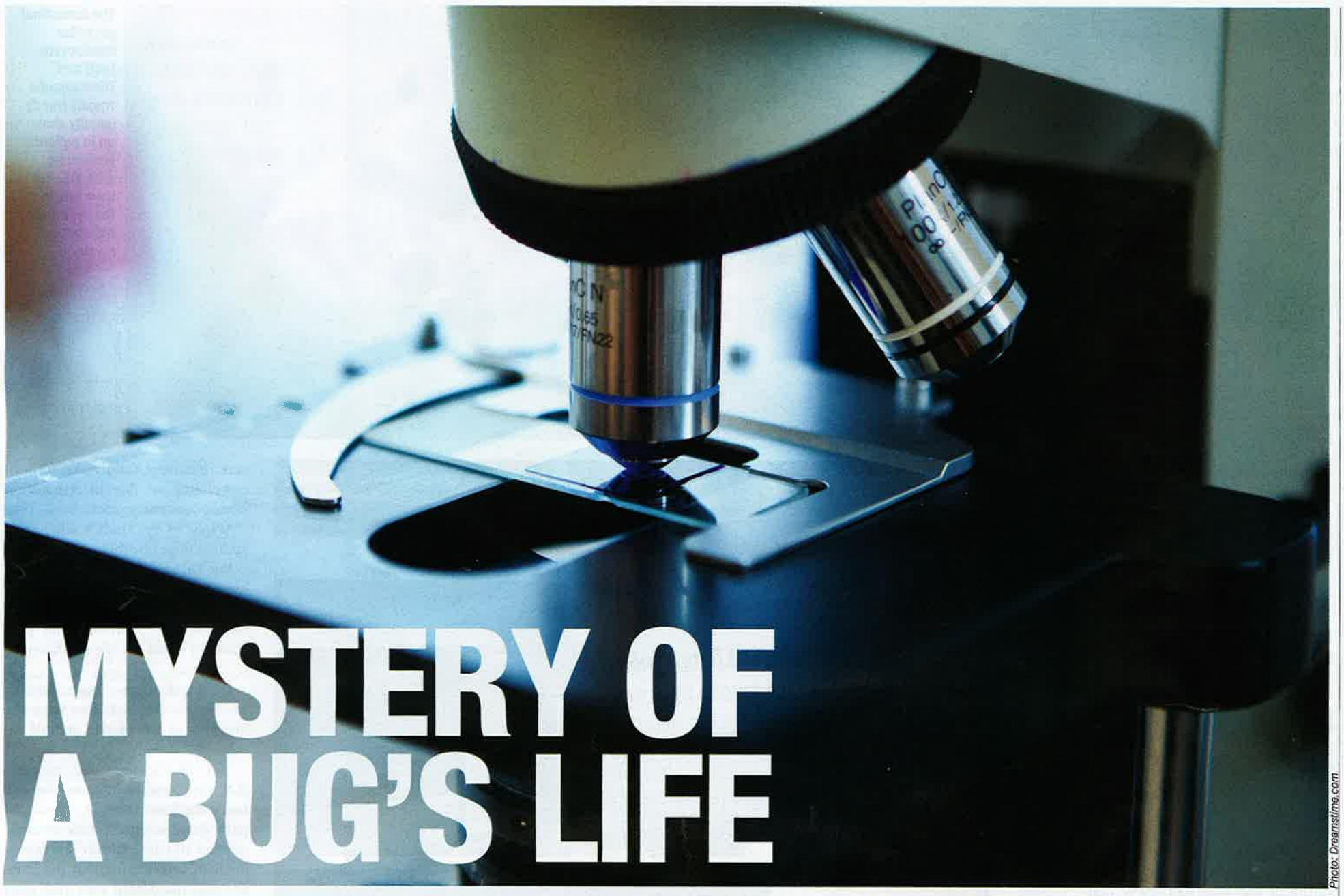


MYSTERY OF A BUG'S LIFE

Photo: Dreamstime.com

Are two controversial parasites responsible for the IBS-type symptoms patients are increasingly presenting to GPs with? TESSA HOFFMAN investigates a medical whodunnit.

PERHAPS the advent of highly sensitive pathology tests is to blame.

GPs seem to be increasingly dealing with two puzzling and controversial intestinal parasites: *Blastocystis hominis* and *Dientamoeba fragilis* which usually show up following PCR testing on patients presenting with IBS-like symptoms.

