

DIARRHEA DIGEST

DIARRHEA DIGEST is an irregular publication of TECHLAB® dedicated to the etiology, diagnosis, and therapy of diarrheal diseases and related aspects of intestinal ecology

SPRING 2005

New Approaches for Crohn's Disease

Several years ago, a teenager went into a McDonalds, ordered a Big Mac, and decided to include a salad, some fruit, and even some fries. The teenager sat down, ate her food, and enjoyed every bite --- without worrying about abdominal cramps, diarrhea, and bleeding. No attack of painful diarrhea, running to the bathroom, trying just to get home and get more comfortable. No more prednisone, a steroid that treated her intestinal inflammation but which caused osteoporosis because it prevented her body from taking up calcium. No more being hooked up to an intravenous tube for night feedings. No more lying awake worrying about having to undergo a colostomy and wear a waste bag. All because she had undergone a brand new experimental procedure. This teenager was the first Crohn's patient to have her immune system rebuilt so that her own cells did not attack her intestine and cause uncontrolled inflammation. Her own stem cells were used for this procedure.

Crohn's disease and ulcerative colitis (UC) form the two main subgroups of inflammatory bowel disease (IBD). Both diseases are chronic illnesses that involve intestinal inflammation but greatly differ in disease presentation and medical treatments. Crohn's disease can occur anywhere along the gastrointestinal tract and can even manifest extra-intestinally in the form of skin rashes and iritis. The characteristic inflammation of Crohn's disease usually affects the small intestine with or without colonic involvement,

and extends deep into the entire thickness of the bowel wall. In severe cases, patients can suffer from fistula, diseased inflamed tissue that burrows through the entire bowel wall and forms sinus tracts that may connect to other tissues and organs. Ulcerative colitis, on the other hand, is confined to the colon and involves only the inner most intestinal lining that comes in contact with the luminal contents. Some cases of Crohn's disease present as UC-like, making it difficult to distinguish from UC even with the use of histological analysis. Surgery is restricted to severe cases of IBD that are refractory to drug therapy and may result in the removal of large sections of bowel and even the entire colon (colectomy).

A diagnosis of IBD is rare in children under 5 years, with the majority of Crohn's disease and UC first occurring in teenagers and young adults. It is estimated that there are approximately a million cases of IBD in the U.S. with about a 50/50 split between Crohn's disease and UC. Epidemiological studies show a significantly higher incidence of IBD in industrialized countries suggesting that too much cleanliness may lead to a weaker immune system and result in autoimmune diseases like allergies and IBD.

Infliximab, worms, and antibiotics

Through efforts of a number of organizations, including the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the Crohn's and Colitis Foundation, and the American Gastroenterological Association, progress has been made into the development of new treatments of Crohn's disease. Infliximab, which targets a protein involved in eliciting inflammation, is among the more notable. This monoclonal antibody, which

WARNING! This newsletter contains explicit intestinal information and portions may be rated BS for content. Readers are advised to proceed at their own discretion.

is a chimeric (mouse/human) antibody, binds proinflammatory TNF- α and appears to be especially useful in the treatment of fistulas.

An alternative therapy that is demonstrating remarkable success is treatment with pig whipworm eggs. The German company called BioCure hopes to launch their product called TSO (*Trichuris suis* ova) for treating IBD patients. *T. suis* is a parasite that does not live very long in the intestine but which survives long enough to apparently help control our intestinal immune responses, according to Dr. Joel Weinstock (University of Iowa). In trials in the U.S. involving 100 patients with Crohn's disease and 100 with ulcerative colitis, the remission rate was 70% for Crohn's and 50% for ulcerative colitis.

There have been a number of theories attempting to explain Crohn's disease as an infectious disease, particularly the involvement of *Mycobacterium avium* subspecies *paratuberculosis* (also called MAP). Recent studies by Dr. Robert Greenstein (VA Medical Center, Bronx) have shown the presence of RNA belonging to MAP in 100% of Crohn's patients he has examined. MAP grows slowly but can be treated with extended doses of antimycobacterial therapy, an approach used by Dr. Thomas Borody (Sydney, Australia), the Director of the Centre for Digestive Diseases. Dr. Borody has utilized a combination of rifabutin, clarithromycin, clobazimine, and ethambutol over a three-year period in his Crohn's patients, and has seen cure rates of 20-25% in his patients. Most of the remaining patients have gone into

remission, with some minor residual symptoms. The patients that he has treated are those who are the sickest. They fly to Australia from the U.S. because none of the traditional treatments they have tried have helped.

