THE ECOSYSTEM

Inside
For a long time, the medical establishment treated viruses and bacteria as the enemy — alien invaders to be exterminated with antibiotics or attacked by the immune system as soon as they breached the body’s walls.

Over the past several years, though, scientists have shown that the body is an ecosystem made up of more than 100 trillion microbes that, in order to maintain a person’s health, must be properly balanced and cared for. These various viruses, bacteria, fungi and protozoa in our bodies — called the microbiome — supply us with critical vitamins, help fight dangerous pathogens, keep the immune system in balance, and modulate weight and metabolism by extracting energy and calories from the food we eat.

“Our bodies are 10 times more bacterial cells than they are human cells,” says Heidi Nelson, MD, director of the Microbiome Program at the Mayo Clinic in Rochester, Minn. “We are finally beginning to understand the microbial populations that we coexist with.”

The idea that we have so many more microbial cells than human cells runs counter to the long-held belief that our health is mostly orchestrated by instructions embedded in our DNA. Scientists worked hard to crack the human genome, but, ultimately, just knowing our genetic codes proved insufficient to actually cure disease. Researchers eventually realized they had to factor in and analyze the human microbiome to get a clearer picture of how health and well-being are maintained.

The identity and abundance of species that compose the human microbiome — which is found throughout the body, including on the skin and in the nose, mouth, tonsils, lungs, guts and genital tracts — vary from person to person, depending on factors like diet, geographic location and medical history. Even the experience of ancestors plays a role, with microbiome patterns passed down from mother to child over hundreds of years.

While those patterns may range from one person to the next, an...
out-of-balance microbiome can make anyone sick, since it influences key biological systems, including the immune system and metabolic function.

Imbalanced bacterial communities in the gut have been associated with metabolic disorders like obesity; gastrointestinal disorders like Crohn’s disease and colitis; the inflammatory reactions underlying asthma; as well as a host of deadly, antibiotic-resistant infections.

And with each passing month, emerging research shows new problems and disorders linked to disturbances in the microbial communities we host. (For more on this, see “The Microbiome-Health Connection,” on page 61.)

The good news is that although we can’t choose our genes, we can affect the health of our microbiome — one factor in how our genes express themselves. This can be accomplished through better nutrition, a more judicious use of antibiotics, and interventions — some rather novel — that repopulate the microbiome with good bacteria.

These types of treatments, says Nelson, are part of an emerging brand of personalized medicine that could revolutionize our healthcare.

“If you have a normal community of bacteria and a healthy ecology, all will go well,” Nelson observes. “The goal is to understand the best kind of balance, and how it gets disturbed, so we can treat it accordingly.”

Making Friends With the Immune System

The microbiome’s most fundamental role in human health is keeping the immune system strong. The importance of the relationship between the microbiome and immunity hit Michael Fischbach, PhD, a few years ago, when he was studying “natural products” — a subset of human medications (including most antibiotics and many chemotherapies) produced by bacteria, plants and other living things in the natural world.

Working out of his lab in the Department of Bioengineering and Therapeutic Sciences at the University of California, San Francisco, Fischbach was looking to discover evermore-potent natural products. To find appropriate candidates, he surveyed DNA from organisms already used to make drugs; then, using gene-sequencing technology, he searched for similar DNA in other microbes, including those of the human microbiome.

To his astonishment and delight, he found that the human microbiome harbored genes with similar codes. Living inside us, these new natural-product candidates were already standing guard, especially in the oral cavity, the gut and the vagina. Without helpful microbes in these regions, experts have found that “risk of serious infection goes up,” says Fischbach.

Fischbach was determined to see how differences in the microbiome might account for differences in human health. One of his findings was that the microbiome “talks to” our body’s natural killer T-cells — the guardians responsible for recognizing and attacking invasive pathogens.

In the human immune system, the body’s own cells present certain proteins on their surface that allow T-cells to recognize them as friendly and thus leave them unscathed. Invasive bacteria, on the other hand, wave the biochemical equivalent of a red flag — causing our T-cells to attack.

Researchers like Fischbach have found that good bacteria talk to the immune system, too, communicating with the T-cells and helping them work harder.

Ultimately, Fischbach and colleagues hope to master the language of the microbiome so that we can better communicate with our own immune systems and find more nuanced paths to health and healing.
Roots of Obesity

In addition to immunity, researchers are also studying the connection between the microbiome and metabolic diseases like obesity and diabetes. “Most people believed that being overweight was simply a direct consequence of the food you consumed and the energy you burned,” explains Yang-Xin Fu, MD, PhD, professor of pathology at the University of Chicago.

But, in 2005, Jeffrey Gordon, MD, of Washington University in St. Louis, and his colleagues began to investigate the interrelationship between diet, gut microbial ecology and obesity. First, they compared the gut bacteria of obese mice with that of thin mice. The two main types of gut bugs in mice, as in people, are *Firmicutes* and *Bacteroidetes*. The researchers found, however, that obese mice have a much higher proportion of *Firmicutes* bacteria, while thin mice have a much higher proportion of *Bacteroidetes* bacteria.

