

Parasites – Uninvited Guests

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All US residents are now exposed to parasites originally seen only in underdeveloped countries or exotic locations due to: increased business/pleasure travel to these areas, changing immigration patterns (influx of foreign nationals/nannies/cooks) from endemically infected areas; the adoption of hobbies (skiing, fishing, rafting, hiking/trekking) which increase the possibility of accidental/intentional lake, stream, or well water ingestion; increase in two working-person households which results in increased eating in restaurants/exposure to food prepared and touched by cooks/food handlers who are frequently from endemic areas/never have had stools checked before or during employment, and who exercise inadequate hand-washing techniques; the increasing demand of our populace for out-of-season fresh fruits and vegetables which must be imported from endemically infected areas; and infectious intestinal problems associated with the worldwide [HIV.sup.+] epidemic. It has become mandatory that all physicians include a travel history as well as a history of all the other risk factors listed above in their patients who present not only with undiagnosed nonspecific diarrhea diseases, but also in those with a presumed diagnosis of irritable bowel, ulcerative Colitis/ Crohn's disease (or exacerbation of either), colon cancer, lactose intolerance, malabsorption, weight loss, nonspecific arthritis, hives and other skin rashes, and central nervous system signs as seizures or a change in mental status. They must also familiarize themselves with the distribution and the major modes of clinical presentation of all the parasites.

In the 40% of Americans who have gastrointestinal symptoms, there is a presumed incidence/prevalence of the following illnesses: irritable bowel syndrome (a functional disorder) diagnosed in 20% of our population; Inflammatory Bowel Disease (Ulcerative Colitis and Crohn's disease) diagnosed in one million people in the United States; lactose intolerance diagnosed in 20% of the adult Caucasian population and 80% of the adult African-American population; idiopathic food allergies and skin rashes diagnosed in 25% of our population; and unexplained arthritis or other musculoskeletal problems diagnosed in 25% of our population -- based on non-consideration of parasites as a cause or exacerbation of any/all of the above illnesses. Indeed, Dr. Leo Galland [1] working with cases diagnosed as irritable bowel syndrome found that 40% of them were due to just one parasite (Giardia Lamblia).

Human protozoan parasites encompass a wide range of type and site specific organisms. Within the intestinal/other areas of the alimentary tract and the urogenital tract -- amoeba, flagellates, coccidia, and one ciliate (B. Coli) may occur in cyst/trophozoite forms. In addition, blood protozoan parasites including the organisms causing Malaria and Babesiosis (Plasmodium and Piroplasm), sleeping sickness (Trypanosomes), Visceral and Cutaneous (kala-azar), Leishmaniasis (Leishmaniae), tissue coccidians (Toxoplasma and Sarcocysti); normally free living amoeba as Acanthamoeba and Naegleri which can cause eye, lung, and disseminated disease (mostly in [HIV.sub.+] patients), and Pneumocystis Carinii, an almost avirulent organism in immunocompetent people, which causes pulmonary, liver, lymph node, spleen, thyroid, adrenal and kidney disease in [HIV.sub.+] patients.

The diagnosis of protozoan infections is generally made on the basis of their recovery and microscopic identification in stained fecal, blood, tissue, urine, or other fluid smears. The identification of protozoa by these methods is much more difficult than the identification of the worms (Helminths) because they are shed in the stool as complete organisms which can be identified microscopically on only one every five days, while the helminths are shed daily and in large numbers. Thus, when looking for protozoa, 1-3 negative exams has a negative predictive accuracy varying from 20% at most laboratories to 50% at the best lab. Fortunately, over the last decade, we have had the development and validation of non-microscopic biochemical Stool Antigen Tests for the three most important protozoan parasites: (Giardia Lamblia, Entamoeba Histolytica, and Cryptosporidium spp). The performance of these tests routinely with any O/P exam increases the positive and negative predictive accuracy of a single stool, fluid, or tissue exam to 99% including any performed on days when the intact parasite is not shed into stool, rendering microscopic diagnosis impossible and thus grossly inaccurate.

The most common intestinal protozoan parasite diagnosed in the United States is the flagellate (Giardia Lamblia). [2] It is responsible for outbreaks of diarrheal disease in: the children/employees in day-care centers; in hikers or trekkers into mountainous areas; in ski resorts or places where people fish or boat; in localities where water purification/filtration to exclude particles [greater than]1 micron in size does not occur; in travelers to countries where food and water are fecally contaminated; in restaurant frequenters/attendees of corporate/private catered events; and the increasing number of households where untested foreign domestic help (cooks/nannies) prepare the meals. [3] All are the result of the policy of no mandatory stool testing of commercial food preparers/handlers, the nonenforcement of strict hand-washing rules and the non-availability of truly germicidal soaps in commercial establishments.

