

NOTE: Some of the pages in this document suggest that specific type of Blastocystis are pathogenic or non-pathogenic. Based on data from the last 6 months, all types of Blastocystis can cause disease, and variation in symptoms is due to host factors, like age and genetics.

Summary of Written Communications to the NIAID from Ken Boorum, Blastocystis Research Foundation

#	Date	Official Contacted	Contact Method	Materials Provided	Response
1	6/15/2007	Dr. Anthony Fauci, Director NIAID	Letter	Copies earlier letters	None
2	6/15/2007	Dr. Ted Nash, Director Gastrointestinal Parasitology Lab	Letter	Copies earlier letters	None
3	6/15/2007	Dr. Alan Scher Co-Director, Laboratory of Parasitic Diseases	Letter	Copies earlier letters	None
4	6/15/2007	Dr. Thomas Nutman Co-Director, Laboratory of Parasitic Diseases	Letter	Copies earlier letters	None
5	6/4/2007	Dr. Ted Nash	Letter	Abstracts from studies, phylogenetic tree of Blastocystis	None
6	6/4/2007	Dr. Alan Scher	Letter	Abstracts from studies, phylogenetic tree of Blastocystis	None
7	6/4/2007	Dr. Thomas Nutman	Letter	Abstracts from studies, phylogenetic tree of Blastocystis	None
8	5/30/2007	Dr. Ted Nash Direct	Letter	Copies of earlier letters	None
9	5/30/2007	Dr. Alan Scher	Letter	Copies of earlier letters	None
10	5/30/2007	Dr. Thomas Nutman	Letter	Copies of earlier letters	None
11	9/29/2006	Dr. Ted Nash	Letter	Book (Note 1)	None

NOTES:

1. Commensal and Pathogenic Blastocystis with Case Studies from Oregon's Willamette Valley

Blastocystis Research Foundation

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June 15, 2007

Dr. Ted Nash
National Institute of Allergies and Infectious Diseases
MSC 0425
4 Memorial Drive
Bethesda, MD 20892-0425

Dear Dr. Nash:

I've enclosed our publication, "A 10-Minute Introduction to Blastocystis," which you may find of value. The document describes which Blastocystis subtypes are pathogenic based on prior research.

As noted in the document, the prevalence of Blastocystis infection in stool samples submitted to clinical laboratories in the United States has risen from 2.6% in 1987 to its current level of 23%. Overseas research and our research suggest that most of these samples are Subtypes 1, 3, and 7 which are associated with symptoms in humans (but probably not their native hosts which are cattle, pigs, and rodents).

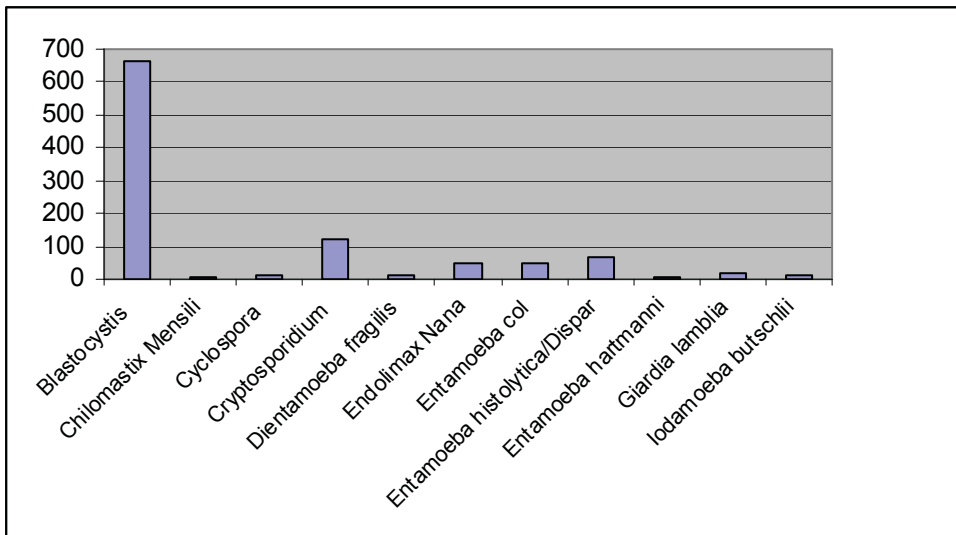


Figure 1. Number of samples testing positive out for gastrointestinal parasites of 2896 Samples analyzed from 48 states during 2000. Data taken from Amin, Omar. Seasonal Prevalence of Gastrointestinal Parasites in the United States during 2000. Am. J. Trop. Med. Hyg., 66(6), 2002, pp. 799-803

Thank you for your attention.

