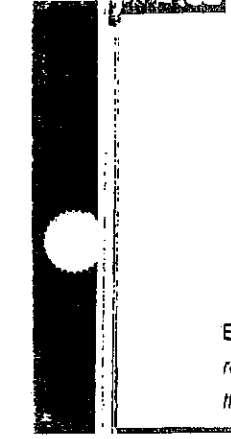
Gut Reactions

A one-cell-thick wall stands between us and disaster.



Escherichia coli, a regular member of the intestinal flora.

By Sherwood L. Gorbach

Although not widely recognized... not the topic of polite conversation—our intestinal tract, like that of other mammals, is the habitat for an amazingly rich population of microorganisms. While the intestine of an embryo in the uterus is sterile, newborns acquire their bowel flora during passage through the birth canal. As the diet of the infant changes from milk-based fare to a more varied diet, the mix of microbes changes, assuming its adult character by the second year of life.

This microflora—mostly bacteria—is usually harmless and occasionally helpful, yet always menacing as a potential source of infection. What separates us from invasion by the potential pathogens in our bowel is a fragile barrier just one cell thick: the intestinal lining. For most of our lives, we generally coexist peacefully with our microflora. But if the intestinal wall is breached by certain species of bacteria (these are a minority of the bowel's total population), a spreading, life-threatening infection develops, known since ancient times as sepsis.

The microbial residents of the stomach and most of those in the small intestine come from the mouth, arriving with saliva and food. These microbes—including streptococci, lactobacilli, and a few fungal species—are relatively sparse, generally less than 10,000 microorganisms per milliliter of intestinal contents. In the lower small intestine (the ileum), some additional species from the large intestine (or colon) migrate up, adding to the resident microbes' numbers and complexity. The most dramatic change, however, occurs in the colon itself, which is separated from the small intestine by a sphincterlike structure known as the ileocecal valve.

The colon is replete with microorganisms, mostly bacteria, with total numbers in the range of 100,000,000,000,000. Their dense concentration there approaches the theoretical limit of what can fit into the given space. More than five hundred different species of bacteria regularly reside in the colon of every living

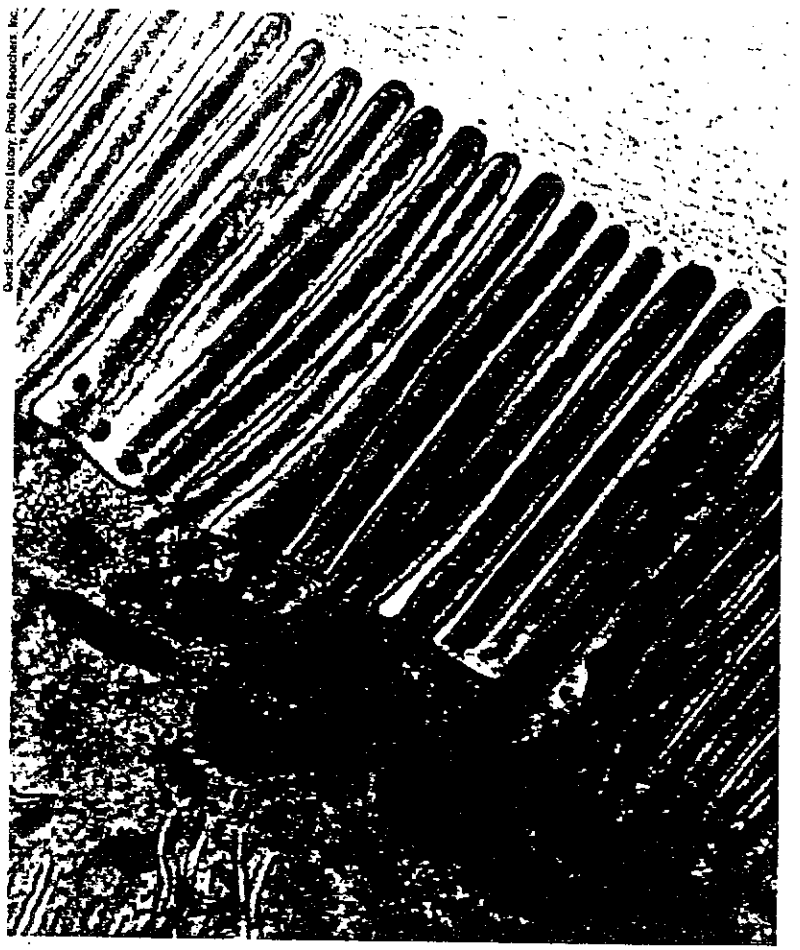
person. Functioning in virtual obscurity from its host, the flora does its daily work of fermentation and metabolism. The colon is a dark and dank place, virtually devoid of atmospheric oxygen, and its bacteria are mostly strict anaerobes—that is, they are adapted to live without oxygen and in fact would perish in its presence. The anaerobes outnumber the other bacteria, such as the well-known *Escherichia coli*, commonly called *E. coli*, by a factor of 1,000 to 1. Hence, the colon is a one-liter anaerobic fermentation vessel that receives nutrients—undigested foodstuffs such as grains, complex carbohydrates, and cellulose—via the regular propulsive motions of the small intestine. This is the good side of the Dr. Jekyll/Mr. Hyde life of our colonic bacteria. Their ability to digest nutrients that have escaped absorption in the small intestine (because they could not be broken down by the enzymes there) provides us with important sources of energy, proteins, and vitamins that would otherwise be lost in fecal evacuations.