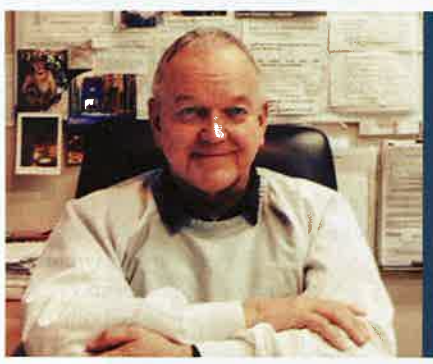
Their detection is meant to help guide treatment options, but in this case, the parasites' appearance seems to have prompted a long list of clinical questions, including the most basic: are they actually responsible for gastrointestinal disease, and if they are pathogens, how should they be managed?

Medicinal approaches

The traditional option for treating these parasites has been a course of metronidazole, but the effectiveness of the antibiotic seems far from proven.

Depending on which study you read, success rates for the treatment of blastocystis, for instance, which is present in 6% of the Australian population according to one study, ranges from a highly impressive 100% to zero.

Professor Thomas Borody — perhaps best known for his pioneering work in faecal transplants — seriously doubts whether metronidazole is the right approach. But in a confused area, he believes he has come up with alternatives.



> 'The unfortunate thing is most GPs will give a course [of] metronidazole, which makes it resistant.'
>
> — *Professor Thomas Borody, founder of the Centre for Digestive Diseases*

He says he has been using various combinations of antibiotics at the Centre for Digestive Diseases in Sydney, which he founded and is the medical director of, for the past 15 years.

This work began when a patient, Jackie Delaney, turned up on his doorstep armed with a positive test result for *D. fragilis* and a bundle of research papers on the parasite.

Ms Delaney, who runs the Bad Bugs blog (www.badbugs.org), claims Professor Borody was the seventh specialist she had seen, and the only one to take her parasite diagnosis seriously. As a result, he finally managed to rid her of the crippling IBS symptoms that had been plaguing her for years.

"The unfortunate thing is most GPs will give a course [of] metronidazole, which makes it resistant," Professor Borody claims.

"Then they send them to us. We really don't know what to do; it's very hard to get rid of.

"We try to pull together medications we've read about that have some effect. Then we say to patients, 'You've got this bug, you've got the symptoms, there's nothing else to target right now; we'd like to get rid of it if you want to.'"

Professor Borody's treatments are still in the experimental phase.

"[These parasites are] extremely hard to kill," he says. "Blastocystis especially, *D. fragilis* is a bit easier.

"We have been developing protocols over the years, but they are changing.

"We started off with single drugs about 15 years ago, then moved to double drugs and that still didn't work. So now we are at various triple combinations of various base drugs, which you can find in the literature."

The drugs include the antiprotozoal iodoquinol and the aminoglycoside antibiotic, paromomycin, which Professor Borody's patients must access through the TGA's Special Access Scheme.

When word got out about the treatments on offer, the centre was apparently bombarded with emails from people from all over the world seeking clinical advice.

Today, Professor Borody says he treats about 30 patients a month with one of four triple-antibiotic combinations.

The three oral treatments eradicate the parasites at rates of about 60-70%, he claims.

But the most promising results, according to Professor Borody, come from a newer experiment: an infusion of iodoquinol, paromomycin and the antiprotozoal agent nitazoxanide delivered directly to the gastrointestinal tract during a day procedure.

This treatment apparently has an 89% eradication rate for blastocystis, according to the interim results of a prospective study of 39 patients currently underway. Professor Borody says an abstract will be submitted to the *American Journal of Gastroenterology* this month.

But the treatments don't work for everyone. Typically, there will be two or three patients a month for whom no treatment is effective, he says.

What does he do then?

"I throw my hands up, and just don't treat them."

To date, Professor Borody says he has published a number of abstracts in peer-reviewed journals, but has never undertaken a placebo-controlled clinical trial because it would be too expensive, unless he discovers a treatment with a success rate of 90%.

There are also those who come to the centre testing positive — often at the behest of a family member — but who are asymptomatic.