Armed with this finding, the researchers then took two groups of germ-free mice and infected one group with the microbes taken from the obese mice and the other group with the microbes taken from the leaner mice. Fed the exact same diet, both groups gained fat; however, the mice that were given bacteria from the obese mice gained excessively. Specifically, when researchers looked at the mice two weeks after exposure, the mice infected with bacteria from the obese mice had a whopping 47 percent increase in body fat compared with a 27 percent increase in the mice given the bacteria from the lean mice. (Interestingly, germ-free mice that were completely sanitized of microbes never put on weight, no matter what the diet.)

Intrigued, Fu and his team at the University of Chicago have spent years trying to find the underlying mechanism of the microbiome-obesity connection, in hopes that manipulating it might help control weight in humans. In a study published in 2012 in *Nature Immunology*, the group reported an exciting find: Specific microbes are needed to absorb energy from food, and it is this metabolic transaction that determines weight gain in the host.

To come to this conclusion, the Chicago team compared normal mice with genetically defective mice unable to produce lymphotxin, a molecule that helps regulate interactions between the immune system and bacteria in the bowel. On a standard diet, both groups of mice maintained a steady weight. But on a high-fat diet, the normal mice put on weight while those lacking lymphotxin stayed thin. As Gordon found in his work, the element mediating the weight gain was the microbiome itself. In normal mice, the high-fat diet triggered a substantial increase in the *Firmicutes* bacteria associated with obesity. But in the mice lacking lymphotxin, who stayed thin no matter what, *Firmicutes* could not grow. The step-by-step interactions were complex, but in the end it came down to the efficiency with which the microbes metabolized food. In mice and humans, microbes associated with obesity required little food and energy to reproduce, and transferred far more calories to the host as fat. Microbes that kept mice and humans thin, by contrast, required a lot of calories, leaving less for their hosts to process. Net effect? A significant metabolic boost.

“One person might have bacteria that eat more than half their calories, leaving that person lean. Another person might seem to gain weight on almost nothing but water.” Often, in situations like these, Fu says, “gut flora play a major role.”

The results suggest that we will eventually be able to manipulate microbes to prevent obesity or enhance energy transfer to the host, says Fu. →

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Rebuilding the Microbiome

A movement is afoot to restore our abused and neglected microbiomes to good health. And some of the first applications have come from doctors who must rely on longer courses of antibiotics to treat resistant or hard-to-beat infections (an approach that necessarily puts the microbiome at risk by wiping out whole species of bacteria and allowing new ones to take their place).

Richard Horowitz, MD, an internist in Hyde Park, NY., and author of the upcoming 2013 book Why Can’t I Get Better? Solving the Mystery of Lyme and Chronic Disease, uses a series of probiotics to replenish the gut with good bacteria after a course of antibiotics. Horowitz says he favors several different strains of high-potency acidophilus, including *Lactobacillus rhamnosus*, which has been shown in many studies to help prevent antibiotic-associated diarrhea, a symptom of an out-of-whack microbiome. It also stops *E. coli*, *Salmonella* and *Shigella* from adhering to the intestinal wall.

Horowitz also often treats the gut simultaneously with “prebiotics” — food ingredients that stimulate growth of organisms in the gut, helping probiotics work better. One prebiotic he favors contains FOS (fructooligosaccharides) to prevent antibiotic-associated diarrhea.

Even when his patients are not on antibiotics, Horowitz feels that pre- and probiotics can often help individuals who are feeling sick and fatigued. “Probiotics produce substances that prevent harmful bacteria and yeast from establishing themselves in the colon,” he explains. The yeast and harmful bacteria, in turn, can generate lactic acid, toxins and hydrogen peroxide, which make the patients feel ill. (For more on probiotics, see ELmag.com/probiotics.)

Sometimes, when disturbances in the microbiome cause serious disease, probiotics and diet aren’t enough. That’s when doctors may employ what is called a “fecal transplant.”

A shift in diet can be similarly therapeutic for the microbiome. Horowitz asks his patients to stay clear of sugar and refined carbohydrates, such as wheat flour, and to load up on plenty of produce.

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During a fecal transplant, human feces that contain a balanced suite of microbes are transferred from a healthy individual to someone with a disease traced to a microbiome in disarray.

Working with Heidi Nelson, MD, and the team at Mayo Clinic, gastroenterologist Darrell Pardi, MD, uses the procedure to help his patients overcome infection with the sometimes-deadly bacterium *Clostridium difficile* (*C. diff*), which causes recurrent episodes of diarrhea. The infection is usually treated with antibiotics, but the organism generates spores impervious to the drugs. And if the microbiome remains sparse, the spores can reseed the gut, causing relapse. Only an intact microbiome can prevent return of the disease.

