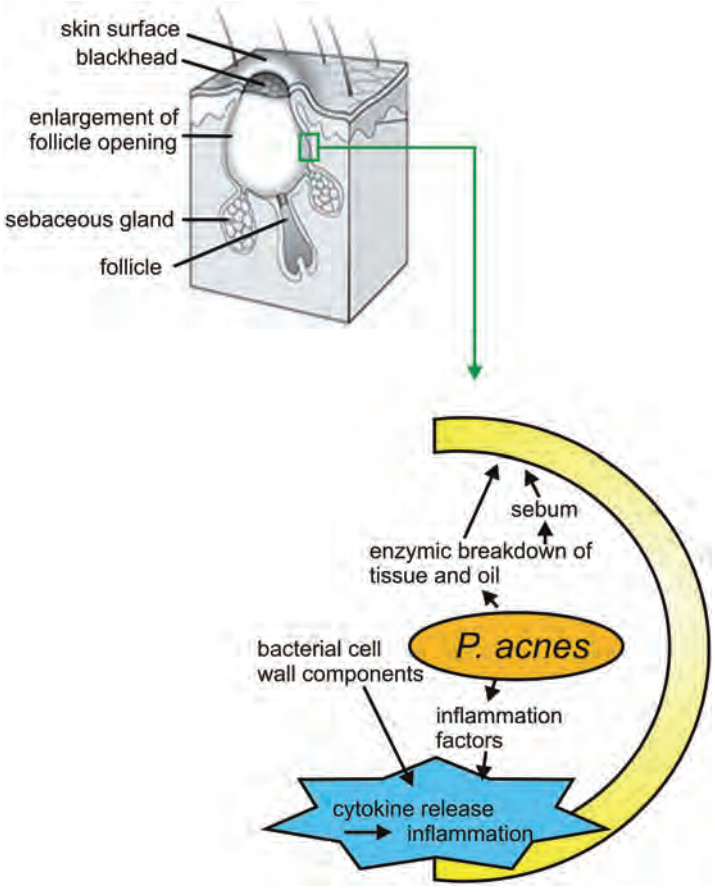

Figure 23 Diagram of the possible role of *Propionibacterium acnes* in the emergence of acne vulgaris. Top: an enlarged sebaceous gland. Bottom: possible interaction of *P. acnes* with surrounding tissue cells. Arrows pointing upward indicate that secreted enzymes degrade tissue, proteins, and fats, thereby providing nutrients to the bacteria. Downward arrows indicate inflammatory reactions caused by factors secreted by *P. acnes*. (Diagram: Holger Brueggemann, Goettingen, Germany.)

normally is not a pathogen but may cause disease when there are favorable conditions for its proliferation. What *P. acnes* is able to do is depicted in Figure 23. On one hand, it secretes enzymes that degrade tissue components and provide nutrients for the bacteria; on the other hand, it causes an inflammatory response that supplies it with water, minerals, and additional nutrients.

Tears serve to protect the eyes from microbial invasion. This fluid contains a number of components that kill bacteria or inhibit their proliferation. The most important one is lysozyme, which destroys bacterial cell walls and therefore kills bacteria. Eye inflammations develop whenever there is a disturbance of the tear

film composition. Conjunctivitis is regularly caused by staphylococci but also by the very dangerous *Clamydia trachomatis*.

The nasal fluid is of the same composition as the tears and protects the respiratory tract from infection. But as we all know, it is not always possible to maintain the relatively low colonization of nose, mouth, bronchia, and lungs. Viral infections can be followed by severe bacterial infections caused by streptococci, *Haemophilus influenzae*, or even *Pseudomonas aeruginosa*. A proliferation of these organisms and of *Neisseria meningitides* in the nose and mouth gets out of control, penetrating barriers and leading to inflammation of the meninges (meningitis).

The urogenital tract may also be populated by bacteria. In addition to lactic acid bacteria, yeasts such as *Candida albicans* can be found in this habitat. Inflammations are often caused by special strains of *Escherichia coli*, which will be discussed in Chapter 29.