The sinister side of the flora is displayed when bacteria manage to penetrate the intestinal wall, causing local destruction and then widespread infection. Perhaps the most common ways bacteria escape involve penetration of the bowel by a knife or bullet wound, or a crush injury, as in an automobile accident. The breach permits the microflora to spread to the organs in the peritoneal cavity and the surrounding muscle and fat. Damage to the intestinal wall can also be caused by a disease process in the intestine itself—for example, a perforated appendix or a colon cancer that has eroded the bowel wall. In each case, the end result is an extensive, spreading infection of the abdominal lining that is known as peritonitis. The free-ranging bacteria released from the bowel enter the bloodstream and produce sepsis, with its accompanying shock syndrome (fever, falling blood pressure, and the resultant compromise of vital organs, such as the liver and kidneys). Since multiple species of bacteria are involved, broad-spectrum antibiotics must be used to control this complex infection, along with judicious surgery to repair the bowel wall.

The intestinal wall can also be damaged by intrinsically virulent bacteria that we consume in contaminated or spoiled food or beverages. *Salmonella* and *Yersinia* preferentially invade the lower ileum, while *Shigella*, *Campylobacter* and *E. coli 0157:H7* seek out the large bowel. In the early stages, only the pathogenic bacteria themselves penetrate the bowel wall, but once this damage has occurred, other members of the resident flora may join the invasion and cause more extensive disease. In most cases involving a specific food-poisoning bacterium, a targeted antibiotic is used, and the infection clears up rather promptly. If other members of the microbial flora are also involved, however, the antibiotic coverage must be expanded to include broad-spectrum drugs to treat what has become a systemic, life-threatening infection.

The third type of bacterial assault on our fragile intestinal lining occurs when the host's immune system is impaired by disease—malignancies and AIDS being the most common such maladies—or by immunocompromising treatments, such as anti-cancer drugs and corticosteroids. In such cases, once the intestinal wall is weakened, the one-cell barrier breaks at multiple sites, eventually disintegrating into a porous membrane. The bacterial flora, no longer contained, spreads rapidly to the abdominal cavity and the bloodstream. Previously harmless microorganisms are thus—ironically—transformed into pathogenic agents of disease, threatening the existence of the host. □

Gut bacteria are usually harmless. Their sinister side emerges when they breach the intestinal wall.



David Scharf/Science Photo Library, Photo Researchers, Inc.

An epithelial cell, with its tall microvilli, on the border of the intestine. Bacteria (not visible here) reside in the bowel cavity (upper right).

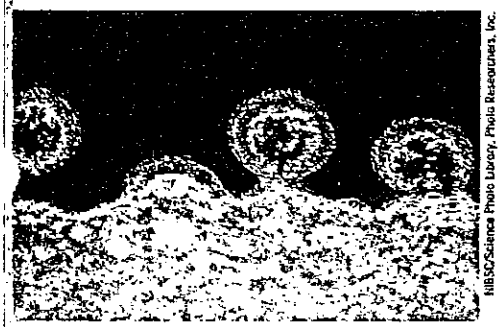
Cast of Characters

A brief guide to agents of infection

Viruses

Viruses come in myriad symmetrical shapes but share a general structure: a core of RNA or DNA surrounded by a protein shell. With no metabolic functions of their own, viruses can survive for limited periods outside the body of the host. Only when they infiltrate living cells do they begin to replicate, usurping the cell's genetic machinery to produce a profusion of viral particles. These "progeny" may burst out of the infected cell or simply bud off the cell membrane, repeating the process until they either destroy the host or are overcome by the immune system.

