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# Treatment of persistent *Pfiesteria*-human illness syndrome

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**ABSTRACT:** *Patients with exposure to Pfiesteria toxin have developed an illness, Pfiesteria-human illness syndrome, characterized by skin lesions, headache, myalgias, conjunctival irritation, bronchospasm, abdominal pain, secretory diarrhea, recent memory loss, and difficulties with number sequencing. Not all patients demonstrated all features of the syndrome. The natural history of Pfiesteria-human illness syndrome shows that most patients' symptoms improve without treatment. This article reports the improvement of symptoms that had persisted for over one month in five patients, which the author attributes to treatment with cholestyramine. These patients were self-referred to the Pocomoke River Rash and Associated Illness Center, a clinic that opened on August 6, 1997, in response to the need for a central facility for diagnosis of human illness acquired from Pfiesteria.*

*Until the Pfiesteria toxin(s) is isolated and characterized, and laboratory diagnostic tests are available, physicians must be able to recognize Pfiesteria-human illness syndrome and intervene when symptoms, particularly memory loss and diarrhea, cause significant impairment in daily activities.*

*There are no precedents for the treatment of Pfiesteria or any dinoflagellate toxin-related human illness reported in the literature. The successful use of cholestyramine reported here may provide a model for understanding dinoflagellate toxin physiology in the human body. This paper reports an uncontrolled observational study. When identification of the toxin is completed, a basis for properly controlled studies will be available.*

Treatment of human illness caused by *Pfiesteria* toxin, *Pfiesteria*-human illness syndrome (PHIS), has not been reported in the medical literature. The diagnosis of acute human illness acquired from exposure to *Pfiesteria* toxin in the wild has only been made<sup>1</sup> and confirmed recently.<sup>2</sup> Acquisition of human illness from intensive laboratory exposure to *Pfiesteria* was reported by JoAnn Burkholder at North Carolina State University in 1995.<sup>3</sup> Since the initial reports of PHIS acquired in the wild, the Pocomoke River Rash and Associated Illness Center, a clinic affiliated with the Edward McCready Hospital in Crisfield, Maryland, has evaluated nearly 50 patients with acute, recurrent, and chronic exposure syndromes. For this report, symptoms lasting longer than four weeks, with or without recurrent exposure to *Pfiesteria*-inhabited water, are considered persistent.

A cohort of five patients with a clinical diagnosis of persistent PHIS were treated in a nonrandomized, uncontrolled manner. The marked clinical improvement in these patients within two weeks prompted this preliminary report. Confirmation by properly controlled scientific studies is not likely to be forthcoming until the toxin of *Pfiesteria* is identified.

The Pocomoke River, located at the lower portion of the Eastern Shore of Maryland, is a tributary of the Chesapeake Bay. Beginning in October 1996, commercial fishermen working on the Pocomoke River began experiencing new symptoms of recurrent conjunctival irritation, unusual skin rashes, recurrent cough, loss of recent memory, headache, crampy abdominal pain, and watery diarrhea. These symptoms coincided with the netting of fish with necrotic lesions. Although menhaden were the most commonly affected species, all species of fish were affected. The lesions were similar to those noted from other waters, including the Neuse River in North Carolina, with low levels of *Pfiesteria* toxin-forming zoospores. Not all the fishermen were sickened; most had several but not all of the illness symptoms. No deaths occurred.

Similar symptoms developed acutely in three patients with brief exposure to the river (i.e., water skiing, swimming) one week before a major fish kill on August 6, 1997. Four cases of PHIS were found in Maryland Department of Environment employees who were working in the water during an active fish kill. On August 19, the State Department of Health organized a multidisciplinary team of university physicians to examine a group of 13 patients with symptoms on August 19.

Consistent abnormalities on neurocognitive testing similar to those seen in at least one of the North Carolina State University laboratory workers were found. Positron emission tomography scans done on five of the identified patients showed global reduction in glucose uptake. Maryland acknowledged the human health risks from *Pfiesteria*, in part based on the severity of the neurocognitive impairment that was not obvious on clinical examination. The political and economic consequences of Maryland's actions were magnified partly because no effective treatment strategies were available other than closure to public use of selected rivers by the state.

The public avoidance of seafood consumption was in part due to the fear of contracting an untreatable illness.

The use of cholestyramine as a treatment for persistent PHIS was developed by the author after his repeated observation that persons who had an acute PHIS syndrome with secretory diarrhea that was successfully treated with cholestyramine also had a concurrent improvement in headache, memory loss, rash, and cough. Treatment lasted two weeks, continuing longer for those who had recurrent exposures. All patients were given one teaspoon of Milk of Magnesia upon arising, and one scoop of cholestyramine mixed in juice four times a day.

#### Case 1

A 56-year-old female Maryland Department of Environment worker was on a boat sorting lesioned fish from nonlesioned fish during an active fish kill on August 7, 1997. She had an abrupt onset of conjunctival irritation, cough, headache, wheezing, and a burning sensation on her exposed skin. The skin subsequently vesiculated and desquamated. Because of memory impairment she was referred by the author to Donald Schmechel, M.D., at Duke University on August 18. Neurocognitive studies were markedly abnormal. Treatment of nasal congestion and bronchospasm with inhaled steroids and bronchodilators improved symptoms minimally. Pulmonary function testing showed forced vital capacity and forced expiratory volume in one second each reduced to 50% of predicted. Memory loss continued.

