# Oral Pig Worm Therapy Curbs Crohn's Disease

BY BRUCE JANCIN
*Denver Bureau*

COLORADO SPRINGS — The "absolutely astounding" recent success in treating Crohn's disease by feeding patients live ova of the pig whipworm opens the door to an exciting new approach to treating autoimmune diseases, J. John Cohen, M.D., declared at a meeting of the Colorado Chapter of the American College of Physicians.

Crohn's disease is characterized by a marked imbalance between T helper cell type 1– and T helper cell type 2–derived cytokine activity. Worm therapy aimed at blunting the proinflammatory T helper cell 1 (Th1) overactivity that defines the disease proved remarkably effective and safe in the groundbreaking initial 24-week open-label study conducted at the University of Iowa.

"I've got no idea whether pig whipworm eggs are going to catch on in clinical practice, but we're now beginning to realize that whether the Th1 or Th2 response dominates in response to a particular antigen determines what the outcome of your infection is going to be. And it looks from this study like we're at the very beginning of being able to manipulate the direction in which the body's immune responses will go," said Dr. Cohen, professor of immunology at the University of Colorado, Denver.

The Iowa study, led by digestive diseases division head Robert W. Summers, M.D., and funded by the Crohn's and Colitis Foundation of America, involved 29 patients with severe longstanding Crohn's disease who consumed pig whipworm ova every 3 weeks. At 24 weeks' follow-up, the disease response rate was nearly 80%, and the remission rate was 72% (INTERNAL MEDICINE NEWS, July 1, 2004, p. 65).

Patient compliance was high. There were no treatment side effects, even among the 14 patients on concurrent immunosuppressive therapy with corticosteroids and/or azathioprine. In fact, subgroup analysis suggested patients on immunosuppressive drugs responded better to worm therapy, as did those with an intact terminal ileum. The Iowa group noted that the observed response rates were far greater than would be expected with placebo and concluded that their data warrant a definitive, double-blind, placebo-controlled trial (Gut 2005;54:87-90).

"I think this is an incredible paper," Dr. Cohen said.

He explained that this novel therapeutic approach followed from the epidemiologic observation that inflammatory bowel disease is largely confined to the developed world, where helminthic colonization is uncommon, and is rare in developing nations, where a great many people carry parasitic worms in the gut.

Cytokines produced by Th1 cell activation—namely interleukin 2 and interferon- —suppress Th2 cells, while the Th2 cytokines (interleukins 2, 5, and 10) exert an anti-inflammatory effect by suppressing Th1. Helminthic infection triggers a powerful Th2 response, both in animal studies and now in the Iowa study participants with Crohn's disease.

Worm infection also appears to activate T regulatory cells. These cells, which comprise about 5% of all T helper cells, produce transforming growth factor- , which markedly suppresses other T cells' immune responses.

"A large focus of future research will be on how to deliver antigen specifically to T regulatory cells to downregulate unwanted immune responses. In the meantime, that's where the worms come in," Dr. Cohen said.

Swallowing the ova of the pig whipworm, *Trichuris suis*, results in brief, self-limited colonization in humans without causing disease. The ova used in the study were collected from pathogen-free pigs and treated to render them free of bacteria.

In a commentary that accompanied the Iowa study, Graham Radford-Smith, M.D., of Royal Brisbane and Women's Hospital, hailed it as "important and innovative." But he offered a cautionary note: Animal studies as well as a single recent clinical case report suggest helminthic coinfection with *Campylobacter jejuni* and perhaps other pathogens may result in septicemia and other serious adverse effects. This raises the possibility that candidates for worm therapy might need to be screened for carriage of selected pathogens.

Such concerns could be bypassed by identifying worm antigens that are responsible for the therapeutic effect and then administering the purified molecules orally. One possible candidate is the schistosome oligosaccharide lacto-*N*-neotetraose, according to Dr. Radford-Smith (Gut 2005;54:6-8). ■

# Gene Variants May Predict Upper Gastrointestinal Disease in Crohn's

ORLANDO, FLA. — Crohn's disease patients with two allelic variants of the *NOD2/CARD15* gene have an increased risk of upper GI disease involvement, Houssam E. Mardini, M.D., reported at the annual meeting of the American College of Gastroenterology.