Although the diagnosis of giardiasis can be made by the microscopic demonstration in stool of cysts/trophozoites in temporary saline/iodine mounts/permanent trichrome stain for its diagnostic trophozoites, the negative predictive accuracy of up to three negative exams is only 50% due to the previously mentioned irregular stool shedding. As mentioned above, this problem was eliminated with the availability of the non-microscopic biochemical Giardia Stool Antigen Test, which increases the accuracy of diagnosis to 99% any day a stool exam is performed. This stool antigen test assumes even greater importance since Giardia Lamblia lives in the small intestine, with the result that physicians faced with one negative microscopic exam, often resort to ultimately non-diagnostic upper G.I endoscopy to make the diagnosis. This results in great financial cost and physical discomfort to the patient, plus unnecessary illness prolongation before the correct diagnosis can be made. This test is not performed routinely in any other lab in the country, and if performed, costs an additional \$20-\$60.

Infection follows the ingestion of as few as 25 cysts (trophozoites would be destroyed by the stomach acidity). [4] In the small intestine the cysts excyst to become trophozoite forms which colonize/multiply there, and eventually adhere to the gut wall at the brush border of the enterocytes via their ventral discs. This process increases epithelial cell turnover and bile salt deconjugation, both of which contribute to the Disaccharidase Deficiency and Malabsorption which is commonly seen in Giardiasis.

The host immune response to the parasite is the other component of the host-parasite relationship. Host immunity, most importantly secretory intestinal IGA antibodies, acting in concert with T cells from the cell-mediated immune system, coordinate the production of anti-Giardia secretory IGA antibodies and produce specific anti-Giardia cytotoxicity which eliminates the trophozoites. There is evidence that anti-Giardia IGA secretory antibodies alone cannot kill the parasite because it produces an IGA protease.

Predisposition to Giardiasis has been documented in patients with commonly variable immunodeficiency or X-linked agammaglobulinemia, in patients with a history of previous gastric surgery with reduced gastric acidity, or with achlorhydria due to vitamin B12 deficiency (pernicious anemia) or medications which reduce stomach acidity that have been prescribed for other stomach disorders. Patients with HIV+ status have impaired immune response to the parasite but do not seem to have more severe disease.

Infection with Giardia Lamblia includes asymptomatic cyst passage, acute symptomatic giardiasis characterized by diarrhea, abdominal cramps, bloating, flatulence, sulfuric eructation, extreme weakness/malaise, nausea and loss of appetite (during which vomiting, fever and extreme abdominal tenderness are uncommon); and chronic giardiasis during which symptoms often include hives, other skin rashes, upper abdominal pain which is often exacerbated by eating -- and which may seem to represent food allergies, dairy and milk intolerance similar to hereditary lactose intolerance, and the production of fatty, floating, and foul smelling stools which represents malabsorption.

The importance of obtaining the three protozoan stool antigen tests (in this case Giardia) at the time of initial evaluation in all patients who present with new headache, malaise, hives or other skin rash, reactive arthritis, biliary tract or gastric disease, new food allergies, intolerance to milk or dairy products, as well as in those patients with diarrhea, cannot be overemphasized. This is the only certain method of not missing a parasite infection by misdiagnosing any of the above serious disorders; at great cost to the patient, both financial and physical.

The only protozoan flagellate of clinical significance to humans is *Dientamoeba fragilis*. This parasite, worldwide in distribution, is contracted by the ingestion of contaminated water or food that is fecally contaminated from the hands of infected food preparers/ handlers. This parasite is capable of causing diarrhea and weight loss. Its diagnosis is difficult because it is excreted intermittently in small numbers, and exists only in the trophozoite form which stains poorly even with trichrome, which is rarely done at commercial laboratories unless a direct or concentrated exam is positive. It will be missed unless an experienced, not work-overloaded technician performs one to several careful microscopic stool exams.

All other intestinal flagellates are considered to be non- pathogenic: *Trichomonas vaginalis*, *Chilomastix mesnili*, *Enteromonas hominis*, and *Retortamonas intestinalis*.