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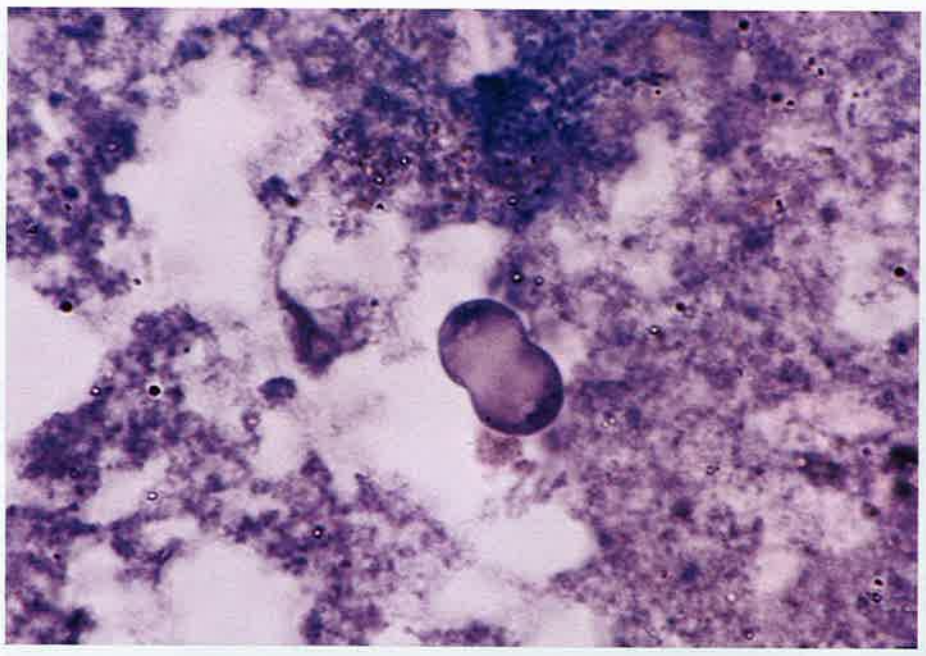

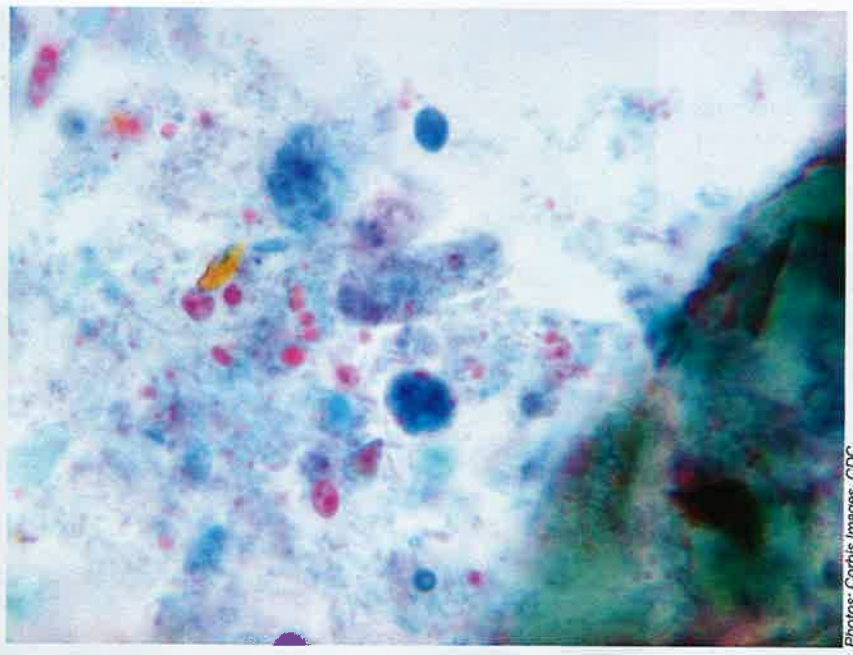

The instestinal parasites blastocystis (left) and *Dientamoeba fragilis* (right) usually show up in patients presenting with IBS. But their role in the sydnrome remains a mystery.

Photos: Corbis Images, CDC

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Professor Borody turns these people away. "I don't treat them because I don't have a 100% efficacy rate and because there is no symptom to improve upon."

Opposing voices

But not everyone approves of Professor Borody's parasite eradication treatments.

Sydney gastroenterologist Dr Katie Ellard is particularly critical of his gastrointestinal infusion treatment, which she says needs to be part of a placebo-controlled clinical trial before it is made freely available.