The Stem Cell Approach

A new somewhat controversial research initiative encouraged by NIDDK and other organizations is the development of stem cells that can help to rebuild the immune system in the gut. There are two basic types of stem cells that have been in the News. Embryonic stem cells are the cells derived from the inner cell mass of an egg within days after fertilization. They are the cells capable of generating any tissue in our bodies. Embryonic stem cells are at the heart of ethical issues because they surround the question of when life begins and whether we should even be using these cells. Adult stem cells are the other type of stem cell. Unlike embryonic stem cells, adult stem cells are obtained from tissues and organs such as the brain, muscle, and from bone marrow. They can be grown *in vitro* and retain the ability to differentiate into various cell types --- cartilage, bone, brain cells, intestine, pancreas, liver --- more than 200 cell types so far. In the lab, for example, fat cells can be differentiated into muscle cells or into blood vessel cells.

Adult stem cells may not be quite as versatile as embryonic cells, but they are autologous. You can collect these cells from a patient and use them again in the same patient, thus minimizing the chance of immunologic rejection. Stem cells are a hot research item because they offer the potential for curing diseases that are chronic and that are difficult to treat or cannot be treated. Heart disease, Alzheimer's disease, different types of bone diseases, diabetes, and intestinal diseases such as Crohn's disease --- a number of diseases that may one day be treated using stem cell drugs.

The basic stem cell procedure for treating Crohn's disease is in place but the number of patients receiving the procedure so far is small. Many of the patients have undergone the procedure at Northwestern Memorial Hospital in Chicago. Some of the patients, most of whom are teenagers or persons in their 20's, have told or are telling their stories online. All are patients in which the more routine treatments are not

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working and the choice of alternative therapies has dwindled to basically nothing.

In the procedure, cells are harvested from the bone marrow. Bone marrow cells are the most primitive cells in the marrow and give rise to all other blood cells, including the immune cells. The patient is treated with medicine to draw the cells into the circulation for collection purposes. Next, the patient undergoes chemotherapy for a four-day period to destroy the immune system. Many scientists consider the immune response in a Crohn's patient to be abnormal because it attacks the intestinal tract. By destroying the immune cells, the attacking cells are destroyed but so are all the other immune cells. This is the basis for rebuilding the immune system by infusing the stem cells back into the patient. Hopefully, the stem cells create a new immune system that no longer recognizes and attacks the intestine. For several weeks, the patient is kept in a sterile environment to allow the "new" immune system to develop. The procedure is very risky because an infection can be fatal. For this reason, it is under much scrutiny because Crohn's disease usually is not fatal. Some question whether the benefits of performing the operation outweigh the risks of the disease. In addition, there are questions as to whether this disease is actually autoimmune in nature and whether the immune system is functional.

The stem cell procedure has been utilized cautiously. It has only been done in extreme cases in which the patient is suffering tremendously and is not responding to more traditional therapies or to newer treatments such as Infliximab. From the online diaries, it is obvious that the concerns with this procedure have been well discussed with the patients. The patients have thought through the ramifications, discussed the procedural risks with family members, and believe that the risks are worth it. Although it is preliminary, the reports to date suggest that most patients have responded well to the treatment, some apparently being cured and the majority of others undergoing remission. In one retrospective study, none of the 10 patients receiving the treatment exhibited IBD except for one patient who had mild symptoms early after receiving the stem cells. In another retrospective study, patients exhibited a reduced Crohn's disease Activity index (which is a measurement of how active the disease is) and were in

remission. All of the patients will be monitored for a number of years for more extensive evaluations, allowing physicians to critically evaluate the status of their patients. So far, the results are very promising. As one of the patients stated, "If it takes a couple of months to have a procedure that could dramatically improve my quality of life, it's a reasonable trade-off. I have a life to live."

The cost of the procedure is high --- between \$100,000 and \$200,000. Fundraisers are being used to help pay these costs since the procedure is still considered experimental, but it's amazing where the money comes from. The Mother of one patient noted that she received a phone call from a telemarketing agent asking for a donation. She said that her daughter had a chronic illness, was receiving a stem cell transplant, insurance won't pay for it, and they have to raise \$100,000. She could not afford to buy anything the agent was selling. The agent responded "Where to send it?" "Send what?" the mother asked. "My donation", the agent said. "I want to help".