Acute and chronic diarrheal diseases have been of major concern to humans since earliest recorded history. (Deuteronomy 23:10 and 23:13). The failed invasion of Russia by Napoleon, the morbidity/mortality of prisoners at Andersonville during the Civil War and the Bataan Death March in the Philippines during World War II were caused as much by infection with *Entamoeba Histolytica* as by military/ prison officials. This protozoan parasite is the third leading cause of parasitic death in developing countries, after malaria and sleeping sickness. [5] It is one of the most important health risks to which travelers are exposed. [6] Twenty to thirty percent of people living in tropical areas and 5% of people living in temperate areas like the United States are infected with the organism. [7] The most subtle break in personal sanitation/hygiene allows the organism to spread and initiate disease.

Cysts of the organism are excreted and if the environment is moist enough can survive in soil or food for weeks. Outside the body the trophozoite form degenerates within minutes, and if ingested while alive, it is rapidly destroyed by the low stomach pH and the gastric enzymes. The cyst form, which readily passes this and all other barriers, is responsible for the prevalence of the infection throughout the world, moving from person to person through fecal contamination of water, vegetables, and fruits, or by direct fecal-oral contact. [8] Interruption of the transmission of *E. Histolytica* would be very difficult because it is dependent on the solving of complex socioeconomic problems and effectuating major changes in human behavior.

Infection begins with the ingestion of the cyst, which passes down the alimentary canal, excysting in the small bowel to the trophozoite, which infects the large bowel (colon) upon reaching it. There the trophozoite encysts to avoid local physical conditions that are not ideal for its continued activity. [9] Disease caused by *Entamoeba Histolytica* is expressed most often as ulcerative and inflammatory lesions of the colon, which result in a complete spectrum of colonic signs and symptoms. [10] (indistinguishable from ulcerative colitis, Crohn's Disease or colon cancer) [10]

Asymptomatic infection -- occurs in 90-99% of infected patients, who are able by unknown mechanisms to spontaneously eliminate the parasite from the gut within 6-12 months. In most studies, the other 1-10% of the infected patients develop symptomatic amoebiasis within five years." [11]

Symptomatic non-invasive (luminal infection) -- Unless the diagnosis of a parasitic disease is considered, the nonspecific nature of the gastrointestinal symptoms often leads the examiner away from the correct diagnosis. Laboratory diagnosis includes the finding of hematophagous trophozoites (intermittently) during stool microscopic exam, stools that are hemocult negative, negative anti-amoebic blood antibodies, but a positive *E. Histolytica* Stool Antigen Test.

Acute invasive dysentery (rectocolitis) - is seen in all age groups, affects both sexes equally, is characterized by a gradual onset over one to three weeks which develops into an illness characterized by fever, leukocytosis, profound bloody-mucoid diarrhea (children may present with rectal bleeding only) with severe abdominal pain and frequently with signs of peritoneal irritation (75% of the patients have developed intestinal perforations). One percent of the cases are complicated by toxic megacolon. This complication is seen most frequently when corticosteroids are prescribed for presumed Ulcerative Colitis, instead of the colectomy that is often required acutely in these patients, who do not respond to anti-colitis drugs. [12]

Laboratory Diagnosis - constant heme-positive stools with far fewer Wbc's than are seen in bacterial or toxin causes of bloody diarrhea, Charcot Leyden Crystals (degenerating eosinophils), only intermittent microscopic identification of the cyst or hematophagous trophozoite form of the parasite under the microscope and most importantly, a positive biochemical *Entamoeba Histolytica* Stool Antigen Biochemical Test that has both a positive and negative predictive accuracy of 99%.

Chronic non-dysenteric syndrome - most patients have persistent symptoms for one to five years consisting of intermittent diarrhea with mucous, abdominal pain, flatulence, and weight loss. [13] They are often misdiagnosed as having irritable bowel syndrome or Inflammatory Bowel Disease unless the diagnostic *E. Histolytica* stool Antigen Test is performed and found to be positive.

Amoeboma - Amoebiasis may present as an annular constricting colonic lesion indistinguishable from a carcinoma. [14n] The case histories are legion of patients who were treated unsuccessfully for colitis or had colectomies for presumed cancer when they really had E. Histolytica infection presenting as a mass lesion of the colon. [14b] The Entamoeba Histolytica Stool Antigen Test is positive and its performance would have insured that the correct diagnosis was made.