Best Regards,

Ken Boorom

Director, Blastocystis Research Foundation
BXXXXX@XXXXXX.net
541-XXX-XXXX

Cc: Dr. Alan Sher
Dr. Thomas Nutman
Dr. Anthony Fauci

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June 4, 2007

Dr. Ted Nash
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Dear Dr. Nash:

This is a follow-up to my earlier letters of 9/29/06 and 5/31/07. In my previous letter, I reviewed the rise in prevalence of Blastocystis infection, from 2.6% of stool samples submitted to parasitology labs, to its current level of 23%. I'd like to tell you more about why this has happened, and why this presents fantastic scientific opportunities for your group, as well as the opportunity to make a significant impact on public health.

The graph on the reverse side of this letter shows a phylogenetic tree of Blastocystis hominis based on research from the Pasteur Institute and Woods Hole Oceanographic Institute [Noel, 2005]. Genetic researchers have found that seven distinct species of organisms of the Blastocystis genus can infect humans – these organisms have different numbers of chromosomes [Carbajal, 1997] and exhibit different behavior in culture [Tan, 2006].

When the “debate” began in 1987, the dominant type of Blastocystis in the United States was most probably the Primate Subtype (#5), which produces harmless vacuolar forms in culture [Tan, 2006]. In Japan, over half of the Blastocystis infections were found to be of Subtype 5 [Kaneda, 2001]

The pathogenic variants – Subtypes 1,3, and 7 – produce huge adhesive amoeboid forms and cause chronic disease [Tan, 2006] [Stensvold, 2006] [Kaneda, 2001]. Their adhesive properties may make them pathogenic, and also may make them difficult to detect with direct microscopy.

I understand your lab's focus is primarily on Giardia, but consider that the natural world shows extraordinary flexibility in its ability to present new pathogens to the population. I believe it is important that we show the same flexibility in addressing these challenges.

In next week's letter, I'll review the problems associated with treating this infection, and include more testimonials from patients and physicians.

For your convenience, I have collected references to *Blastocystis* publications with their abstracts onto a web page – you may view the abstracts, and in some cases entire papers for the references in this letter:

<http://www.bhomcenter.org/lab>

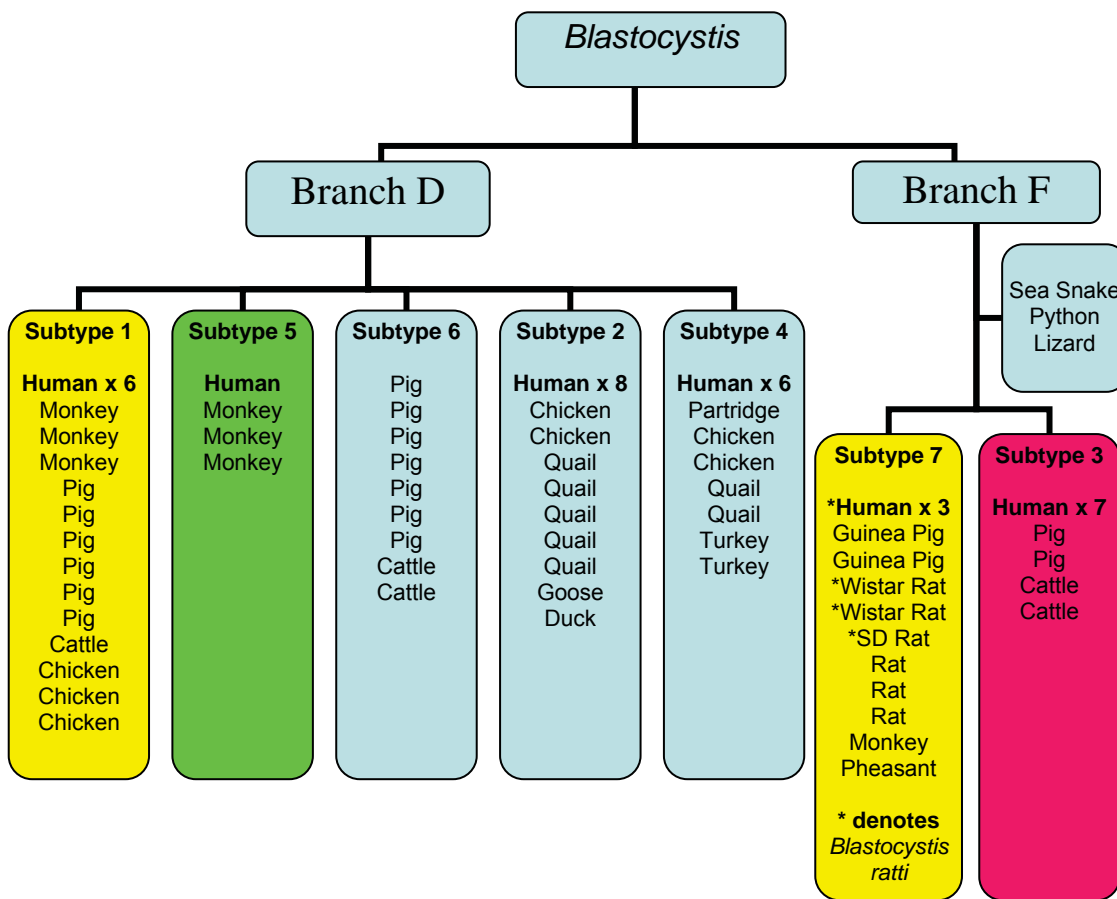
Thank you for your attention.

