

A HUMANITARIAN FOCUS LEADS TO SEMINAL DISCOVERIES ON THE CAUSES AND IMPACT OF DIARRHEA IN YOUNG CHILDREN

Richard L. Guerrant, MD

2014 Maxwell Finland Award for Scientific Achievement Awardee

Dr. Richard L. (Dick) Guerrant is an international leader who has devoted his career to the study of gastrointestinal pathogens. Dr. Guerrant's seminal discoveries of how cholera and *Escherichia coli* toxins cause diarrhea, coupled with his fieldwork defining the long-term impact of childhood diarrhea on physical stunting and cognitive impairment, produced a sea change in thinking on how to reduce the devastating impact of enteric infections worldwide.

Dr. Guerrant's interest in alleviating the effects of childhood diarrhea is rooted in his first trip to the Congo in the late 1960s. Even as a young professional, he recognized the devastating impact of childhood diarrhea, especially in areas where good nutrition and clean running water were scarce. Diarrhea causes an estimated 3,000 deaths among children each day in such areas.

That first trip cemented one of Dr. Guerrant's core beliefs that "poverty is the greatest disease facing humanity." His work in Bangladesh, South

Africa, and especially Brazil, where he has long and deep ties, showed him that there is "no cultural difference in what it means to lose a child as a parent." These beliefs have driven Dr. Guerrant to improve the lives of children in resource-poor areas by attacking persistent diarrhea—a major cause of morbidity, mortality, and economic drain. That drive not only led to the discovery of the major pathogens implicated in persistent diarrhea, but also to some surprising findings about its genetic determinants, and to the development of an oral treatment that not only rehydrates but also helps to repair damage in the gut of affected children.

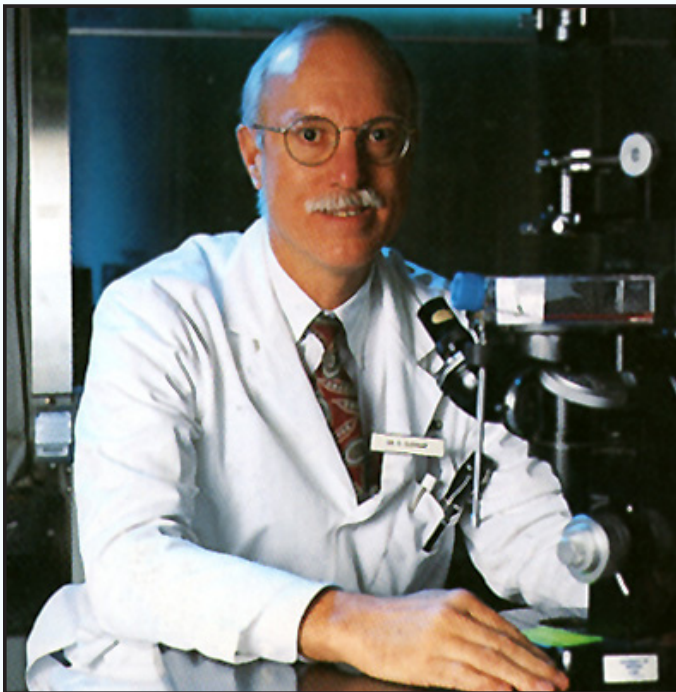
The National Foundation for Infectious Diseases is proud to honor Richard L. Guerrant, MD with the 2014 Maxwell Finland Award for Scientific Achievement in recognition of his hallmark contributions to better understanding of the causes, long-term effects, and treatment of persistent or chronic diarrhea.

It is especially fitting that Dr. Guerrant should receive this award since Dr. Finland was his first attending physician when he began his internship in medicine on the Harvard Medical Service of the Boston City Hospital.

DEFINING PERSISTENT DIARRHEA PATHOGENS AND RECOGNIZING LONG-TERM IMPACTS

Following his training under the mentorship of Dr. Finland, Dr. Guerrant did early fieldwork on cholera in Bangladesh and a fellowship in cholera research at Johns Hopkins. This work led to Dr. Guerrant defining the mechanisms by which *Enterotoxigenic E. coli* (ETEC) produce a cholera-like diarrhea. With collaborators, Dr. Alfred Gilman and Dr. Ferid Murad, he defined the mechanisms by which two specific ETEC enterotoxins produced rapid intestinal fluid activation (the heat-labile toxin via adenylate cyclase, and the heat-stable toxin via activation of guanylate cyclase).

Defining these mechanisms was key in Dr. Guerrant's development of a glutamine derivative-based oral rehydration and nutrition or repair therapy (ORRT) that increased the ability to effectively rehydrate affected children. The addition of alanyl-glutamine improved the oral rehydration formula used for decades by stimulating even greater sodium iron absorption. For this breakthrough, Dr. Guerrant was honored as the University of Virginia's 1997 Henderson Innovator of the Year.



But even while acknowledging the severe morbidity and mortality of *acute* diarrheal illness, Dr. Guerrant's keen clinical eye opened the window to better understanding of the heavy burden of repeated *chronic* enteric infections in children. To illustrate, Dr. Guerrant describes "Carlos," a young boy who never made much noise or caused any fuss. He sat quietly in the corner. Unlike so many children in his village, he had not succumbed to the effects of malnutrition and acute diarrhea. But when Dr. Guerrant found out that this boy, who appeared to be about 5 years old, was actually 9 he began asking more questions.

While Carlos never had an acute, life-threatening infection, he suffered persistent diarrhea during his first two years of life. Dr. Guerrant began to notice many more children just like Carlos. Repeated infections created a cycle of illness throughout a critical period in childhood development. Could those persistent infections in the first two years of life be at the root of the physical and cognitive stunting?