"One of my patients was referred there by a GP after [treatment with metronidazole failed]. She had the infusion and then had severe diarrhoea for six weeks. It did settle, but it made me think it was a result of the infusion," says Dr Ellard who is secretary of the Gastroenterological Society of Australia.

Adding to the mystery is whether blastocystis and *D. fragilis* are truly pathogens.

But Professor Borody says there is no puzzle and brands those who continue to question their pathogenesis as "uneducated, non-investigative people who are in the backwaters of gastroenterology".

"[The bugs] cause symptoms, no one doubts that. With blastocystis, we just don't know at this stage which strain.

"The controversy is finished. It's only in the minds of those who have no knowledge."

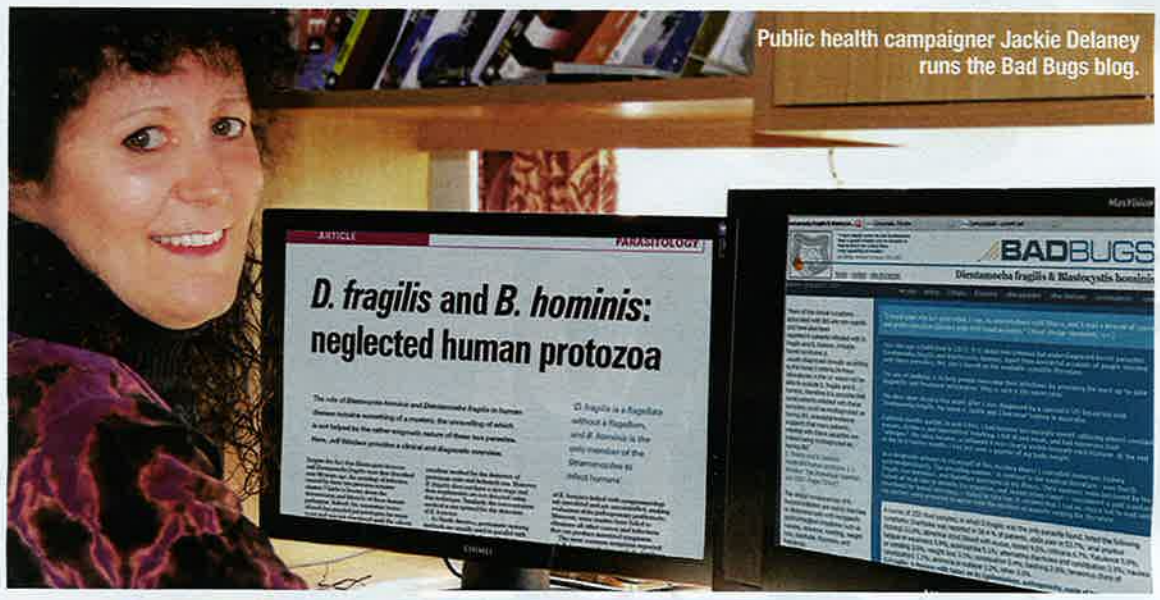
Pathogenic problems

But for others, the controversy is alive and well. Dr Harsha Sheorey is a consultant medical microbiologist at St Vincent's Hospital, Melbourne. He says increased uptake of PCR testing for patients presenting with IBS-like symptoms has caused an explosion in detection rates of both parasites, and along with them, treatment headaches for doctors.

"Most labs were testing by microscopy until a couple of years ago, and that only picks up high numbers of those bugs. We were probably missing low numbers," Dr Sheorey says.

"As a result, more GPs are trying to treat these organisms thinking they are a pathogen. [But] there is no effective treatment at this stage."

Nor are there any conclusive studies that show that either parasite is pathogenic, he says.



Public health campaigner Jackie Delaney runs the Bad Bugs blog.

'Most of us don't know what a positive test means and what the appropriate treatment is, if any.'

— *Dr Harsha Sheorey microbiologist, St Vincent's Hospital, Melbourne.*

"Studies have shown that these two bugs are not associated with IBS," says Dr Sheorey, whose laboratory carried out about 3500 PCR tests last year. "At the same time, there are other studies assuming these to be associated with IBS, but most conclude more studies need to be done to prove this."

Dr Sheorey goes as far to say that the use of metronidazole does more harm than good.