Best Regards,

Ken Boorom

Director, Blastocystis Research Foundation
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541-XXX-XXXX

Cc: Dr. Alan Sher,
Dr. Thomas Nutman



Phylogenetic tree of *Blastocystis* (Noel, 2005) color-coded according to pathogenicity. Isolates in this tree have different numbers of chromosomes (9-13), but medical practice refers to every *Blastocystis* isolate from a human as *Blastocystis hominis*.

GREEN (The Primate Isolate)=Identified by researcher as non-pathogenic [Kaneda, 2001] Over 50% of infections in a Japanese study were from this variant. But this variant is almost never found in symptomatic patients.

RED (The Cattle Isolate)=Identified by every recent study as pathogenic [Stensvold, 2006] [Kaneda, 2001] [Tan, 2006].

YELLOW (The Farm Animal Isolate and the Rodent Isolate)=Identified by some researchers as pathogenic [Stensvold, 2006] [Puthia, 2006]

Literature Referenced:

Noel C, et al. *Molecular phylogenies of Blastocystis isolates from different hosts: implications for genetic diversity, identification of species, and zoonosis*. J Clin Microbiol. 2005 Jan;43(1):348-55. PMID: 15634993.

Stensvold R, Brillowska-Dabrowska A, Nielsen HV, Arendrup MC. Detection of *Blastocystis hominis* in unpreserved stool specimens by using polymerase chain reaction. J Parasitol. 2006 Oct;92(5):1081-7. PMID: 17152954

Kaneda Y, Horiki N, Cheng XJ, Fujita Y, Maruyama M, Tachibana H. Ribodemes of *Blastocystis hominis* isolated in Japan. Am J Trop Med Hyg. 2001 Oct;65(4):393-6. PMID: 11693890

Tan TC, Suresh KG, Thong KL, Smith HV. PCR fingerprinting of *Blastocystis* isolated from symptomatic and asymptomatic human hosts. Parasitol Res. 2006 Sep;99(4):459-65. PMID: 16628457

Puthia MK, Sio SW, Lu J, Tan KS. *Blastocystis ratti* induces contact-independent apoptosis, F-actin rearrangement, and barrier function disruption in IEC-6 cells. Infect Immun. 2006 Jul;74(7):4114-23. PMID: 16790785

Blastocystis Isolates from less developed countries (Far East, Middle East, South America) are often the zoonotic (non-primate) types such as 1 and 3. Vacation travelers return to the US from these countries with chronic infections. Infections with these variants are difficult to detect with direct microscopy. Physicians in the United States do not understand the genetic diversity of *Blastocystis*, so they can not understand why these patients develop chronic gastrointestinal illness and inflammatory bowel disease.

Physicians lack guidelines for treatment – Metronidazole is now failing in most cases that are reported to the Blastocystis Research Foundation. Patients can not find treatment. They remain infected and pass the infection on to their communities.

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1: [Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi](#), 2006 Jun;24(3):187-91.

