At Least, a Cure for Crypto?

The parasite killing PWAs may be near defeat -- if only doctors

July 1, 1997 By Marni Halasa

“Picture this: You’re in the hospital. You’re bedridden. You’re dehydrated. You’re fatigued. You’re losing so much weight that the nurses can’t find your veins anymore for your IV medications. And your little sister, whose diapers you used to change, is now changing yours. It was terribly debilitating.”

When Miami PWA Mark Snorden was hospitalized for cryptosporidiosis five months ago, he weighed 115 pounds, could barely walk without the support of a cane and was being fed intravenously.

“I had faced my own mortality a long time ago,” Snorden continues. “I had been HIV positive for 11 years and was, for the most part, asymptomatic. But crypto changed all that. It threw my mortality right into my face. I had never been so close to death.”

Today, Snorden has made an incredible comeback. After four months of treatment with an experimental drug called nitazoxanide (NTZ) and the removal of his Cryptosporidium-infected gallbladder, he has been able to quash the infection and resume a normal life. Twenty-five pounds heavier, he has more energy than ever and is now interviewing for retail jobs near the beach, while planning to return to the avocation he loves -- volunteering to help HIV positive children.

In the past 15 years, AIDS researchers have focused on finding drugs to treat HIV, placing therapies for opportunistic infections on the back burner of medical technology. But in the case of life-threatening cryptosporidiosis, persistent activist pressure has belatedly produced the first tidbits of research -- still too little, and for many, too late -- that may eventually lead to a cure, or at least a viable treatment. The scientific community faces a prickly challenge from Cryptosporidium, a tiny, single-celled protozoal parasite found in the feces of infected cows, other animals and humans. Crypto can contaminate the water supply through farm runoff or sewage leaks. Once in the body, it embeds itself in the gastrointestinal tract, disrupts the body’s vital nutrient-absorption process and causes severe diarrhea, dehydration and malnutrition. Meanwhile, although crypto is responsible for the deaths of thousands and is estimated to cause 10 percent to 25 percent of AIDS-related diarrhea, there is growing concern in the AIDS community that physicians are not taking the disease as seriously as they should.

“A lot of people have had crypto, but you never hear people give voice to it,” explains Richard

Banks, a New York City architect who was once hospitalized for the infection. “Why? Because of Americans’ innate fear of anything to do with the bowels. Doctors don’t like to deal with it. Patients don’t like to talk about reverting to the diaper stage. It’s something that mortifies most men and women.”

Another reason may be that the FDA has yet to approve any drug for this disease, although some 90 compounds have been tried. Because clinical trials of several potential treatments are still in preliminary stages, most physicians are awaiting more evidence of which drug works best.

Thus far, three of these therapies -- NTZ, Allicin and hyperimmunized bovine colostrum -- have emerged as particularly promising. Meanwhile, some clinicians argue that the most effective way to contain the infection is by boosting one’s immune system. And early reports suggest that immune-stimulating antiretroviral combinations with a protease inhibitor might become an important tool in vanquishing crypto.

But before choosing any treatment, a doctor must make the correct diagnosis. For many PWAs, that has been a problem. In the summer of 1995, John Tidrick, Jr., a chef in Akron, Ohio, watched his partner of six years, Tim Ortiz, slowly die of crypto. According to Tidrick, Ortiz’s symptoms of watery diarrhea, extreme weight loss, lack of appetite and fatigue did not persuade his doctors to test him for the parasite. It was Tidrick himself, as he put it, “just an idiot off the street,” who “had to insist” that the doctors test Ortiz for Crypto. The test came back positive, but Ortiz received no effective treatment.

Such medical laxity, according to Leanna Standish, PhD, principal investigator at the Bastyr University AIDS Research Center, amounts to malpractice. “From my experience, one of the first things that a responsible physician looks for in an HIV positive person complaining of diarrhea is Crypto. That should be standard practice.”

But James Learned, deputy director of the PWA Health Group, a treatment buyers club in New York City, says that isn’t always the case. “There are still many doctors out there who believe that diarrhea is just part of having HIV. So they don’t look for a cause.” Referring to the practice of offering only standard antidiarrheal medicines, he adds, “PWAs shouldn’t accept ’This is all we have.’ If you like your doctor, it’s pretty tough to keep demanding good stool and lab samples. But that’s what people need to do.” In fact, many experts recommend doing three separate stool analyses on three successive days to boost the chances of an accurate diagnosis.

