

A process of elimination

In the future, patients with stubborn and even fatal diseases may have the option of undergoing fecal transplants to overcome 'bad' bacteria and replace them with beneficial ones. Judy Siegel-Itzkovich reports

It seems that while the Creator allowed a wide variety of diseases to inflict mankind, He also provided the world with a "medicine cabinet" of natural substances that can treat and even cure these disorders. All researchers have to do is to discover and apply them.

Substances contained in various plants, minerals and other natural resources have been suggested over the millennia and proven scientifically in the last few centuries to alleviate diseases.

Some proposed substances have been bizarre. Body wastes like urine have been suggested by complementary medicine "therapists" for medicinal or cosmetic purposes. The fifth prime minister of India, Morarji Desai, boasted to American TV viewers in 1978 that he drank his own urine to cure his illness, and suggested that "urine therapy" was "the perfect medical solution for the millions of Indians who cannot afford medical treatment."

However, its alleged benefits have still not been proven, and "urine therapy" has not caught on.



DR. NITSAN MAHARSHAK (Tel Aviv Sourasky Medical Center)

NOW THE other kind of human body waste – feces – has entered the spotlight and actually been proven in mice and even in humans to be beneficial when transplanted for treating and even curing a variety of diseases. Numerous articles have proven these claims in serious medical journals, and non-profit "banks" of feces from healthy donors have been set up in various parts of the world. Fecal donors undergo more stringent tests than those who give blood.

Fecal microbiota transplantation (FMTs), also known as stool transplants, have been allowed by the US Food and Drug Administration for various severe gastrointestinal infections that can otherwise be dangerous and even fatal. The FDA approves it with certain restrictions, such as the patient having to sign a consent form, but it doesn't have to be carried out as part of a formal clinical trial. Thousands of FMTs have already been performed in the US.

While stomach-turning, the idea of treating gastrointestinal disorders with fecal matter should not be considered outrageous. Rabbits and other animals lick their own feces without getting sick. Other plant-eating mammals such as hipopotamuses, elephants, pandas and koalas are born with sterile intestines, so to colonize them with beneficial bacteria, they eat their mothers' feces. Veterinarians routinely take care of cattle and sheep by feeding them the contents of part of the stomachs of healthy animals.

In fact, stool transplants were used on humans in China thousands of years ago, when its medical literature described cooking up "suspensions" of it to treat diarrhea and food poisoning. Some 400 years ago, a Chinese expert named Li Shizhen wrote "recipes" for "yellow soup" made from stool and water to be drunk by people with gastrointestinal problems. Even Beduins have been known to serve camel stool to treat dysentery caused by pathological bacteria.

Since 2014, Tel Aviv Sourasky Medical Center has had the country's first fecal (bacteriotherapy) transplant

clinic for treating and even curing Clostridium difficile infection (CDI), which can result in problems from diarrhea to pseudomembranous colitis. Dr. Nitsan Maharshak of the hospital's department of gastroenterology and hepatology will co-chair the "Microbiome" session at the IATI-Biomed 2016 conference, on May 24 to 26, in Tel Aviv together with Sourasky colleague Prof. Zamir Halpern.

Born in Israel, Maharshak studied medicine as part of the IDF's academic program, studied internal medicine at Sourasky and then spent a year carrying out immunology research at the Weizmann Institute of Science, followed by specializing in gastroenterology at the hospital.

Maharshak, who recently gave an interview on the rather queasy subject to *The Jerusalem Post*, spent 2010 to 2012 on a research fellowship at the University of North Carolina School (UNC) of Medicine, accompanied by his ophthalmologist wife and two young children (the third was born in the US). A Tel Aviv University Sackler Faculty of Medicine graduate and gastroenterologist whose main field of interest is inflammatory bowel diseases, Maharshak received a joint American Physicians Fellowship/Israel Medical Association Fellowship and a Crohn's and Colitis Foundation of America (CCFA) grant to study the microbiome with University of North Carolina expert Prof. Balfour Sartor. The UNC specialist in internal medicine, microbiology and immunology is co-director of its multidisciplinary center for inflammatory bowel disease (Crohn's disease, ulcerative colitis and pouchitis) research and treatment and continues to remain very active in the field. The young Israeli doctor studied the interaction between bacteria and the immune system of mice.

