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Immune System's Double Duty

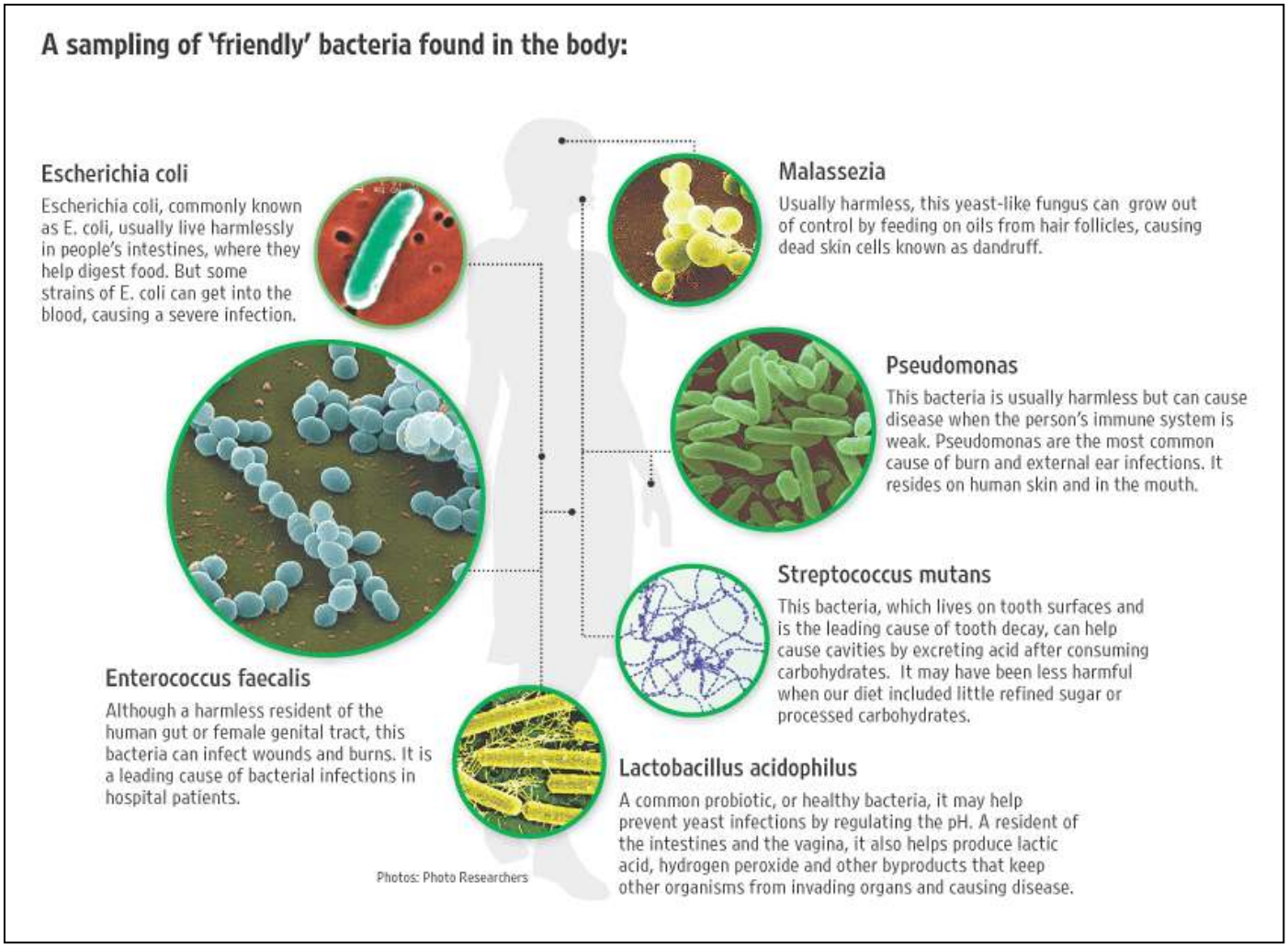
By MARK SCHOOFS August 28, 2008; Page A10

We're not only human after all.

New genetic technology has revealed that the human body swarms with more benign bacteria than ever imagined -- more than 2,000 species, whose cells outnumber the body's own by a 10-1 ratio. But that isn't such a bad thing. Many of these bacteria are needed for tasks such as the digestion of nutrients and the development of organs.

That such a vast microbial community is permitted to thrive in our bodies upends the notion that the immune system's role is simply to attack invading microbes. A growing number of biologists believe that, in addition to its protective role, the immune system acts as a master regulator of our microbial menagerie, working "to maintain communities of bacteria in balance," said Margaret McFall-Ngai, a University of Wisconsin biology and immunology professor. She is a creator of this hypothesis, which conceptualizes the immune system as keeping each species in its proper niche and quantity.

If confirmed, this hypothesis could have wide-ranging consequences for medicine because a growing number of health problems, from inflammatory-bowel disease to obesity, have been linked to bacterial communities out of balance, as opposed to a lone pathogen.