To restore his patients, Pardi obtains stool from a patient’s family member or a designated donor on the clinic staff. He then puts the sample into a fancy blender — a machine called a “stomacher,” used in the food industry to test toxins in foods — and separates solid matter from microbes to create a liquid. The microbe mixture is then transferred to the patient by enema or colonoscopy tube. Of the 16 relapsing *C. diff* patients Pardi treated last year, 14 have been cured. “There have been no complications or side effects,” he says.

Pardi’s original field of interest is inflammatory bowel disease (IBD), an often-devastating disorder caused by inflammation in the GI tract that can cause abdominal pain, vomiting, diarrhea, rectal bleeding and severe intestinal cramps. New research, says Pardi, shows that imbalances in the microbiome may be at the root of IBD. If he has his way, he’ll ultimately be treating a subset of patients with IBD and other immune or inflammatory diseases — including diabetes, multiple sclerosis, even arthritis — with fecal transplants instead of risky, immune-suppressing drugs.

First, of course, the Mayo team must determine which organisms do or don’t drive which disease. With up to a thousand microbial species inhabiting the human gut alone, “powerful gene sequencing and computational systems will have to parse large amounts of data to provide a framework,” Nelson explains. “The ultimate goal,” adds Pardi, “would be a kind of super-probiotic or ‘poop pill,’ made up of the microbes that work best in each particular case.

In the meantime, many health experts are working on other ways to manage and manipulate the microbiome, instead of waging wholesale war against it.

“Antibiotics are extraordinarily important drugs that have saved countless lives, and they will always be a crucial component of the physician’s arsenal,” notes Fischbach. But, “in the future, it might be more common to see antibacterial therapies that are specific to pathogens and that spare the friendly bacteria.”

The Microbiome-Health Connection

An out-of-whack microbiome — the community of bacteria, viruses, protozoa and fungi that live in our bodies — can spell disaster for our health. Here are just a few conditions that can result.

Sinusitis. Chronic rhinosinusitis (CRS), characterized by inflammation of the nasal passages, accounts for more than 500,000 emergency room visits a year in the United States alone. It can cause congestion, fatigue and depression. It’s also been linked to asthma, meningitis and aneurysms.

Recent evidence suggests that a depleted microbiome in nasal passages may be at the root. A team from the University of California, San Francisco, compared nasal passages of 10 CRS patients with 10 healthy people, finding far less diversity in the microbiomes of the CRS group overall; overgrowth of a single organism, *Corynebacterium tuberculostearicum*, was implicated in the disease. Another experiment depleted mice microbiomes by treating them with antibiotics for seven days; later, treated and untreated mice were exposed to *Corynebacterium tuberculostearicum*. Only those with the treated, depleted microbiomes had symptoms of sinusitis.

Infant immune deficits. Breast-fed babies obtain microbes from mother’s milk, an elixir that ends up enhancing early microbial colonization of the gut. This enriched microbiome, in turn, alters the expression of genes involved in immunity, conferring enhanced resistance to pathogens — an advantage that formula-fed infants, with less diverse microbiomes, do not possess.

Type 2 diabetes. An international team of scientists found that a specific pattern of intestinal microbes can increase the risk of type 2 diabetes, a metabolic disease that prevents the body from properly utilizing sugar for energy. The pattern can serve as a biomarker, enabling those at risk to alter diet to prevent onset of disease.

Asthma. Scientists at the University of British Columbia in Canada showed that antibiotics given to mice early in life permanently shift the mix of bacterial organisms in the gut, disrupting the immune system and the inflammatory response throughout life. Higher risk of allergic asthma is a result. (Presumably, this is something that microbiome therapy could, at some future date, correct.)

Psychiatric disease. Evidence suggests that supplementing with certain probiotics can treat anxiety and other psychiatric ills. To study this, researchers from the Alimentary Pharmabiotic Centre in Ireland fed a popular probiotic called *Lactobacillus rhamnosus* to mice and found significantly fewer stress-, anxiety- and depression-related behaviors than those fed broth alone. Not only did the bacteria improve behavior, they also helped reduce levels of the stress hormone corticosterone.

Cancer. A study published in *Science* suggests that inflammation — resulting from infection, injury or other bodily insult — changes the ecosystem of the gut, allowing cancer-causing pathogens to invade and increasing the risk of colorectal cancer.

Clostridium difficile. A highly infectious and resistant pathogen that causes recurrent bouts of diarrhea, *C. diff* can run amok in imbalanced microbiomes, such as those where antibiotics have wiped out beneficial bugs. A study published in *The Journal of Infectious Diseases* found that patients with persistent *C. diff* had much less bacterial diversity than patients in a control group. When it comes to treating *C. diff*, fecal transplants greatly outperform antibiotics, *The New England Journal of Medicine* reported this year, because they repopulate the microbiome.