Treatment of one scoop of cholestyramine with one ounce of 70% sorbitol (to prevent constipation), four times per day was begun on September 17, 1997. By October 3, pulmonary function testing improved forced vital capacity to 98% predicted and forced expiratory volume in one second to 70% predicted, with nearly full restoration of memory.

#### Case 2

A 47-year-old male fisherman had recurrent episodes of conjunctival irritation, cough, wheeze, headache, memory loss, and severe abdominal cramping beginning in October 1996. He stopped work on the river in May 1997 with improvement in eye and lung symptoms. His memory loss and cramping persisted. He returned to the river on August 11, 1997, assisting the Maryland Department of Natural Resources in investigating and monitoring fish kills in many adjacent waterways. His symptoms recurred promptly. Treatment with cholestyramine, one scoop four times a day, was begun on August 30. By September 6, his symptoms had abated markedly. The patient returned to work in *Pfiesteria*-inhabited waters and his symptoms returned.

#### Case 3

A 33-year-old male waterman was healthy until October 1996, when he developed abdominal cramps, watery diarrhea with occasional incontinence, chronic cough, a 40 lb weight loss, and headaches. He was treated for pneumonia six separate times between October 1996 and July 1997. Memory impairment was

documented on neurocognitive examinations and a positron emission tomography scan was abnormal.

The patient was treated with inhaled steroids, bronchodilators, and clarithromycin with cessation of diarrhea and improvement in lung symptoms about the time of the river closure. Memory loss continued. With re-exposure to the river his respiratory symptoms and diarrhea recurred.

Cholestyramine and sorbitol treatment was begun September 7, 1997. Despite continued river exposure, a follow-up examination on October 2 revealed his memory loss to be dramatically improved. He continued on low-dose cholestyramine with a multiple vitamin. He uses bronchodilators rarely, as needed. A subsequent neurocognitive examination showed improvement.

#### Case 4

A 32-year-old commercial diver had extensive wet suit exposure to water on the Wicomico Creek later, shown to have *Pfiesteria*. He had gradual onset of cramps, diarrhea, skin lesions, headache, and memory loss beginning in July 1997.

Treatment with cholestyramine and sorbitol was begun on September 25, 1997. Neurocognitive examinations done the next day were markedly abnormal. The patient had symptomatic improvement within three days. He stated that he could tell when the dose of cholestyramine was "wearing off" by recurrence of abdominal cramping. At follow-up two weeks later, the patient was asymptomatic and had returned to work. Subsequent neurocognitive examination showed minimal improvement only. The patient continues to work in the area waters. He continues to use two scoops of cholestyramine daily.

#### Case 5

A 44-year-old male Virginia Marine Fisheries worker had extensive exposure to the Pocomoke River beginning in July 1997. Coworkers, including Maryland Department of Natural Resources commander, noted impairment in the patient's memory. He also had abdominal cramps and skin lesions. The patient was referred for treatment by the patient described in Case 2. Memory loss was documented by an inability to remember a five-number sequence (0/5) and a four word list (1/4).

Treatment was initiated on September 25, 1997, with fading of skin lesions, improvement in memory, and elimination of abdominal pain by October 3.

#### Discussion

As our knowledge of PHIS expands, laboratory markers for the illness should become available. Neurocognitive testing, the fingerprint of the illness, is expensive and not readily available, however, a clinical diagnosis of PHIS can be made. Although the illness can be self-limited, the persistent symptoms of these five patients improved rapidly with cholestyramine treatment.

Studies of brevetoxin, a different dinoflagellate toxin, in rats<sup>4</sup> show prompt clearing with an IV dose, within 24 seconds, with

Table 1. *Pfiesteria* symptom complex

Immediate effects	Within 24 hours
Skin burning	Rash
Conjunctival injection	Headache
Cough	Abdominal cramps
Wheeze	Exercise-induced asthma
Sore throat	
Within 3 hours	Persistent
Myalgia	Rash up to 2 months
Headache	Memory loss of up to 6 months
Memory impairment	Neurocognitive deficits (unknown duration)
	Bronchospasm
	Secretory diarrhea

uptake by muscle, metabolism by the liver, with excretion into the intestine. Sherwood Hall, from the Food and Drug Administration, Shellfish Poisoning, and Mark Poli, a brevetoxin expert, have endorsed continuing work with cholestyramine (S. Hall, M. Poli, personal communications).

The hypothesis for consideration is that the *Pfiesteria* toxin causes an acute human illness and, in some patients, a persistent human illness. The toxin, a nonspecific irritant of skin and mucous membranes, passes quickly from alveoli into blood following aerosol or droplet inhalation. The toxin is postulated to be absorbed into muscle, with equilibration into lipid tissues such as brain and surfactant in lung. The toxin is excreted into bile with enterohepatic recirculation.

Cholestyramine may bind toxin in the small intestine, permitting excretion in stool, depleting the toxin from lipid reservoirs. The clinical symptoms fit such a proposed model (Table 1), with conjunctival irritation and cough being early onset symptoms, followed by myalgias, headache, and memory loss. Bronchospasm and abdominal symptoms are late manifestations.

Recurrence of symptoms with repeat exposure suggests a lack of protective immune response to the toxin. Although cholestyramine is not a totally benign treatment, the resolution of headache, memory impairment, and bronchospasm suggests strongly that treatment of the gastrointestinal tract affords an opportunity to reduce the body burden of toxin.

The prompt improvement in persistent symptoms with use of cholestyramine may provide a therapeutic option for the practicing physician faced with the clinical problem of profound memory impairment and disruption of normal daily life that *Pfiesteria* can cause.

#### References

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