For a single-celled host organism, such as a bacterium, viral infection is usually lethal (see "Do Viruses Control the Oceans?" page 48). Plants, too, are extremely susceptible: viruses rank second only to fungi as crop destroyers. In humans, viral illnesses run the gamut from inconsequential to major. At least thirty-five types of papilloma viruses are responsible for warts. Rhinoviruses produce the universal and incurable common cold. Measles, HIV/AIDS, influenza, dengue hemorrhagic fever, and hepatitis B—all caused by viruses—kill millions annually worldwide (see "The World's Top Ten Infectious Killers in 1997," page 46). Less widely known is the fact that 15 to 20 percent of cancers (including malignancies of the cervix and liver) are of viral origin (see "Catching On to What's Catching," page 34).



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Budding immunodeficiency viruses

In response to a viral invasion, animals produce antibodies that can, if the host survives, confer immunity to subsequent infection by that virus. Vaccination with a weakened or noninfectious form of the virus also stimulates production of immunity-conferring antibodies.

Bacteria

Bits of cytoplasm surrounded by a membrane, bacteria are the most abundant living things on earth. These unicellular beings comprise two kingdoms—the archaebacteria, found in extreme environments (such as hot seafloor vents), and the eubacteria, ubiquitous in soil, water, and both on and in the bodies of animals. More so than plants, animals are appealing habitat for bacteria, providing the moisture, food, and substrates that these microbes require for survival. Millions harmlessly colonize our skin and orifices as well as our respiratory and intestinal tracts. Some gut bacteria are useful house guests, providing essential vitamins and keeping fungi and harmful bacteria in check by competing for space and nutrients.

Bacteria that are innocuous in one part of the body may cause problems elsewhere—as when intestinal bacteria escape into the bladder or peritoneal cavity. But most disease bacteria come from the outside—such as tuberculosis bacilli that are inhaled in moisture droplets. Some bacteria cannot survive in air; *Clostridium tetani*, for example, secretes its deadly nerve toxins only after gaining access to the body's internal tissues through punctures, burns, and surgical wounds. Pathogenic *Escherichia coli* (a different strain from the *E. coli* that normally inhabits our intestines) causes internal hemorrhaging when consumed in contaminated food.

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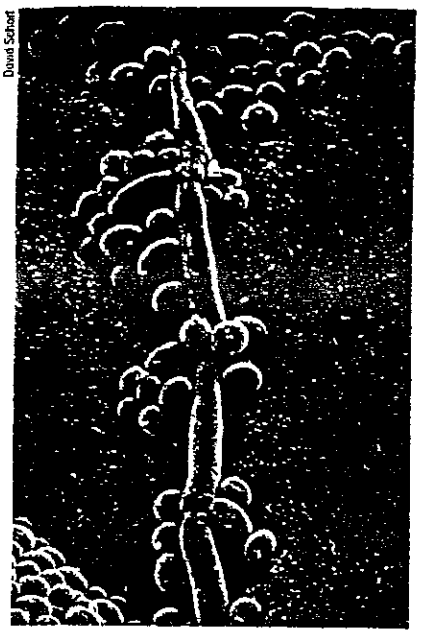
Streptococcus faecalis

Of the ten major types of infection killing humans today, five—acute lower respiratory infections, tuberculosis, diarrheal diseases, whooping cough, and tetanus—are caused by bacteria.

Fungi

Fungi—the yeasts, molds, smuts, mushrooms, and mildews—constitute their own kingdom in the natural world. As purveyors of human misery, they take a backseat to bacteria and viruses. Some live harmlessly in the dead cells of our nails, hair, and feet, but most are soil dwellers. The few that regard humans as habitat cause annoying maladies such as yeast infections, athlete's foot, and the misleadingly named ringworm. As for the rest, we (and other animals) manage to fend them off with naturally occurring substances in our skin, blood, sweat, and saliva.

A little over a decade ago, however, a key study signaled a change: researchers found that nearly 40 percent of patients dying from hospital-acquired infections were being felled by fungi. The reason was a good news/bad news tale. Most people with compromised defenses—those with AIDS, cancer, organ transplants, and severe burns (as well as premature babies)—were surviving longer because of improved treatments. But fungi such as *Candida* (a common inhabitant of our mouth and other orifices) were taking advantage of catheters, needles, and incisions to enter the tissues of these immune-suppressed patients.