D. Lyerly

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Getting Tiny with Taenia

We live in a diet-crazed nation. Millions of Americans have modified their eating habits in an effort to lose those unwanted pounds, some with greater success than others. There seems to be a diet for anyone and everyone who wishes they had a smaller waistline. From Atkins to South Beach to the Grapefruit diet, the options

are limitless. However, so are the opinions about these diets. Fad diets have existed for as long as we have been concerned about our bodies and some of these meal plans have been worse than others. The Vinegar diet and the Bland diet were both popular at one point. Individuals prescribing to the Vinegar diet were required to swallow 2-3 teaspoons of vinegar before each meal while Bland dieters simply avoided fatty, flavorful foods. While neither of these sounds appealing, neither is as bad as the Tapeworm diet, which has to be one of the most disturbing and infamous methods for losing weight.

First popularized in the 1920's, the Tapeworm Diet required individuals to ingest the eggs of this intestinal parasite. The origin of these eggs is unclear, but most were swallowed as pills. Once the worm matured in the intestine, it would attach to its host's small intestine, live off the blood and probably eat anything passing through. The worm was left alone (in other words, no treatment) only until the unwanted pounds were shed. After that, the worm was removed. How? The three most common ways involved hot milk, steak, and a cookie. While these three methods are slightly different, supposedly all relied on the worm to "come looking for the food item" placed outside its host. Think about that --- it's easy to understand why most of the public didn't cling to this diet for long. The potential side effects of a tapeworm infection were enough to deter most people from seeking this form of weight loss.

This diet relied on the three species of tapeworms that infect humans, *Taenia saginata*, *Taenia solium*, and *Taenia asiatica*. These worms are found in cattle, pigs, and fish, respectively. *T. asiatica* is found mostly in Asia while the other species are found worldwide. The pork tapeworm, *T. solium*, uses pigs as its definitive host. Humans, the intermediate host, are infected by consuming raw or undercooked pork products. The lifecycle for *T. saginata* is not very different from its pig counterpart. Except for cattle being the definitive host, the lifecycle of both parasites is nearly identical, with one notable exception. The oocysts, or larval stage of *T. solium*, do not differentiate between definitive and intermediate host. If humans ingest this larva, it will migrate through the host intestine into the tissue and lodge itself in the muscle where it will wait to be consumed,



The Minnesota based Museum of Questionable Medical Devices sells posters in their gift shop that advertise sterilized tapeworm eggs as a miracle weight loss drug. Bob McCoy founded the museum and has since then moved it to The Science Museum of Minnesota and retired.

a condition referred to as cysticercosis. This is problematic for the host, mostly because the larva can migrate to the brain, causing neurological problems, including seizures and speech problems. Outside of this condition, which is very difficult to treat, other symptoms of infection include abdominal cramping, mal-absorption of nutrients, weight loss, the shedding of tapeworm segments and possible bowel obstruction. Because tapeworms can grow to lengths nearing 25 feet, or about as long the average human intestine, its easy to understand how this could happen.

It is little wonder that people have questioned the authenticity of the tapeworm diet. Although its not possible to believe everything on the web, a simple search reveals many sites claiming this diet is, in fact, real and even very effective. Maria Callas, an opera singer, has been accused of using this diet as a form of weight loss. While

she did indeed suffer from a tapeworm infestation, it was the result of her inclination for raw and undercooked beef. As recently as last year, a press release claimed that this was the latest diet craze in Hollywood. Celebrities dined at restaurants that served undercooked meat contaminated with tapeworm larva, and paid over \$100 for the dish, just to get a tapeworm infection. There are several websites that advertise tapeworm diet pills, but no site has them listed under products for sale. One site even proclaimed the effectiveness of the tapeworm diet (www.tapewormdiet.org) --- we're sure it does, but only under pretty extreme conditions. According to this site, the diet should be available to the Public after they clear up their legal issues. Another search turned up a message board of postings for individuals looking to purchase diet pills containing tapeworm eggs. There are just as many sites claiming this diet is nothing more than an urban legend, much like what happens when you drink soda while eating Poprocks candy --- you blow up.

The variety of diets available to the masses is amazing. Anyone can go to ediets.com or any one of the many other diet websites available and look for the plan that best suits their weight loss goals. There are also a variety of diet pills available that claim to suppress appetite, increase metabolism, or prevent fat and carbohydrate absorption. It's easy to understand why some of these diets have disappeared. After reading about some of these diets, especially the Tapeworm diet, the Atkins plan doesn't sound so bad.