The drug often fails to eradicate the parasites and often increases symptoms by destroying the gut's 'good bugs', he says.

He points to a Danish randomised, double-blind placebo trial of 96 children with dientamoebiasis, which found that metronidazole did not significantly reduce gastrointestinal symptoms compared with placebo, and the drug's eradication rate fell from an initial 63% to 25% eight weeks after treatment.[1]

Another study shows the probiotic *Saccharomyces boulardii* had higher clinical cure rates for blastocystis than metronidazole (94% vs 73%) 2. And it turns out that garlic, used in another study, was shown to be as effective as metronidazole at suppressing the parasite's growth. [3]

Dr Sheorey advises GPs not to treat either parasite with antibiotics in almost all cases, and instead look for other causes [of symptoms] such as food intolerance or stress.

He also says Australian labs should stop testing for these parasites.

"Most of us don't know what a positive test means and what the appropriate treatment is, if any," he says. "What we do know is the drugs don't clear these parasites most of the time, and the drugs do more harm than good by upsetting the normal gut flora. After all, we are taught in medicine [to] first do no harm."

Another view

There is a third argument in the parasite debate. Dr Damien Stark, a senior hospital scientist in the microbiology department at St Vincent's Hospital, Sydney, is part of a team that has studied *D. fragilis* for more than 12 years. The team has published more than 40 articles in peer-reviewed journals.

Dr Stark and his colleagues say despite the evidence in favour of doing so, there has been a 100-year "struggle" for *D. fragilis* to be recognised as a pathogen.

"Unfortunately, the lack of an animal model for dientamoebiasis hinders our ability to demonstrate its pathogenity," they wrote in a 2011 review of *D. fragilis* carriage in humans, which outlined several reasons why the organism should be considered in the diagnosis of gastrointestinal disease.[4]

Dr Stark tells *Australian Doctor* the two parasites are very different and should not be "lumped together".

However, the balance of scientific evidence "would indicate that both organisms may have the potential to cause gastrointestinal symptoms under certain circumstances and research is needed into both these parasites to ascertain the exact role [they] play in [gastrointestinal] disease," he says.

Numerous studies have shown a clinical correlation between *D. fragilis* clearance and resolution of symptoms, Dr Stark claims.

He also rejects suggestions that metronidazole does not eradicate it.

"Our research has shown that *D. fragilis* strains are sensitive to metronidazole and the newer 5-nitroimidazoles in vitro," he says.

"When metronidazole resistance is reported, it is difficult to confirm whether this is due to true resistance, treatment failure due to non-compliance, or due to re-infection from a common source.

"None of the studies adequately address these possibilities."

But Dr Stark won't be drawn on how GPs should treat patients with IBS symptoms who test positive for the parasite. "Currently, no gold standard exists for the treatment of *D. fragilis*."

Dr Stark says more funding is urgently needed for what he describes as a neglected area of science.

"Of all the intestinal parasites that are found in humans, we still know the least about *D. fragilis*. Its pathogenic potential, mode of transmission and life cycle are still poorly defined. Considering that the parasite was discovered over 100 years ago, it is disturbing that these questions are yet to be answered.

"Given the clinical and diagnostic confusion that this parasite is causing to both clinicians and patients, we would like to see more groups studying it."

Following guidelines

In the meantime, many doctors will have to turn to the Therapeutic Guidelines, which advise GPs to only consider using metronidazole for blastocystis in symptomatic patients after other infectious or non-infectious causes have been ruled out.

The clinical significance of blastocystis is controversial, the guidelines say, with some studies showing no correlation between its presence and gastrointestinal symptoms.

The document is a little more definitive about *D. fragilis*, finding that the parasite is often associated with gastrointestinal symptoms that resolve with treatment. Symptomatic patients should be treated with doxycycline or metronidazole, the guidelines say, adding that paromomycin may also be effective.

Most GPs dealing with the steady stream of patients in search of symptoms relief will be hoping that greater insight into these bugs' lives is coming sooner rather than later. ●

References

1. *Clinical Infectious Diseases Advance Access* 2014; online. See: http://1.usa.gov/1FWsUcc
2. *Parasitology Research* 2011; 108:541-45.
3. *Parasitology Research* 2011; 109: 379-85.
4. *Gut Microbes* 2011; 2:3-12.