David Scharf

Candida albicans

Plants are more vulnerable than animals to infection by fungi. Wind-borne fungal spores have caused such well-known and devastating epidemics as Dutch elm disease and the potato blight that led to the great Irish famine of the 1840s. Lesser known but economically significant ailments of today include karnal bunt disease in wheat and root rot in trees.

Fungi, which compete with other microbes for niches in the ecosystem, produce chemical defenses to ward off their bacterial rivals—a conflict that benefited humans when fungal defense chemicals were used to create penicillin, the mighty antibiotic that cures bacterial diseases from pneumonia to syphilis.

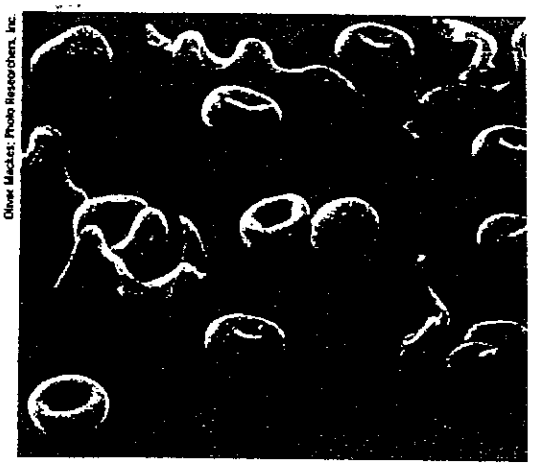
Prions

American biochemist Stanley Prusiner won a Nobel Prize in 1997 for his work on proteinaceous infectious particles, which he nicknamed prions. Unlike all other pathogens, prions have neither DNA nor RNA. They are rogue forms of normal proteins found in the brains of healthy birds and mammals. Once a prion appears (either by mutation or by transmission from an infected individual), it spreads by inducing its nearby normal counterparts to undergo a similarly malign metamorphosis. Over the long run, the accumulation of prions destroys the brain, riddling it with holes.

All diseases presumed to be caused by prions are slow acting and fatal. They have been identified in many vertebrates, including humans, cats, mink, deer, and farm animals. The most common is scrapie, transmitted to sheep and goats either in contaminated fodder or passed from mother to offspring. Bovine spongiform encephalopathy, perhaps better known as mad cow disease, is a variant of scrapie. Creutzfeldt-Jakob disease—a rare brain affliction of humans believed by many to be another scrapie variant—can be inadvertently transmitted during brain surgery and organ transplantation. Kuru, a prion-associated disease discovered in a New Guinean tribe in the 1950s, was attributed to the ritual practice of eating the brains of the dead. When the practice was abandoned, kuru virtually disappeared.

Protists

Protists, also called [illegible], are single-celled organisms that range in appearance from whip-tailed flagellates to bloblike amoebas. On average, protists are about a thousand times larger than bacteria and also differ from them in that their single cell contains a nucleus. Found worldwide in soil, oceans, and freshwater, most protists live by preying on other, smaller microbes. By doing so, they check the growth of groundwater bacteria and foster soil fertility.


Oliver Meckes; Photo Researchers, Inc.

Trypanosomes among blood cells

Many of the protists are free-living, while others cannot survive unless they colonize animal hosts. The flagellate *Streblomastix*, for example, lives symbiotically in the intestines of termites, gaining food and shelter and simultaneously helping its host digest wood. *Naegleria fowleri* lives independently in North American lakes and streams but is an opportunist that can cause a life-threatening brain infection if it enters the nose of a human swimmer.

Infection by parasitic protists is not always serious; a large proportion of people in the United States, for instance, have been infected by *Toxoplasma* without even knowing it. Some protists, like *Pneumocystis carinii*, run rampant in hosts with weakened immune systems. Still others are mass killers, devastating the blood, respiratory, and gastrointestinal systems of their hosts. *Leishmania*, a protist transmitted to humans by sand flies, damages the spleen and liver of hundreds of millions of people worldwide. In 1997 sleeping-sickness trypanosomes in the bloodstream killed 100,000 people (and countless livestock) in Africa, and the plasmodia that cause malaria are estimated to kill 2.7 million people annually in the Tropics.