[Impact of blastocystis hominis infection on ultrastructure of intestinal mucosa in mice]

[Article in Chinese]

[Zhang HW](#), [Li W](#), [Yan QY](#), [He LJ](#), [Su YP](#).

Department of Occupational Health, College of Public Health, Zhengzhou University, Zhengzhou 450052, China.

OBJECTIVE: To observe the ultrastructural change of intestinal mucosa in mice infected with *Blastocystis hominis*, and to study the pathogenic mechanism of *B. hominis* infection. METHODS: 20 Kunming mice were randomly divided into 4 groups: group A treated with immunosuppressant (dexamethasone), group B without immunosuppressant, group C as normal control and group D as immunosuppressant control. Groups A and B were then orally infected with 20(4) cysts of *B. hominis*. Groups C and D were treated as control by infusing same volume of Locke's solution. Six days after inoculation, mice in each group were killed and mucosa of ileocecum was observed by transmission electron microscope (TEM) and scanning electron microscope (SEM). RESULTS: Under SEM, *B. hominis* located in enteric cavity and on the surface of ileocecum mucosa. Individual parasites also invaded into mucosa and its fold. Partial destruction of microvilli on the mucosa was observed. TEM observation indicated a reduction of microvilli on the surface of absorptive cells. Mitochondrial edema, rough endoplasmic reticulum dilatation and degranulation were found on absorptive cells and goblet cells. Lymphocyte infiltration and eosinophilia were found in intercellular stroma. Pathological changes in group A were more serious than that of group B. No abnormal change on the mucosal ultrastructure was found in groups C and D. CONCLUSIONS: *B. hominis* infection causes significant ultrastructural lesion on the ileocecal mucosa in mice. Immune status of the mice can affect the degree of the lesion due to infection.

PMID: 17094618 [PubMed - in process]

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 1: [Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi](#). 2005 Dec 30;23(6):444-8.**[Experimental infection of mice with *Blastocystis hominis*]**

[Article in Chinese]

[Yao FR](#), [Qiao JY](#), [Zhao Y](#), [Zhang X](#), [Yang JH](#), [Li XQ](#).

Department of Immunology and pathobiology, Medical School, Xi'an Jiaotong University, Xi 'an 710061, China.

OBJECTIVE: To seek a better pathway and proper number of parasites for *Blastocystis hominis* (B.h) infection in normal and immunocompromised ICR mice. METHODS: (1) 10(4), 10(5) and 10(6) B.h, cultured in RPMI 1640 medium from 3 generations were used to infect mice through oral and rectum; (2) 10(6) B.h were used to infect immunocompromised mice through rectum. The reproduction of B.h in gastrointestinal tract and the pathologic changes in the tissues were observed. RESULTS: Mice were infected by B.h through either oral or rectum. The infected immunocompromised mice showed slow locomotion, depressed, lethargy, and descended body weight. Some infected mice discharged mucus feces, a few of them died during the experiment. Parasites were found in the whole gastrointestinal tract. Severe edema, hyperemia and congestion were observed in the tissues of jejunum, ileum, cecum and colon. The epithelia of small intestine and colonic mucous membrane showed exfoliation, inflammatory cell infiltration in submucosa, and structural changes in glands. CONCLUSION: Mice were more susceptible to *Blastocystis hominis* infection through rectum than orally. The parasites can be found in the whole gastrointestinal tract of mice, and can breed rapidly and cause significant pathological change in the gastrointestinal mucosa in immunocompromised mice.

PMID: 16566218 [PubMed - indexed for MEDLINE]

 1: [Parasitol Res](#). 1997;83(4):319-25.**Experimental *Blastocystis hominis* infection in laboratory mice.**[Moe KT](#), [Singh M](#), [Howe J](#), [Ho LC](#), [Tan SW](#), [Chen XQ](#), [Ng GC](#), [Yap EH](#).

Department of Microbiology, Faculty of Medicine, National University of Singapore, Republic of Singapore.

Young (less than 8 weeks old) immunocompetent BALB/c mice became infected with *Blastocystis hominis* after inoculation of fecal cysts orally and of in vitro axenic-culture forms intracecally. This study confirmed that the fecal cyst was the form responsible for external transmission and that the mode of transmission was by the fecal-oral route. The infection was self-limiting and the infected BALB/c mice appeared normal except that some of them showed weight loss and lethargy. Both vacuolar and granular forms were found in the cecum, but only cyst forms were observed in the colon. Histological examination of the cecum and colon showed intense inflammatory-cell infiltration, edematous lamina propria, and mucosal sloughing. It is apparent that although *B. hominis* is not invasive, it is capable of causing pathogenesis in BALB/c mice.