And scientists emphasize that diarrhea in PWAs often has multiple causes. Peter Anton, MD, a gastroenterologist and researcher at the UCLA Medical School, says, “Infection -- with one or more viruses, bacteria and parasites such as Crypto -- is a major contributor. But intolerance of dairy products, fat malabsorption, drug side effects, bacterial overgrowth in areas like the small intestine, and even irritable bowel syndrome may also cause diarrhea -- singly or in tandem.” Anton cautions physicians not to jump to conclusions if a crypto treatment appears to bring no improvement. “Before labeling a therapy a failure, it’s vital to carefully evaluate all possible contributing causes of diarrhea. Each must be treated for the patient to improve.”

Once diagnosed with crypto, the treatment saga for many PWAs begins with paromomycin (Humatin), an FDA-approved drug for amoebic infections. It is the most commonly prescribed treatment for cryptospordiosis. Most studies -- though not all -- have shown improvements in from one-half to two-thirds of those on the drug, and some doctors report that higher-than-usual doses (up to 1,000 mg, four times per day) may help those for whom the standard dose (500 -- 750 mg, four times per day) is ineffective. A combination of paromomycin and either azithromycin (Zithromax) or roxithromycin (Ruclid) -- both approved MAC drugs -- has shown mixed results in clinical trials.

But the drug making health practitioners sit up and take notice is the one that saved Mark Snorden from death -- NTZ, approved last year in Mexico to treat parasitic infections. Three Mexican trials found the drug highly effective for PWAs with crypto and very low CD4 counts. Data from two were especially impressive: In one study, 98 percent of 30 PWAs resolved their diarrhea after eight weeks on the drug. Another study of 15 PWAs found that diarrhea was eliminated in 11 and stool tests became negative in all 15 after two to four weeks.

These results encouraged the manufacturer, Unimed Pharmaceuticals, to arrange a small U.S. trial. In a study at Cornell Medical Center last year, 28 patients for whom other treatments failed received NTZ for eight weeks. Half had partial or complete elimination of diarrhea, and 36 percent showed partial or complete elimination of Crypto in their stools. Generally, those on the highest doses did best -- indeed, the PWA Health Group charges that some participants were given doses known from prior research to be inadequate. The only side effect found so far, according to the Health Group, has been a green tint to urine and semen.

Patient access to the drug, however, has been plagued by difficulties that have cost lives. In March 1996, the Health Group started a waiting list of people with crypto seeking the drug. It took until June to forge an agreement with Unimed’s Mexican licensee to import NTZ -- and by then, half of those PWAs had died. (Since a successful activist campaign in 1988, the FDA has allowed personal-use importation of AIDS and cancer drugs approved in other countries.)

But this channel was quickly jeopardized when U.S. Customs officials seized the second shipment en route to New York City, claiming the Health Group was illegally importing an unapproved medication. To keep a supply of product on its shelves, the Group was forced to go through a European pharmaceutical broker, requiring transoceanic shipping that boosted the price to PWAs. After a four-month standoff, the shipment was released and the Group was fined $1,000. Today, the Health Group offers NTZ at monthly prices ranging from $165 (1,000 mg/day) to $330 (2,000 mg/day).

For the many PWAs who can’t afford these prices, the Health Group spent much of last year pressuring Unimed for a compassionate-access program, along with two clinical trials -- one for adults, the other for children. But Unimed’s president, Robert Dudley, says, “Because we have been trying to collect the data very carefully, we have not been in favor of AIDS buyers groups having free access to NTZ. I think it undermines what we’ve been trying to do [quickly enrolling clinical trials] and it can potentially have a negative impact on the timing necessary to get the

drug approved." (Unimed says it is aiming for FDA approval -- and thus prescription availability -- of NTZ by mid-1998.)

James Learned of the Health Group responds: "Unimed reneged on its promise to run a higher-dose adult trial. So how could legal personal-use imports block enrollments in a nonexistent trial? Dudley's bluster seems mostly about trying to cover up his company's clear decision to stop spending any money on developing NTZ."