Immunology, the science of the immune system, emerged from the germ theory of disease developed by Robert Koch, Louis Pasteur and other scientific luminaries of the 19th century. Because these pioneers focused mainly on the disease-causing potential of microbes rather than on their beneficial qualities, says Prof. McFall-Ngai, they conceived of the immune system as a zealous defense against microorganisms, a perspective that has guided immunology since.

An early attempt to rethink this notion came about 14 years ago, when Polly Matzinger, now a senior investigator at the National Institute of Allergy and Infectious Diseases, posited that the immune system doesn't attack all microbes, only those that signal danger by killing, injuring or stressing human cells. Such murdered cells would put out different chemical signals than cells that

die a natural death, triggering the immune system's counterattack. This theory is controversial, but biologists increasingly are being forced to grapple with how the immune system tolerates beneficial bacteria.

Until recently, scientists didn't realize the scale and diversity of our teeming microbial population because most bacteria that live in the body can't be "cultured" -- grown in a petri dish. Only in the past decade, aided by advances in genetic technology, were scientists able to grasp the magnitude of our resident microbial population.

Some scientists think the notion that the immune system regulates benign microbes is simplistic. While the immune system manages some of our bacteria, says Stanford immunology professor David Relman, many microbes have evolved to exploit the immune system, engineering ways to evade attack or even to goad the immune system into targeting competing bacteria.

Swiss researchers recently showed how salmonella bacteria produce a subset of "kamikaze" fighters. Making up about 15% of the total salmonella population, these suicide salmonella secrete a chemical flag that tricks the immune system into killing them—and, more important, virtually all of the benign bacteria around them. Freed from the competition of the body's benign gut bacteria, the majority of salmonella bacteria can move in and cause disease.

Last year, the National Institutes of Health launched the $115 million Human Microbiome Project to inventory and study the bacteria that live in us and, because our skin is host to bacterial multitudes, on us.

Our benign bacteria appear crucial to good health. Laboratory mice that are bred to be germ-free are less healthy: They are leaner than normal mice and must be fed special diets. Their hearts are smaller, and the capillaries that carry blood to certain tissues are stunted. Even their immune systems don't develop properly.

One part of the immune system includes macrophage cells that gobble up invaders and are equipped with sensors called Toll-like receptors. Like a bloodhound sniffing a piece of a fugitive's clothing, TLRs recognize a few microbial fragments that are present in almost all bacteria. Once TLRs "smell" such a fragment, they mobilize the immune system to kill the bacteria. It was thought that macrophage cells with TLRs didn't sense beneficial or neutral bacteria in part because such bacteria were protected by the lining of the gut and other organs, called the epithelium, which was believed to keep macrophage cells on one side and bacteria on the other.

But in mouse experiments, Yale University biology professor Ruslan Medzhitov discovered that TLRs do sniff out benign bacteria in the gut. Even more surprising was that sensing these bacteria doesn't lead to an immune-system seek-and-destroy mission. Instead, it prompts the body to strengthen the lining of the gut, helping to prevent bacteria from permeating the intestinal wall and colonizing other organs. That is important, because bacteria such as most strains of E. coli are harmless in the intestines but can cause disease if they infiltrate the spleen or liver. In fact, if the TLRs don't encounter the fragment present in beneficial bacteria, the lining of the gut deteriorates and lesions open in it.Prof. Medzhitov, who accepts that the immune system might manage our microbial communities but adheres to the view that its primary function is to fight disease, believes cancer patients might eventually benefit from this finding. Chemotherapy often causes similar injuries to the gut lining. But because chemo also weakens the immune system, many cancer patients are prescribed antibiotics to prevent infections such as pneumonia. Those antibiotics can indiscriminately kill the very bacteria needed to maintain the gut lining, exacerbating the intestinal side effects of chemotherapy.

Although years of research lie ahead, Prof. Medzhitov says that the molecular fragment smelled by the TLRs might someday be given as a drug to help chemo patients maintain the lining of their gut.In the womb, human fetuses are virtually germ-free; we start acquiring our benign bacterial community when we begin our passage through the birth canal. While all humans share broadly similar types of bacteria, an individual's precise mix of species is as unique as a fingerprint. Despite this variation, the immune system knows which microbes to let colonize the body and which to purge. In many cases, pathogenic bacteria that the immune system attacks are closely related to benign strains that it leaves alone. How the immune system knows when to attack is one of the great questions in immunology.

As remarkable as the co-evolution of microbes and the immune system may be, modernity is presenting new problems.Contemporary food is highly processed, favoring bacteria that thrive on nutrients such as refined sugar. Research has shown that obese people carry different bacterial communities in their guts than lean people. Other research suggests that because of an American diet heavy in meat and saturated fat, African-Americans tend to have different communities of bacteria in their colons than Africans in Africa -- correlating with the Americans' starkly higher rates of colon cancer.

Learning the optimal composition of benign bacteria, many researchers believe, might eventually help medicine treat disease, if not prevent it.