A prolonged acute-chronic irritable bowel syndrome may follow any of the above amoebic colitides, and its pattern is often similar to mild Ulcerative Colitis." It can be diagnosed by the constant negativity of the biochemical Entamoeba Histolytica Stool Antigen Test while positive anti-amoebic antibodies seen during cases of invasive intestinal amoebiasis may still be present.

Acute Post-Amoebic-Colitis - a rare complication of treated amoebic colitis. It has a pattern similar to Ulcerative Colitis, with recurrent bouts of mucous and bloody diarrhea that is unresponsive to anti-amoebic therapy, and is often associated with high titers of anti-amoebic antibodies. [16] The Entamoeba Stool Antigen Test however is always negative.

In all the above syndromes, all cases misdiagnosed as non-parasitic illnesses would have been correctly diagnosed if the biochemical E. Histolytica stool antigen had been performed. Ninety-five percent of all labs do not ever perform this test. All the others except for the Tropical Medicine Lab in New York City use the generic E Histolytica stool antigen test which does not distinguish E. Histolytica from the microscopically identical but non-pathogenic E. Dispar which causes no illness and needs no treatment.

Cyclospora organism in stool previously named blue-green Algae or "large Cryptosporidium" are primarily seen in immunocompetent adults and children, although they have been seen as a cause of illness in HIV+ patients. Infection is worldwide, commonly linked to contaminated water ingestion, and is most frequently acquired in Nepal where rainy season outbreaks have commonly been reported. [18] Outbreak infections in the United States have been reported from a contaminated water tower in Chicago, and between 1994-1998 from the ingestion of strawberries imported from Guatemala for out of season consumption. [19] In this latter instance, despite extensive investigation, the manner in which the berries were contaminated was never adequately determined. In all hosts, the predominant characteristic of infection with this parasite is prolonged, and watery relapsing diarrhea frequently associated with weight loss; (less frequent nausea, vomiting, and crampy abdominal pain with fever may occur. [19] The mean duration of diarrhea in untreated patients has ranged from 1943 days. [20] Acid fast staining of feces followed by microscopic examination is the recommended method of diagnosis. Organisms have also been observed in duodenal aspirates, [21] and in small bowel biopsies with the use of electron microscopy. [22]

Cryptosporidium is an intracellular protozoan parasite linked to gastrointestinal disease in turkeys (1955), bovine animals (1971) and first found in two cases of human diarrhea in 1976. [23] Although Cryptosporidium's 20 species have been identified in 60 countries, and on six continents Cryptosporidium parvum is recognized as being the only species responsible for clinical illness in humans and other mammals. In 1982, human Cryptosporidium infection achieved increased significance when the CDC designated its presence alone as enough to make diagnosis of AIDS Syndrome in HIV+ patients. [24] By 1986, 3.6% of 20,000 AIDS patients already had Cryptosporidiosis at the time of their CDC notification, with a case fatality rate of 61%. [25]

Cryptosporidiosis has been reported without predisposition to gender in individual of all ages, from a three day old infant to a 95 year-old patient. Children less than two years of age may be more susceptible to infection; perhaps reflecting increased fecal-oral transmission in this age group, lack of protective immunity from prior exposure, or relative immunologic immaturity. [26] The elderly may also be at increased risk for Cryptosporidium infection, perhaps related to normal immunosenescence. Prevalence based on detection of active Cryptosporidium oocyst excretion in fecal specimens is greater in less developed countries: related to a relative lack of clean water and sanitary facilities, crowded households and/or animal reservoirs in close proximity to residences. Excluding documented outbreaks, prevalence rates range between 1-3% in the more industrialized countries of Europe and North America, and 5-10% in Africa, and Asia. [27] Cryptosporidium infection has been reported after the ingestion of as few as 10 oocyst in immunologically compromised patients [28] and as few as 3000 oocysts in totally healthy patients. [29] Transmission between family, household members, sexual partners, children in day-care centers/their caretakers, and health care workers/ their patients is well established. [30] Spread may be hand to mouth or, through contact with contaminated items, such as diapers or linens. Animal to person transmission may occur from household pets, as well as laboratory or farm animals (most commonly calves, rodents, and rabbits). Waterborne outbreaks have been reported in travelers to Leningrad, the Caribbean, Egypt, Mauritius, Mexico, Nepal, Pakistan, and New Guinea. [31]

The only method used to diagnose these infections is fecal examination. The formerly accepted methods of microscopically examining stool using an acid-fast stain or by fluorescent antibody microscopy is grossly inadequate: due to the low numbers of oocyst excreted and the variable pick up of the acid-fast stain for the former; and the general unavailability of microscopes suitable to perform fluorescent antibody testing for the latter. The gold standard today is the performance of an ELISA biochemical examination of stool for cryptosporidium stool antigen (which is 99% accurate). Hospitals or commercial labs never perform it as part of an O/P stool exam unless specifically ordered (and then at an additional cost of \$30-60 to the patient).