So far, you've only discussed the body surfaces that normally are not very densely populated in healthy humans. They don't account for the one thousand grams of bacteria mentioned.

Yes, but we will eventually get to the "inside story," as it was called by Laurie Comstock, Professor at the Harvard Medical School, after a short remark about the microflora in our mouth. We find three major habitats for bacteria in the oral cavity, the moist lining of the mouth (mucosa), the teeth, and the saliva. Saliva is a source of nutrients for bacterial growth, but saliva also contains components that inhibit the colonization of bacteria on surfaces such as the teeth. Saliva is essentially a very dense bacterial culture with about 100 000 000 (100 million) cells per ml. A human being produces approximately 750 ml of saliva per day, so at the same time we swallow approximately 75 000 000 000 (75 billion) bacteria daily.

What kind of bacteria do we swallow?

The microflora of the mouth is dominated by streptococci. Most of these species are benign. In addition to a dozen *Streptococcus* species, more than thirty additional bacterial species can be found in our mouth.

How are bacteria involved in the formation of dental plaque?

Bacteria have developed mechanisms to prevent being washed off by saliva. They form so-called biofilms, more or less sticky layers consisting of sugar molecules, with the bacteria inside. Dental plaque is a problem because the streptococci residing in the biofilm produce lactic acid that directly attacks the tooth enamel.

By the way, the sugar (saccharose from sugar cane or sugar beets) in our food favors the development of plaque because bacteria such as *Streptococcus salivarius* cleave the sugar into glucose and fructose. These bacteria grow on the glucose and produce lactic acid. At the same time, the fructose is polymerized to the macro-

molecule levan, which contributes to the biofilm on the surface of the teeth. Plaque development is less favored when syrups from starch, enzymically converted first to glucose and then to a mixture of glucose and fructose, are used in our food.

What is the difference?

The difference is as follows: saccharose is a disaccharide in which glucose and fructose are linked chemically. When this disaccharide is cleaved by microorganisms, the glucose produced serves as growth substrate and fructose is polymerized. In glucose/fructose mixtures, both sugars are utilized for growth.

Now we come to the inside story, that of the great diversity and the various activities of microorganisms primarily in the large intestine, which has moved to the center of interest of microbiologists, geneticists, and medical doctors. This is where most of the one thousand grams of bacteria within us is located. There is practically no other habitat in nature where a bacterial population reaches such a high density. As we all know, our well-being and health is very much affected by the composition of the intestinal flora. We often hear about the intestinal bacterium *Escherichia coli*, because it is the best-studied organism. However, in the large intestine, *E. coli* represents less than one thousandth of all bacterial cells present therein. Since *E. coli* is most easily isolated and identified, it is used as an indicator of fecal contamination. The main "bugs" in the intestine are *Bacteroides* and *Eubacterium* species, for example, *Bacteroides fragilis* and *Eubacterium rectale*. Anaerobic bacteria often escaped culture-dependent detection because they used to be cultured in the presence of air, and the oxygen in the air is toxic to many anaerobic microorganisms.

So most people do not know which bacteria contribute to the microbial community in our intestine?

Correct, *Escherichia* coli is present, but it represents a very small proportion thereof, but it's still a little more complicated. We speak of the human microbiom when considering the intestinal bacteria as a whole. It is represented by hundreds of bacterial species, and the total number of different genes in them exceeds the genes of the human genome by a factor of 100. Admittedly, these are mainly genes that code for enzymes required for the degradation of the various compounds arriving in the intestine. These compounds are the large remainder of food ingredients that escape digestions by human enzymes and absorption in the small intestine. The composition of the intestinal microbiota adjusts to the substrate supply, so it differs in vegetarians as compared to people who regularly eat meat. There also exists a correlation between obesity and the kind of "intestinal microbes" present. Pharmaceuticals also have a great effect: for example, treatment with antibiotics may lead to a depletion of the beneficial bacteria and a preponderance of the pathogen *Clostridium difficile* in the intestinal microbiota (see Chapter 29).

How do we humans benefit from the intestinal microflora?