PMID: 9134552 [PubMed - indexed for MEDLINE]

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May 30, 2007

Dr. Ted Nash
National Institute of Allergies and Infectious Diseases
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Dear Dr. Nash:

This is a follow-up to my earlier letter of September 29, 2006 (enclosed) concerning research into Blastocystis infection in the United States.

For the last several months, our group has been working with an infectious disease researchers with several Universities and the United States Department of Defense. We have replicated the results of Stensvold, et al. (enclosed) with chronically ill patients from Oregon and California and sequenced pathogenic Blastocystis isolates from US patients.

Over the coming weeks, I will be updating your group and your section head regarding this research. This information will include information on which variants of Blastocystis are pathogenic, our finding regarding invasive infection, and the use of PCR testing to identify Blastocystis infection in patients previously diagnosed with functional bowel disorders such as "Leaky Gut Syndrome" and Irritable Bowel Syndrome.

I haven't heard back from you on my previous communications. I believe it would be of substantial public health benefit to have your group more engaged in this work. According to the attached chart, there are perhaps 5 gastrointestinal parasitic diseases of major importance in the United States. Blastocystis is by far the most common, and we are the only group in the country organizing research into this area.

I've enclosed some e-mails I've received from doctors and patients for your consideration. I'm going to ask that the doctors who contact me begin to copy your group on their e-mails, because I think it is important for you to know what a problem this infectious disease has become.

Thank you for your attention.

Best Regards,

Ken Boorom

Director, Blastocystis Research Foundation
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Cc: Dr. Alan Sher,
Dr. Thomas Nutman

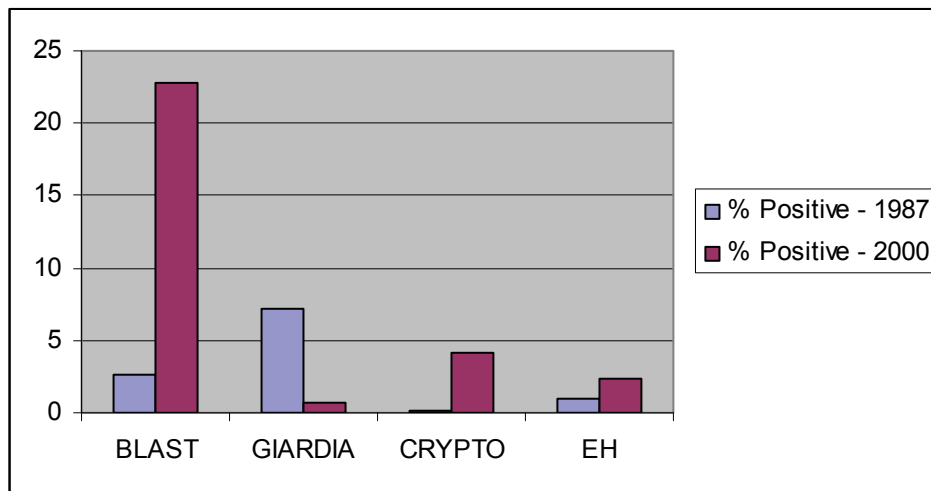


Figure 1 – Comparison of Prevalence of *Blastocystis* and other common intestinal parasites in 1987 and 2000. *Giardia* infection has decreased, but the frequency with which *Blastocystis* is found in stool samples submitted to labs has increased from 2.6% to 23%. This is consistent with BRF’s findings that pathogenic variants from Less Developed Countries (LDC’s) are imported into the United States by returning travelers, and establishing endemic infections in communities. The variants are also resistant to Metronidazole no research has been done to provide guidance to physicians. Additionally, the symptoms have become more severe and suggest the new types are invasive: the symptoms now include chronic skin rash and joint pain. US doctors do not understand the genetic diversity present in this genus, and parasitology labs are not able to identify the pathogenic forms reliably. Data reported from Good Samaritan Hospital in Oregon corroborates the finding that *Blastocystis* is now found at a rate ten times higher than *Giardia*.