After the Cornell trial ended in October 1996, it took until March 1997 -- six months later -- for a larger follow-up study to begin. (Although Dudley acknowledges the longer-than-usual launch time, he refuses to comment on the reasons for the delay.) The new trial, by the federally funded AIDS Clinical Trials Group (ACTG), is now enrolling in six cities. "It's unfortunate that Unimed left it up to the ACTG to take the research initiative," Learned says. "The ACTG can be notoriously slow and crypto is a disease where people need treatment fast."

Mark Snorden is a case in point -- delays in access to NTZ almost killed him. He remembers making frantic phone calls from his hospital bed. "I'm calling Unimed, my doctor, friends and family. No one could get me the drug. The Crypto didn't say to me, 'OK, since you don't have any NTZ, we'll wait,'" he says. Once he was treated with NTZ, however, positive things began to happen, especially after increasing his dose from 1,000 to 3,000 mg a day. "Pushing up the dosage was when the effects started to kick in. Since then, my most recent stool test has come back negative for Crypto. I have so many friends who can't kick Crypto, so the fact I got rid of it is really a feather in the cap of NTZ."

Last October, after five months of pressure by the Health Group, Unimed agreed to expand its previously small-scale open-label (uncontrolled) trial to include all people with crypto who qualified. This allowed no-charge access to the drug, but some categories of PWAs were excluded, and each participant was randomly assigned to a particular dose, with adjustments allowed only once a month. Now that the ACTG trial has opened, Unimed has blocked open-label access to PWAs living in cities participating in that trial.

John S. James, editor of AIDS Treatment News and a longtime observer of drug development, wrote last year that NTZ's convoluted journey provided "a textbook case of how institutions cannot be trusted to govern in the best interests of those they rule, and why those directly affected need their own power and their own voice. Without the PWA Health Group, the patients who obtained the drug from them would be without effective treatment."

Meanwhile, a modernized version of an ancient herbal remedy is also making slow but steady headway in the crypto research pipeline. One person who's gotten good results is Richard Banks, the architect. When he contracted cryptosporidiosis, he made sure to commute as little as possible. "I found myself getting to a destination as fast as possible so I could be near a bathroom," says Banks. "I was terrified of having an accident I couldn't control." He decided to try Allicin, a highly concentrated liquid extract of garlic's active ingredient that is widely used in Chinese hospitals to treat bacterial and fungal infections. Banks had lost 45 pounds, dropping from

his normal weight of 190 to a mere 145. Through an alternative medicine connection, Banks heard of Qing Cai Zhang, MD, a practitioner of Traditional Chinese Medicine in New York City who prescribes and sells the treatment. To Banks, who had suffered horrible side effects from the antiparasitic Flagyl, treating the infection with a natural, nontoxic agent was appealing.

“I had lived in Europe for three years,” Banks says. “Europeans taught me to dice garlic at the table if you felt sick, down it with soda water and by the next morning you’d be fine. That treatment had worked for me in the past, so using garlic made perfect sense.” Within two weeks of starting a regimen of three vials of liquid Allicin per day, Banks had more energy and was able to resume his regular activities. Within a month, his stool sample tested negative for Crypto. Several months later, he was back to his normal weight. “My doctor, a famous gastroenterologist, was flabbergasted that I was cured,” Banks says.

Such reports of Allicin’s effectiveness encouraged the Los Angeles -- based AIDS Research Alliance (ARA) to launch a small clinical trial in 1995. In that study, 20 PWAs with advanced cryptosporidiosis took high doses of Allicin for six weeks. A year ago, ARA reported that 10 of the 16 participants evaluated showed a significant reduction in symptoms caused by the parasite. Most encouraging was the finding that four of the eight patients who took Allicin for more than six weeks today continue to show no evidence of the parasite in their bodies.