There is no reliable palliative or curative treatment for Cryptosporidiosis. In immunocompetent patients, the diarrhea is ultimately self-limited, although there have been reports of persistent oocyst excretion for up to 85 days. During this period, the patients will experience amelioration of their symptoms with the ingestion of electrolyte solutions and over the counter/Rx requiring antidiarrhea agents. Over the last 20 years, over 95 interventional agents (mostly antibiotics of various classes) have been tried to treat Cryptosporidiosis in HIV+ and other immunocompromised patients, with only a few resulting in symptomatic improvement in the diarrhea, none with parasite eradication. [37] There are no placebo-controlled treatment trials for human Cryptosporidiosis and only a few prospective and open labeled. Thus treatment reports are anecdotal and come from isolated case reports. Flagyl, Azithromycin, Quinacrine, and Paramomycin have yielded unsatisfactory treatment results. Albendazole (400 mg p.o. b.i.d. for 3-4 weeks) has yielded symptomatic relief but no parasitologic cure. Octreotide, Fumagillin and Propamidine Isethionate are all promising. Recently the use of human immunomodulators as bovine transfer factor and HEC (Hyper Immune Bovine Colostrum) from breast milk have appeared to show great promise in small groups of these patients. [38]

The Microsporidia are obligately intracellular spore forming protozoa (consisting of over 1000 species) capable of infecting a wide variety of both vertebrate and invertebrate hosts. Host specificity, once considered highly restricted may not be, because human infections with traditionally non-human species have been demonstrated. [39] Nonetheless only five genera have been implicated in human disease: Enterocytozoan, Encephalitozoon, Pleistophora, Nosema and Septata. [40]

They are however, truly ubiquitous in our environment: they infect many types of insects, common food fish as salmon, monkfish, and freshwater snails; they are released into the Western US environment for the biological control of destructive grasshoppers and locust, and accordingly are found in surface and pond water. [41] The presence of microsporidial spores in surface water samples suggests the possibility of environmental or zoonotic sources of infection, but no human microsporidia infection has yet been identified from such sources. [42]

Likely methods of transmission include fecal-oral contamination for, intestinal microsporidiosis; sexual transmission may explain the often-extensive urinary tract involvement seen in infection with several species.

Almost all of the increasingly recognized cases in humans have been in persons HIV+ or otherwise immunocompromised or in immunoprivileged anatomic sites in patients with otherwise normal immunity. HIV+associated intestino-biliary-pancreatic infections, primarily with *E. Bieneusi* continue to be the most frequently recognized form of human Microsporidiosis. Reported cases have increased from 47 in 1990 to over 500 cases now. Except for one study showing asymptomatic carriage in 27% of HIV+ patients, all other studies confirm a strong correlation between the presence of organisms and diarrheal diseases. [43]

In HIV+ patients intestinal infection with *E. Bieneusi* is characterized by the gradual development of chronic diarrhea, abdominal pain, vomiting, fever and weight loss. Patients typically report from 3-10 bowel movements per day (range from 1 to over 20 movements per day). Stools are loose to watery, less voluminous than in Cryptosporidiosis, (unless co-infected with invasive intestinal pathogens), non-bloody and without fecal leukocytes. Diarrhea seems to be worsened by most foods, and is most often worse in the morning. Diarrhea for 21 to 48 months has been reported, and deaths attributable directly to *E. Bieneusi* are as high as 56% of infected patients.

Infection in non-HIV+ immunocompromised patients has included: CNS infection with seizures and meningitis; eye involvement present as conjunctivitis, corneal involvement, keratouveitis and hyphema, diffuse myopathy with abnormal EMG and nerve conduction studies.

The diagnosis of Microsporidiosis is dependent on the microscopic demonstration of the organism using modified chromotrope 2 R stain, Gram or Giemsa stain or in infected tissues or body fluids (stool, duodenal aspirates, bile, sputum, bronchiolar lavage, and conjunctival scrapings). [44]

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