"When I returned to Sourasky, an article appeared on FMT in *The New England Journal of Medicine*, so while the subject of using feces to treat diseases naturally invites jokes, the scientific community already didn't think it was science fiction. After you

take care of a desperate patient and he recovers, I feel more satisfaction from this one-time treatment for patients than from anything else I do."

While no other Israeli hospital has a dedicated FMT clinic, a handful have done a few cases.

"Sheba Medical Center performed one on a girl; Meir Medical Center gave fecal transplants to a few patients with Crohn's disease; Shaare Zedek treated a few CDI cases, and Kaplan Medical center a few with CDI and obesity. Soroka University Medical Center is seriously planning to give FMT treatments," said Maharshak.

The average human digestive tract is colonized by as many as 1,000 types of microorganisms, most of them harmless under normal circumstances and some of them beneficial. When the gastrointestinal system goes out of balance, however, the harmless bacteria can multiply wildly and cause illness. CDI is one of the worst offenders, as the bacteria release poisons that attack the lining of the intestines. CDI, which is one of the main causes of infectious diarrhea, ranges from a transient illness to one that kills the patient. Besides loose stool many times daily, CDI can cause serious stomach pain, fever, loss of weight and even blood or pus in the feces. In some cases, it can even puncture a hole in the intestines.

People susceptible to CDI include the elderly; people who have taken antibiotics (that kill off beneficial bacteria) or have been hospitalized frequently; and long-term residents of geriatric institutions. Others at high risk are individuals with a weak immune system or kidney disease or have been treated for cancer or colon diseases. The prevalence of CDI has risen significantly in the last 20 years, said Maharshak, and in the US alone there are as many as 700,000 annual cases, including 29,000 deaths.

The figure for single CDI infections in Israel is 3,000 to 4,000. Of these, 300 to 400 have repeated, serious cases. That is the number of patients who would benefit from feces transplants, Maharshak sug-

gested. CDI will disappear as a result of fecal transplants, he predicted.

The treatment is not yet part of the basket of health services, so Israeli patients – and they are beating a path to his door – pay about NIS 2,000. A suitable (unpaid) donor is only one in 10 after intensive lab tests are conducted. Donors must be non-smokers; may not have taken antibiotics for weeks before the donation or be taking a wide variety of medications. Those barred from donating blood also may not give feces. It is preferable that the donations come from thin or normal weight donors and not from the overweight.

"We issue advertisements for donors that are answered by staff members and students." Would-be donors can give up to 30 times so that if some unknown pathogen is discovered, they don't cause an epidemic, added Maharshak.

It might be possible to take stool from children, who are more likely to have healthy gastroenterological systems.

"But taking it from a baby is risky, because they have a different population of bacteria, at least until the age of three. After that, it might be an option, but I don't know of anyone who does it, and child recipients might later become obese or suffer from some other bacteria-mediated disease. We don't know yet how to do the diagnostics," said Maharshak.

"In the future, potential donors would undergo bacteria sequencing to find those that would be the best. "But it's very important not to transmit diseases to the recipient, therefore the donors go through a meticulous screening process. The feces cannot be heated, as this would kill beneficial bacteria as well as dangerous ones. The stool is mixed with a saline solution, homogenized and filtered."

It is inserted via colonoscopy, gastroscopy (into the stomach, below the pylorus) or as an enema. Swallowable capsules have already been shown to be effective as a therapy for CDI, and few companies are working on commercializing it" said Maharshak, "but I don't see it

becoming a matter of just going to a pharmacy and buying a pill of freeze-dried feces for any disease in the near future. The transplant must be suited to the patient," said the Sourasky gastroenterologist. The side effects, such as abdominal discomfort and temporary constipation, are very minimal.