But as with NTZ, access to Allicin depends on one’s ability to pay high out-of-pocket prices. The liquid form of Allicin, manufactured by the Chinese health ministry, is only available in the United States through Zhang, the New York physician, who sells it directly for $240 for a month’s supply (two 30 mg ampules per day) and wholesales it to two PWA buyers clubs (Healing Alternatives Foundation, or HAF, in San Francisco and Direct AIDS Alternative Information Resources, or DAAIR, in New York City), which charge, respectively, $258 and $120 for a month’s supply. Michael Onstott, an HAF board member, believes Zhang should offer a compassionate-use program. “Allicin is not covered by insurance. At current prices, that leaves this treatment out of reach of most PWAs.” The capsule form is available through DAAIR for $39 a month. But advocates of Allicin disagree about whether the capsule is as effective as its liquid counterpart.

A far cheaper -- but as yet untested -- alternative, according to Alejandrina Rodriguez (not her real name), mother of an HIV positive 6-year-old girl in upper New York state, is crushing five bulbs of fresh garlic into a liquid to be taken immediately. “Who knows if the Crypto is really gone?” says Rodriguez, who gave her daughter 30 ccs twice a day. “But she feels so much better. We saw results within seven days. Now she can go to Girl Scout meetings, take art classes and attend Sunday School.”

Meanwhile, this summer the ARA is launching a larger, three-city trial of Allicin with three arms: By itself, in combination with Humatin and in combination with another experimental agent to be determined. After the study gets under way, ARA hopes to arrange with the Chinese government for a direct supply of Allicin to U.S. buyers clubs. But as an unpatentable product with no big company behind it, Allicin is unlikely to win FDA approval -- the key to coverage by public and private insurance.

Yet another promising crypto treatment may soon emerge -- from the barnyard. At the University of California at San Francisco, researchers led by John Cello, MD, chief of gastroenterology at San Francisco General Hospital, are working on a potent formulation of bovine colostrum, an immune-globulin treatment that uses antibodies found in the milk of cows that have been vaccinated with Crypto (not to be confused with regular bovine colostrum sold in health food stores). “The way cows prevent lethal diarrhea in a calf is by transmitting in milk an antibody to Cryptosporidium,” Cello explains. “What we’re doing is harvesting those antibodies from the milk protein of a hyperimmunized cow.”

Last December, results were published from Cello’s study of Sporidin-G, a colostrum product manufactured by GalaGen. After three weeks, the 12 Crypto-positive patients on the powder form had an average 49 percent reduction in stool weight (a measure of diarrhea’s severity). Everyone who had lost weight before the study stabilized or gained weight on the treatment. No major side effects were found. A larger, multi-city study is under way and Cello expects FDA approval within a year.

Many AIDS doctors remain skeptical of the experimental crypto treatments. Donald Kotler, a leading New York City AIDS gastroenterology researcher and clinician, argues, “Sure, some people do OK on Allicin or NTZ. But crypto is a life-threatening disease. I don’t want to recommend something that just works OK.” Decreasing symptoms is the focus of his treatment. “I spend most of my time finding ways to keep the T-cells up, viral load down and to decrease diarrhea volume and maintain patients’ nutritional status through specialized oral diets. I’m not really thinking about a cure.”

Kotler is among the growing ranks of researchers who believe that the best treatment for cryptosporidiosis, as for other opportunistic infections, is “optimizing immune function with combination antiretroviral therapy.” Clinicians agree that PWAs with 200 or more CD4 cells are often able to spontaneously clear the infection in less than a month.

Two reports from last winter’s Human Retrovirus Conference appeared to confirm the effectiveness of protease combination treatment. Both involved small studies of PWAs with crypto and low CD4 counts -- 9 and 12 participants, respectively -- which found diarrhea elimination, weight gain and clearance of parasites in most of those on this therapy.

With or without an effective treatment, “prevention is key,” Kotler admonishes, “because we don’t know a lot about the disease. [See ”Crypto Prevention Guidelines,“ p. 78.] We’re just starting to learn how to make the diagnosis in the first place. We’ve only known about crypto for the past 15 years, while we’ve known about tuberculosis for the past 100. Everyone wants science to go faster, but I don’t know if it can.”

But other researchers are more upbeat. “I’m very optimistic about the future,” says Cello. “When I look at all the work going on about crypto, I think we are very close to finding an answer to this ubiquitous parasite. It’s definitely on the horizon.”