Genetic testing of patients in an inflammatory bowel disease database revealed that six of nine patients with Crohn's disease in the upper GI tract had two allelic variants of the *NOD2/CARD15* gene. In comparison, a significantly lower percentage of patients without upper GI disease had two allelic variants of the gene (4% of 169).

"Our data suggest that patients with two *NOD2/CARD15* allelic variants should be carefully evaluated for upper GI involvement," Dr. Mardini and his associates said in a poster presentation.

*NOD2/CARD15* is so far the only gene that is highly associated with Crohn's disease.

Four of the patients with upper GI disease had homozygous allelic variants, whereas none of the patients without upper GI disease were homozygous for an allelic variant.

Wild type alleles of *NOD2/CARD15* occurred in 68% of the patients without upper GI disease; another 28% of those without upper GI disease had one allelic variant.

Compared with patients who did not have upper GI disease, significantly more of the patients with upper GI involvement had a family history of inflammatory bowel disease (19% vs. 44%), were male (41% vs. 78%), and were younger at diagnosis (25 years vs. 17 years).

Osteopenia or osteoporosis developed significantly more often in patients with upper GI disease than in those without (33% vs. 9%).

**—Jeff Evans**

# *CBT Relieved Depression In Patients With IBD*

Adolescents with inflammatory bowel disease and either major or minor depression showed a significant reduction in depressive symptoms after 12 sessions of a manual-based cognitive-behavioral therapy program, reported Eva Szigethy, M.D., of Children's Hospital Boston and her associates.

In a pilot study, 11 adolescents aged 12-17 years participated. Seven patients had Crohn's disease and four had ulcerative colitis, with an average of 40 months' duration (J. Am. Acad. Child Adolesc. Psychiatry 2004;43:1469-77).

Scores on the Children's Depression Inventory dropped from 16.18 before treatment to 4.82 after treatment. At baseline, all the teens reported depressed mood and anhedonia; 10 reported sleep disturbance and fatigue.

Although illness severity remained the same, the adolescents' own perception of their physical functioning improved by the end of the study period.

**—Heidi Splete**

# Probiotic Drink Cut Cases of Antibiotic-Associated Diarrhea in Hospital

BY JEFF EVANS
*Senior Writer*

ORLANDO, FLA. — Daily intake of a lactobacilli-fermented milk may help prevent antibiotic-associated diarrhea in hospitalized patients, Natalie A. Fortier reported at the annual meeting of the American College of Gastroenterology.

Few of the published studies on the use of probiotics to prevent antibiotic-associated diarrhea have had a strong randomized, placebo-controlled design, said Ms. Fortier of the University of Montreal.

The daily drink, which contained 50 billion colony-forming units of live *Lactobacillus acidophilus* and *L. casei*, was associated with significantly fewer cases of antibiotic-associated diarrhea (7 of 41 patients) than was a placebo drink composed of lactoserum that was devoid of any microorganisms (16 of 43 patients).

Ms. Fortier and her colleagues at the university defined antibiotic-associated diarrhea as three or more liquid stools in a 24-hour period in the randomized, double-blind trial.

The researchers provided the active treatment or placebo daily to adult patients with an average age of 70 years on the 7-10 days that they were taking antibiotics.

The researchers then obtained follow-up from the patients for 21 days after they stopped taking antibiotics.

The patients began prophylactic treatment in the first 48 hours after starting antibiotics, which were primarily for upper respiratory tract infections.

Those with active diarrhea, GI bleeding, inflammatory bowel disease, *Clostridium difficile* infection in the last 3 months, a high risk of an immunocompromised state, lactose intolerance, or a regular intake of probiotics were excluded from the trial.

Diarrhea associated with *C. difficile* occurred less often in patients who received the active treatment (1 of 41) than in placebo patients (7 of 43), although the difference did not reach statistical significance.

Actively treated patients had a significantly shorter median length of stay in the hospital, compared with patients who received placebo (8 days vs. 10 days).

Ms. Fortier and her associates obtained their results from a multivariate analysis after controlling for risk factors for antibiotic-associated diarrhea and *C. difficile*–associated diarrhea as well for the fact that significantly more placebo patients received -lactam antibiotics (67%) than did actively treated patients (41%).

Side effects—mostly of a GI nature—occurred in nearly half of patients in each group, she said.

The active and placebo preparations were provided by Bio-K+ International Inc., Laval, Que., which manufactures and markets the active treatment. ■