THE AMAZING thing is that FMTs will eventually be offered for a wide variety of disorders, most of them not connected to the gastroenterological system. Bacteria and inflammation are involved in many diseases, explained Maharshak, and the pathogens have influences on the metabolism and all organs. "Good bacteria can improve insulin sensitivity, even though it is not dramatic."

"The obese suffer from inflammation; psoriasis and Type II diabetes also involve inflammation. My wife, who is an eye specialist, and colleagues are now looking into evidence that non-infection eye diseases also involve bacteria."

Lab experiments on mice showed that thin rodents had different types of bacteria than the obese and that FMT from a thin mouse to a fat mouse resulted in loss of weight only when combined with the right diet. A similar study in humans, looking at the beneficial effects of FMT from thin persons to obese, type II diabetes patients, has been recently initiated by Maharshak at the Sourasky. Research on Parkinson's disease, a progressive neurological condition, will begin at Soroka soon.

"The logic behind it is that it starts with constipation and that bacteria can create and metabolize neurotransmitters like L. Dopa, of which there is a lack in Parkinson's patients."

Certain types of bacteria in the gut can leverage the immune system to decrease the severity of stroke, according to new research on mice at Weill Cornell Medical College in New York. In a study, just published in *Nature Medicine*, mice received a combination of antibiotics. Two weeks later, the researcher induced the most common type of

stroke (ischemic stroke) in which an obstructed blood vessel prevents blood from reaching the brain. Mice treated with antibiotics experienced a stroke that was about 60 percent smaller than rodents that did not receive the medication.

The microbial environment in the gut directed the immune cells there to protect the brain, the investigators said, shielding it from the stroke's full force. The findings suggest that modifying the microbiotic makeup of the gut can become an innovative method to prevent stroke. These findings interested Maharshak, but he added that he "couldn't predict if it will work in humans."

The need to make "bad bacteria" disappear and add "good bacteria," he said, "sounds easy, but biologically, it is very difficult. You have to be very exact. We don't know how to grow half of the bacteria in the body. And in the future, we will know how to change the diet to support the good bacteria."

Identical drugs work differently in two patients, Maharshak said. Some succeed, while others don't, because of differences in each patient's flora. Pharmaceutical companies might be able to make more efficient drugs by sequencing the patients' bacteria. This will truly be personalized medicine, he asserted.

Asked about the potential of viruses, fungi and bacteriophages (viruses that infect and replicate within a bacterium) for transplants and not just bacteria, the doctor said this was a possibility, but it's harder to grow them and do sequencing.

"Bacteria don't have to be enemies," he concluded. "They can be our friends. The possibilities are endless. This medical field will bring about a new world."

"In 10 or 20 years, we will have a much better understanding of pathology, the biology of diseases and diagnostics. Treatment with other drugs will change because we will know the microbiome in each individual. It could be that young people could save freeze-dried samples of their feces to save for treating them when they are older."

E. coli survive predatory bacteria by playing hide and seek

Most of the body's disease-causing bacteria are made harmless by the protective effects of the immune system. Those that manage to evade the immune system can be killed by antibiotics, but bacteria are becoming more and more resistant to a growing number of antibiotics. But Hebrew University of Jerusalem researchers, who published their findings in *Proceedings of the Royal Society B*, say that studying the struggle between bacterial predator and prey could generate alternatives to these drugs.

Consider *Bdellovibrio bacteriovorus*, a bacterial predator that is an efficient killer of gram-negative bacteria (those that don't retain the crystal violet stain used to make positive identification possible), such as the prevalent *E. coli* bacterium. It is present in soil and, just like *E. coli*, it grows in the human gut, where a complex ecosystem of bacterial inhabitants exists.