Krista Tygrett

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The Tapeworm Diet, www.tapewormdiet.org

Clostridium difficile Outbreaks

An ongoing outbreak of *C. difficile* disease in Canada has been in the news because of how severe it is. It has been estimated that in 2004 in the Montreal area alone, over one thousand people died with *C. difficile* antibiotic-associated diarrhea. *C. difficile* was not claimed to be the

cause of all these deaths, but we consider the close association of this highly toxigenic anaerobe with the high number of deaths to be striking. Studies similar to those in a recent Pittsburgh outbreak are underway to determine the toxinotype of strains associated with the problem in Canada.

The "toxinotype" profiles of clinical isolates of *C. difficile* appear to be broadening. Two major groups (typical and atypical) of toxigenic *C. difficile* are recognized and have been subcategorized into 17 (or more) toxinotypes based largely on restriction polymorphisms. The "typical" strains include those that produce toxin A and toxin B comparable to the toxins produced by *C. difficile* VPI strain 10463, considered by many to be a prototype strain. This type of isolate is responsible for most cases of *C. difficile* disease. Until recently, the "atypical" strains were characterized by their ability to produce an altered, more active toxin B while carrying a truncated toxin A that is not expressed. Now an isolate has been identified that carries the genetic makeup to produce an atypical toxin B plus a typical toxin A. In these isolates, the atypical toxin B is very much like the lethal toxin of *C. sordellii* (toxin LT), which has a broader ability to target and inactivate the G-proteins that regulate our cytoskeletal system. As a result, the atypical B is more toxic than typical toxin B. The toxin A in the recent clinical isolate appears to encode a 10463-like toxin A.

Another group of clinical isolates have been identified that carry the gene for a third toxin, designated Cdt. Cdt is a binary toxin (i.e., it consists of two nonlinked polypeptides) very similar to iota toxin from *C. perfringens* and *C. spiroforme*. In *C. spiroforme*, which is an animal pathogen, iota toxin has been shown to be a virulence factor. *C. difficile* isolates from the outbreak in Pittsburgh have been shown to carry all three toxin genes --- toxin A, toxin B, and Cdt. In addition, the outbreak strain appears to have increased resistance to fluoroquinolone. In the Pittsburgh outbreak, there was a higher incidence of *C. difficile* disease, and infected patients exhibited worse symptoms (e.g. speed of progression) and poorer outcomes (e.g. colectomy, death).

Have these isolates been around for some time and we simply are now seeing them for the first time because we have better diagnostic

tools? Or are we creating a hotbed of opportunity for *C. difficile* to exchange DNA through “over-prescribed” antibiotics? Whatever the cause, we all need to realize that *C. difficile* disease is not decreasing. Instead, outbreaks are increasing and they now are being caused by isolates that are potentially more dangerous.

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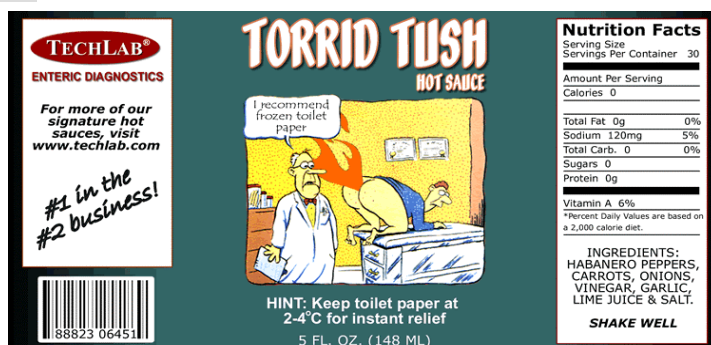
A Salute to Dung!

Coprolites, derived from Greek origins meaning dung stone, are fossilized dung. The town of Bassingbourn, England, was once a hotbed of coprolite mining, and the villagers are now trying to decide whether to have a statue of dung to represent the town. This has become such a big decision that it's making International headlines. In the 19th century, coprolite mining was big in this part of England. In fact, turning the coprolites into fertilizer was a primary business of the town. Pockets of fossilized dung were concentrated in the area partly by the way in which the tides washed through the region. Local villagers found that the washed coprolites had a high phosphate content, and that the coprolites could be turned into powder through a lot of backbreaking digging and smashing. Mining the coprolites was hard work as evidenced by local medical records showing a lot of hernias in the village population. The villagers would take the coprolite powder and mix it with sulfuric acid, turning it into a superphosphate, making it the world's first super fertilizer. As a result of this discovery, profits from sale of the fertilizer supported

the growth of the town, leading to new churches and town buildings. The local economy grew, but the growth was accompanied by inflation due to the booming business, creating some problems for the town. The coprolite business lasted about 40 years, but fizzled due to competition with fertilizer companies from other parts of the World. Presently, the townspeople are at odds as to how best represent the town. Some feel that coprolite mining led to the growth of the area and that their coprolite history is something to be admired. Others feel that their proposed statue, which will have four bronze beach ball-sized dung globes on top of a 3-foot brick platform and a price tag of about \$20,000, will make them a laughing stock and damage their reputation. The fate of the statue is being watched internationally as far away as Australia, Canada, and Bangladesh. Locally, the outcome is probably being eyed by local pigeons saving up for guano target practice.