—*Rachel Zoffness*

Next time someone points the finger at you for passing gas, you'll have the best defense science can offer: "It wasn't me. It was *them*. . ."

THE BACTERIA INSIDE MY GUT

by George Liles

Let's face it: Everybody does it. Madonna, the Fresh Prince—everybody. Every day. In fact, most of us pass gas an average of 14 times a day.

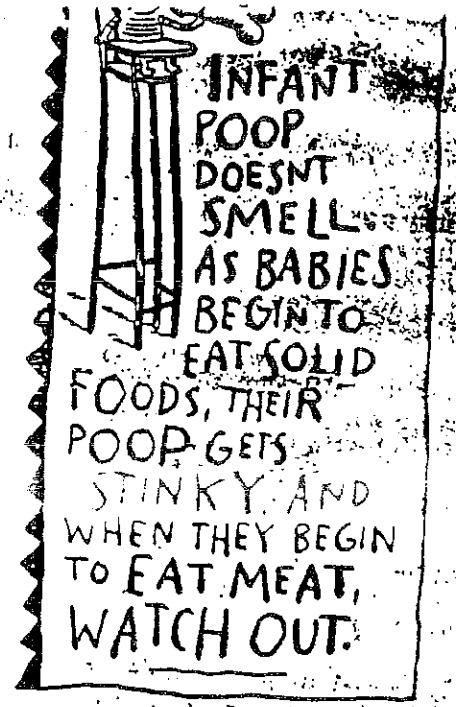
> PEOPLE HAVE BEEN KNOWN TO EXPLODE DURING SURGERY WHEN ELECTRICAL OPERATING EQUIPMENT IGNITED GAS IN THEIR INTESTINES.

The weird thing is that even though everybody does it, it's nobody's fault. The phenomenon scientists call *flatulence* is simply a result of having millions of microbes living in your large intestine. They hang out munching on food *you* can't see. What they give you back is gas, the fuel that makes you fire. Some thank you for a nice place to live and free meals, eh?!

EATERS DIGEST

It all starts before the food even gets into your mouth. Just the thought of your mom's special 18-secret-ingredient lasagna gets your mouth watering. You

(Continued on page 17)



(*Continued from page 15*)

take that first bite and start chewing the food into smaller pieces. At the same time, *digestive enzymes* in your saliva start to break the food down *chemically*—into the simple *nutrients* of which it's made.

Having savored your mom's handiwork, you swallow, sending the partially digested food to your stomach, where still other enzymes go to work on it to release more nutrients. Three or four hours later, the food, now resembling a mashed-up milky liquid, passes into your small intestine. There, the digestive process continues and the nutrients are absorbed into your blood for all of your cells to use.

But hold on: Your body doesn't have enzymes to digest *everything*. Take those infamous beans (*please*), not to mention cabbage, cherries, watermelon, and a host of other *high-fiber* foods. These foods contain lots of *oligosaccharides*, a group of sugars found in some plant fibers. Your body has no enzymes to digest oligosaccharides, so foods containing them pass undigested into your *colon* (the five-foot-long large intestine). That's where the bacteria go to work.

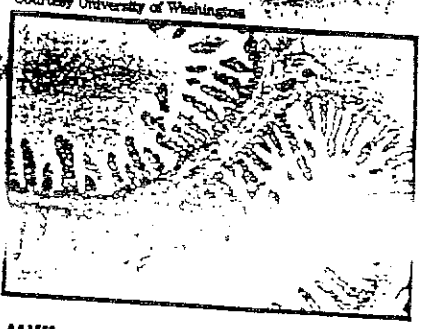
THEY DID IT!

More than 5,000 species of microbes hang out in this lower end of your *gut* (the name scientists give to the whole digestive tract from mouth to anus). The bacteria couldn't ask for a better home. The colon is warm and moist—a perfect environment for growth and reproduction. And it contains none of those acids that kill bacteria in the stomach and small intestine. Best of all, it offers a steady food supply. All the microbes have to do is kick back and wait for your leftovers to drop in.