This ferocious bacterial predator enters its prey and devours it from the inside while dividing into four or six offspring and then explodes its prey and starts its hunt for the next. *B. bacteriovorus* is a formidable opponent because it is not only an efficient killer, but also very fast. Although the bacterium itself is less than one micrometer long, it can

reach speeds of 160 micrometers per second, making it the "world champion" in speed swimming and 10 times faster than *E. coli*.

"Knowledge of defense and attack mechanisms in bacteria is crucial for future development of potential alternatives to antibiotics," explained Dr. Daniel Koster, from the university's department of ecology, evolution and behavior.

"*B. bacteriovorus* kills bacteria by a whole different mechanism of action than classical antibiotics, and as such, predatory bacteria might in the future constitute a viable alternative to these antibiotics," said Koster, who led the research along with scientists from the Kavli Institute of Nanoscience at in the Netherlands.

To understand how *E. coli* is able to survive in the presence of such an effective predator, the researchers created two different environments for the bacteria – open and fragmented. In the open environment, which can be compared to a bare open surface, *E. coli* had no chance of surviving, as most of the population was eliminated within a couple of hours. But it proved surprisingly able to maintain a healthy population in an environment with many small chambers.

But *E. coli* was able to survive in the frag-

HEALTH SCAN

• By JUDY SIEGEL-ITZKOVICH

mented environment: "It seems that groups of them 'hide' in the many corners of the fragmented environment, where they readily stick as biofilms that probably protect them against *B. bacteriovorus*. Our findings provide important information because in natural environments, such as our gut, the bacterium also lives in fragmented spaces."

It is not yet known precisely how *E. coli* is able to defend itself against predatory bacteria, but the research contributes to the understanding of their behavior, and this could become an alternative to antibiotics in the future. "In the future, predatory bacteria could be genetically modified to specifically target harmful bacteria, while leaving benign bacteria untouched. As such, *B. bacteriovorus* might be more selective than the antibiotics currently in use, and anti-bacterial treatment might not require the widespread extermination of the gut flora that is of importance to human health, he concluded.

SMS FROM BEERSHEBA HOSPITAL
Soroka University Medical Center in

Beersheba has introduced a new service that will calm patients and relieve tension and uncertainty. Hundreds of people arrive at the emergency department every day, and all of them want to speak to doctors or nurses about their condition. Now they can receive SMS messages in their cellular phone with information on the stages of their treatment until they are discharged. There are five types of messages: one sent after reaching the reception desk; what doctor will see them; the name of the nurse in charge, the arrival of blood tests at the lab and the doctor's decision whether the patient will be hospitalized or sent home. The SMS also provides data from a number of computerized hospitalized systems in the hospital.

GREEN TEA COMPOUND BLOCKS RHEUMATOID ARTHRITIS

Researchers at Washington State University have identified a potential new approach to combating the joint pain, inflammation and tissue damage caused by rheumatoid arthritis.

Their discovery was recently featured on the cover of *Arthritis and Rheumatology*, a journal of the American College of Rheumatology. Rheumatoid arthritis is a debilitating

autoimmune disorder that affects the small joints of the hands and feet, causing painful swelling that progresses into cartilage damage, bone erosion and joint deformity.

"Existing drugs for rheumatoid arthritis are expensive, immunosuppressive and sometimes unsuitable for long-term use," said Salah-uddin Ahmed, the lead researcher.

His team evaluated a phytochemical called epigallocatechin-3-gallate (EGCG) with the anti-inflammatory properties found in green tea. Their study suggests that EGCG has high potential as a treatment for rheumatoid arthritis because of how effectively the molecule blocks the effects of the disease without blocking other cellular functions.

"This study has opened the field of research into using EGCG for targeting TAK1 - an important signaling protein - through which proinflammatory cytokines transmit their signals to cause inflammation and tissue destruction in rheumatoid arthritis," said Ahmed. The researchers confirmed their findings in a pre-clinical animal model of human rheumatoid arthritis, where they observed that ankle swelling in animals given EGCG in a 10-day treatment plan was markedly reduced.