References:

1987 Data: Kappus KK, Juranek DD, Roberts JM. Results of testing for intestinal parasites by state diagnostic laboratories, United States, 1987. *MMWR CDC Surveillance Summary*. 1991 Dec;40(4):25-45. Pubmed ID: 1779956

2000 Data: Amin OM. Seasonal prevalence of intestinal parasites in the United States during 2000. *Am J Trop Med Hyg*. 2002 Jun;66(6):799-803. Pubmed ID: 12224595

Good Samaritan Data: Hogue, Theresa. Parasite Blamed for Growing Number of Stomach Disorders. *Corvallis Gazette-Times*, January 13, 2007.

Blastocystis Research Foundation

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September 29, 2006

Dr. Ted Nash
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Bethesda, MD 20892-0425

Dear Dr. Nash:

I'd like to follow up on the contacts I made with your office earlier regarding Blastocystis infection.

Enclosed, please find a copy of the medical reference our group has published on this subject. A copy of the updated introduction is attached to this letter. The text will be available on Amazon.com in a few weeks.

I hope you will agree with me that these findings are significant, and imply that certain variants of Blastocystis need to be treated like an infectious disease. My group believes a more virulent strain with *Entamoeba histolytica* like properties has been imported into the United States in the last 10 years from Asia and the Middle East, is significantly under-diagnosed.

As a patient support group, I believe our accomplishments to date have been remarkable. We have published the first clinical reference on the disease; we are working with a medical diagnostics company to develop a serum antibody test along the lines that NIH researcher Zierdt used; we have an offer from the Pasteur Institute to determine where the pathogenic variants found in Oregon fit into the phylogenetic tree published last year (Noel, 2005). We are working with another medical diagnostics company to develop a PCR test specific to the pathogenic variant.

We feel that we've given the NIH and CDC a real "head start" in addressing this infectious disease. However, we are funded by patients who are sick themselves and we can't replace the functions of the NIH. We would welcome your office's assistance in addressing this infectious disease. The NIH could assist by updating doctors on the recent research into this disease; organizing the sequencing of the genome of a pathogenic Blastocystis variant; and by developing clinical trials for second line treatments for chronically infected patients.

Thank you very much for your attention.

Best Regards,

Ken Boorom

Director, Blastocystis Research Foundation
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Introduction

For almost 30 years, *Blastocystis* infection has been an enigmatic and often tragic phenomenon. Doctors have been unable to understand how this protozoan-like parasite could be commensal in some patients, and pathogenic in others. The tragedy is that first-line treatments often fail, leaving patients with a lifelong infection which significantly reduces the quality of life, and can be disabling in some patients. The ambiguity of the infection has hampered research into the pathology of the disease, and the development of reliable treatments.

In the last two years, molecular biologists have made extraordinary advances in understanding this infection. They have found that the organism labeled *Blastocystis hominis* is not one species. New research has shown that up to seven sub-types of *Blastocystis* have been lumped together under the name *Blastocystis hominis*. These newly discovered subtypes are genetically diverse enough to be considered individual species. This discovery was followed by the report that the organism that causes disease is genetically distinct from the harmless type, and exhibits radically different behavior in a special culture. When placed in context with earlier studies showing the phylogenetic relationship between the *Blastocystis* genus and the *Entamoeba* genus, this result should be expected. *Entamoeba* is a genus of organisms, with harmless species, and pathogenic species which kill 100,000 people each year. Like *Entamoeba*, some species of *Blastocystis* are harmless, and some are pathogenic.

This information has left us with an enormous problem, and enormous potential. We can now make the choice to invest in study of this organism, and potentially identify the cause of enigmatic gastrointestinal diseases which have plagued our society. We are also left with the realization that some *Blastocystis* species can be pathogens, possibly as dangerous and invasive as their cousin *Entamoeba*. Some variants may be responsible for unexplained degenerative diseases. New variants can be introduced into communities where they can spread, infecting individuals, families, and children. We lack the tools to monitor, control, and treat such infections.

Moving forward, it is essential that we develop tests to identify the pathogenic variants of *Blastocystis*. The finding that the pathogenic variants assume amoeboid forms, and are concentrated into a narrow clade should make the design of a PCR assay possible. We need to identify undiagnosed cases of infection, and identify the vectors of the infection. We must define the mechanism by which the organism causes disease. It is imperative that we develop reliable treatments for the infection, and also develop methods for preventing the infection.