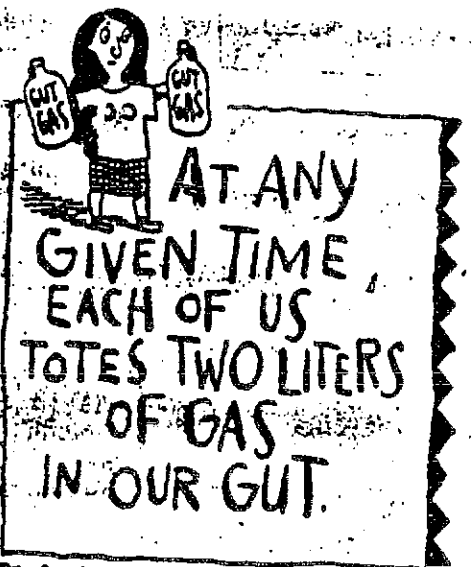
Then it's feeding time. To these critters, your leftovers represent opportunity, not waste. That's because the microbes have the enzymes to break down foods *your* enzymes can't touch. And they do the same thing with their food that you do with yours: They *metabolize* it, converting the nutrients to energy or using them to build new cell structures.

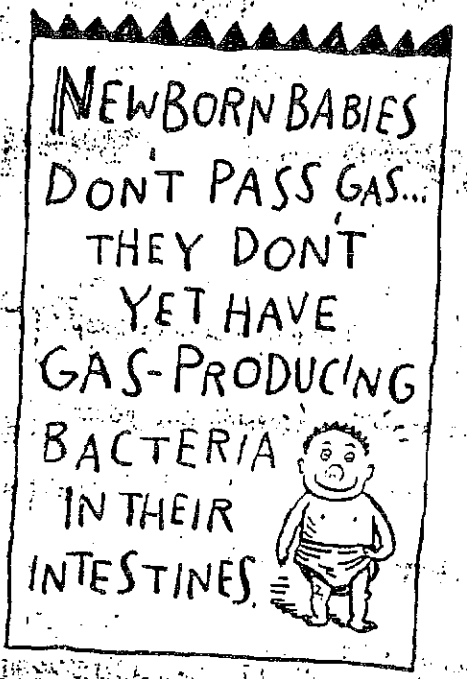
"Toot" bad for us that they do it right on the spot, in our large intestines, because in the process of metabolizing nutrients, the bacteria give off gaseous wastes. (We too produce gas when our cells

Courtesy University of Washington



Millions of villi: **Food isn't really *inside* you until its nutrients enter your bloodstream, where they're available for all your cells to use. This *absorption* of nutrients occurs in the small intestine, which is well-equipped for the job. Its lower end is lined with millions of tiny fingerlike projections called *villi* (above). The walls of the villi are only one cell thick, so nutrients can easily pass through and into tiny blood vessels on the other side.**

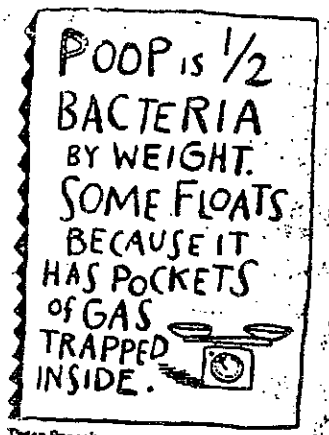




metabolize nutrients, but it exits our bodies via our lungs.)

You may be familiar with some of the bacteria's gases: nitrogen, oxygen, carbon dioxide, hydrogen, and methane. They make up most of the air you breathe, and a good 99 percent of the "atmosphere" in your large intestine. But they're not the ones that smell. It's the other one percent you have to watch out for.

No one's exactly sure which of the other 200 trace gases is the stinker. The prime suspects are *skatole* and *indole* (both by-products of protein digestion) and *sulfide* gases, which are responsible for the smell of rotten eggs.



Peter Spacek

WHAT CAN I DO?

Maybe you're thinking you can stop this nasty business—kill off the bacteria by refusing to feed them the foods they like (anything you can't digest, that is).

The bad news: Most foods contain at least some indigestible fiber for bacteria to feast on. And it wouldn't be very healthy to avoid them. Nutritionists and doctors say fiber helps prevent certain kinds of cancer and may prevent heart disease.

The good news: Scientists are looking at ways to make the best-known offending foods a bit less offensive. For example, people who have difficulty digesting milk can now take enzyme supplements that do their digesting for them—no milky leftovers for the hungry bacteria in the large intestine.

One scientist is going after the granddaddy of them all: the bean. He wants to genetically engineer beans with fewer oligosaccharides to deprive the bacteria of at least some of their feast.

For now, though, one thing is certain: The old playground ditty is true. Beans (and all other indigestible foods) are a musical fruit. But remember, the *bacteria* are the ones tooting the horns. ■