Above all, our microbiota suppresses the settlement of pathogenic bacteria in our intestine. We just mentioned *C. difficile* as an example of a pathogen that takes over if the beneficial microbiota is depleted. Another role of the microflora is the detoxification of poisonous compounds arriving in the intestinal tract. Last but not least, we benefit from the nutrients resulting from microbial activities in the intestine, also vitamin K. Michael Blaut (Potsdam-Rehbruecke, Germany) will give us a more detailed description:

> "One of the major tasks of the intestinal microbiota is to convert indigestable carbohydrates (dietary fiber) to acetic, propionic, and butyric acids. Butyric acid provides 70 percent of the energy required by the epithelial cells of the large intestine whereas acetic acid serves as energy source in the peripheral tissues. Propionic acid is an important building block for gluconeogenesis in the liver, i.e. the synthesis of sugars. Many substances found in plant-derived foods are bioactive, i.e. they have a health-promoting effect. However, some of them first need to be activated by the intestinal microbiota to become biologically active. For example, linseed and rye contain polyphenolic compounds, such as secoisolariciresinol and matairesinol (very complicated names), which are converted to enterodiole and enterolactone. The latter presumably are preventively active against breast and prostate cancer.
>
> The intestinal microbiota also affects the metabolic fate of pharmaceuticals. Hydrophobic (fat-soluble rather than water-soluble) compounds are oxidized in the liver and then linked by so-called phase-2 enzymes to glucuronic acid molecules or sulfate, to make them water soluble. The majority of these conjugated compounds is discarded in the urine via the kidneys, but a considerable amount appears in the intestine together with bile fluid. There, the conjugated compounds are hydrolyzed by bacteria. The products, again hydrophobic, are reabsorbed and transported back to the liver where they are retransformed into conjugated compounds that reappear in the intestine. This process, the enterohepatic circulation, results in a longer retention time of any such compounds.
>
> The bile acids are also subject to enterohepatic circulation, but they are primarily conjugated with glycine and taurine. In addition to hydrolyzing the bile acid conjugates, intestinal bacteria modify the sterol skeleton of the bile acids, leading to secondary bile acids. There is good experimental evidence that secondary bile acids are tumor promoters in colon cancer.
>
> The intestinal microbiota affects not only the metabolism of the host but also the development and maturation of the immune system. It plays an important role in the maturation and proper functioning of the innate and the adaptive immune system. The intestinal microbiota helps the immune

system to distinguish between pathogenic and harmless bacteria. The immune system learns to fight pathogens and to tolerate nonpathogenic bacteria and food antigens. Failure of this kind of tolerance leads to inflammation. Oral tolerance is perturbed in humans suffering from inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. In addition, the intestinal microbiota supports the barrier function of the intestinal epithelium that prevents the growth of pathogenic bacteria. It is noteworthy that the intestine contains approximately 70 percent of all immune cells of the body."

This is a very competent account on the importance of our intestinal microbiota. The information is challenging, but it is important to know that the intestinal bacteria not only grow at the expense of dietary fiber and other materials but also fulfill important functions.

After all this information, I have quite a different view of my insides. But how does the composition of the intestinal microbiota differ in babies? This difference is apparent to parents who have changed their baby's diapers, or nappies.

It is interesting that the intestinal microbiota of babies is dominated by bacteria that are considerably less important in adults: *Bifidobacterium* species and related bacteria. These are lactic acid bacteria that produce large amounts of acetic acid in addition to lactic acid. In newborns, the microbiota originates from the mother and the environment. Within the first days of life a microbial community dominated by bifidobacteria develops, especially in breast-fed babies. Bifidobacteria in infants are favored by certain oligosaccharides present in human milk and by the low pH. In addition, the presence of certain amino acid containing compounds promote the growth of these microorganisms. After weaning, the intestinal microbiota of the infant gradually shifts toward that of an adult. This process may take two to three years.

So in an ideal world you don't think about gastric ulcers and diarrhea?

Of course, but first the good side of bacteria, their role in various habitats outside our body, has to be made clear. Their bad side will be discussed toward the end of this book, in Chapter 29.