From Fiber to Fuel

Remember how early settlers used buffalo chips for fuel? Some day in the not-too-distant future, we may be driving cars based on the same principle. In fact, the stuff we flush down our sewers could be the source of the fuel. The BBC NEWS recently carried a story describing a vehicle powered by manure. The picture in the article indicated that the vehicle was a mini-van of some type, so we're talking about enough power to move a pretty good-sized vehicle. The power source for the fuel is the methanogenic bacteria that live in our intestines. The anaerobes in our large intestines eat the bits of food that our small intestine leaves behind, and the methanogens utilize H₂ and CO₂ to produce methane gas, which is energy-efficient. Some of us are more able to do this than others (I guess that could be seen as a compliment). Cows, who



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put away a lot of grass each day, are an exceptionally good source of methane. The millions of cows that are raised on this planet release tons of methane into the atmosphere each day. The methane certainly is not good for our atmosphere. Environmentally speaking, it's worse than releasing CO₂ into the air.

What makes the concept of "fecal fuel" especially attractive is the fact that unlike the fuels we now use, this "biogas" energy source is entirely renewable and totally organic. Plus, by using it as an energy source, we get rid of something that's not good for the air we breathe. So in a nutshell, we grow the grass to feed the cows who make the fuel that makes our wheels go round. The possibilities are unlimited. One day in the future, instead of looking for a Service Station selling gas at \$\$\$\$ a gallon, perhaps we'll look for a Rest Stop along the Interstate, pull in, visit the restroom, and then fuel up with energy-efficient and environmentally-friendly methane. This way, both you and the car will be ready to go!

Toilet Entrepreneurs

Two entrepreneurs recently put their time on the John to good use. The first invention to get our attention is the Big John Toilet Seat. It seems that the regular plastic toilet seats just don't hold up the new steroid-popping, Big Mac crowd. This jumbo seat is more than 2 inches thicker than the regular old WalMart special so it won't break at an inopportune moment. With a weight limit of 1200 pounds, it would seem to have an adequate safety factor built in. Obviously, it is also a lot wider to fit a larger rear end, the hinges are beefed up and the hole is bigger. The toilet-inspired inventor, Mr. Aitan Levy was quoted in the Los Angeles Daily News as saying that "Everybody wanted one, large people break seats all the time. It's unbelievable the response we are getting". You can find out where to buy one at the website www.bigjohntoiletseat.com. Last we checked, they were just under \$100.

The second invention keeps your cat or your brat from unrolling the toilet tissue all over the bathroom floor. The simple latch only costs \$6.95. It was invented by a former Clinton White House Staffer (no not HE). She also makes little stickers for your child's shoes with a picture of a duck for left shoes and puppy for

right shoes --- whatever happened to straw foot, hay foot? OK, go ahead and laugh up your sleeve --- but she says sales should go over \$1 million this year.

WARNING: Insert Ear Plugs Prior to Flusing! Another market might be warning signs for the bathrooms of those of you who have "pressure-assisted toilets". A big jolt of compressed air pushes the water down the drain in these babies and it sounds like a turbo hurricane just visited your bowl. You definitely should wait until you get up to push the lever. But the big selling feature is that they are strong enough to "flush a cat". Perhaps they could use a Big John Toilet Seat too ...

You've heard the line "*What happens in Vegas stays in Vegas?*" Thank goodness it does! Supposedly a hypnotist at one of the big shows was using a watch to work his magic --- you know the line, you are getting sleepy --- and had many of the people in the audience under his spell. Suddenly the watch slipped out of his hand, fell onto the floor and broke. The hypnotist exclaimed "Oh crap." The hotel staff spent three weeks cleaning up the hall.

Upcoming Meetings

Digestive Disease Week, Chicago, IL, May 14-19, 2005.

American Society for Microbiology, Atlanta, Georgia, June 5-9, 2005

45th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, Sept. 21-24, 2005

American Society of Tropical Medicine and Hygiene, Washington, DC, Dec. 11-15, 2005

Fifth International Conference on the Molecular Biology and Pathogenesis of the Clostridia, Nottingham, England, June 21-25, 2006

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