With colleagues in Brazil, Dr. Guerrant demonstrated exactly that. Early childhood diarrhea and enteric infections have a lasting impact on physical and cognitive development. By age 7, an affected child in northeast Brazil might experience up to a six-inch growth shortfall. The cognitive deficit is no less astonishing. The same child might lose up to 10 IQ points.

Examining the cognitive deficit more closely, Dr. Guerrant and his colleagues were surprised to find that they were not phonetic, as they expected, but semantic. These semantic deficits are similar to those found in patients with Alzheimer's disease. Dr. Guerrant, who has seen first-hand the effect of Alzheimer's in his own family, says these deficits are "sad in an elderly person, but absolutely horrific in a child."

He and his colleagues proceeded to pursue the deficit's genetic determinants and surprisingly discovered that the risk gene for Alzheimer's, ApoE4, was protective against the cognitive deficits associated with the heavy diarrhea burdens early in life. "This finding was 180 degrees different from what we expected," says Dr. Guerrant. "The children with the ApoE4 gene were protected from the cognitive consequences of repeated bouts of diarrhea while those without the gene suffered the semantic cognitive loss."

This finding adds to the list of known antagonistic pleiotropies. In this case, the risk gene for Alzheimer's is protective against the cognitive deficits seen with heavy diarrhea burdens early in life. Similarly, people who carry the sickle cell trait are resistant to malaria, and cystic fibrosis carriers are immune to cholera and other diarrheal illnesses. Together these findings are illuminating theories about why and how certain genes have evolved in humans.

DR. GUERRANT'S ONGOING WORK EXPLORES NEW FRONTIERS IN ENTERIC DISEASE

Dick Guerrant has no intention of resting on his laurels after 39 years of distinguished scholarship and service. His long-standing National Institutes of Health (NIH) grant continues to support collaboration in northeast Brazil, where he is now looking further at the effect of the ApoE4 gene in selected follow-up populations.

Dr. Guerrant is also helping to lead a \$30 million eight-site Bill and Melinda Gates Foundation supported project, "Malnutrition as an Enteric Disease (MAL-ED)." This state-of-the-art project will examine the impact of repeated gut infections in the first few years of life on long-term physical and cognitive outcomes. Children are being enrolled at birth at sites in Africa, Latin America, and Asia and the team hopes to follow them for a long enough period to assess their cognitive function at 6 to 9 years of age, when more accurate and robust measurement is possible.

"Few individuals have made greater clinically relevant contributions to biomedical science over the last 30 years"

—Charles (Chuck) Carpenter, MD, Professor of Medicine, Warren Alpert Medical School of Brown University

Through another Gates grant, Dr. Guerrant is working to identify innovative biomarkers to test for enteropathy in young children. "The results of this study combined with results from the multicenter MAL-ED study will prime us to know how and where to test interventions that will help repair the injury to the intestinal tract from repeated enteric infections," says Dr. Guerrant, "so we can prevent the long-term physical and cognitive damage associated with them."



A DEEP LOVE OF APPLIED SCIENCE, MENTORSHIP, AND TRAINING

After graduating from the University of Virginia (UVA) School of Medicine and completing his training at Harvard/Boston City Hospital, NIH, and Johns Hopkins, Dr. Guerrant returned to UVA where he has been on staff for nearly 40 years. This pattern has been repeated by those he has trained.

He has recruited and trained more than 150 postdoctoral fellows and students who are becoming global leaders in tropical medicine. More than 70 are from Brazil, China, Ghana, the Philippines, and South Africa. All have returned to their home countries to become leaders and to develop models of sustained, productive international collaboration. His work serves as a model of how to reverse “brain drain” and increase capacity where it is needed most. In addition, he has trained literally hundreds of UVA students who have worked through global health scholarships in developing areas abroad.

Dr. Guerrant credits this to the inherent commitment among those seeking training in UVA’s program along with reliance on input from colleagues in the applicant’s home country on the selection process. He also believes his program’s focus on learning from the fellows—not just teaching—is a philosophy that benefits both student and teacher.

Dr. Guerrant has received a long list of honors. He was elected to both the Institute of Medicine and the National Academy of Sciences in 2003, where he has been the chair of the Board on Global Health since 2010. The Infectious Diseases Society of America (IDSA) honored Dr. Guerrant with the Walter E. Stamm Mentor Award and the Joseph E. Smadel Lectureship, which is named for a physician whose work, like Dr. Guerrant’s, created a bridge between the laboratory and frontline physicians. Dr. Guerrant also chaired the IDSA committee that developed practice guidelines for management of diarrhea.

Dr. Guerrant is past-president of the American Society of Tropical Medicine and Hygiene (ASTMH), which awarded him the Walter Reed Medal recognizing his distinguished accomplishments in the field of tropical medicine. According to William A. Petri, Jr., MD, PhD, Chief, Division of Infectious Diseases and International Health, University of Virginia Health System, “As past-president of the ASTMH, Dr. Guerrant has been instrumental in shaping tropical medicine training in the US. He is an outspoken voice for the urgency of international health as a transcendent human value.”

Reflecting his long and deep commitment to his work and colleagues in Brazil, Dr. Guerrant is Professor Honoris Causa at Unid de Farmacologia Clinica. He also received the Emilio Ribas Medal of the Brazilian Society of Infectious Diseases.

Back at home, Dr. Guerrant received the highest academic honor at University of Virginia, the Thomas Jefferson Award, in 2010. Two years later Governor Bob McDonnell honored him as the 2012 Outstanding Scientist of Virginia.

Dr. Guerrant is the author of over 550 scientific and clinical articles, reviews, and major textbook chapters. He is also editor of six books, including the leading textbook in its field, “Tropical Infectious Diseases: Principles, Pathogens and Practice.” He is also author of “At the Edge of Development: Health Crises in a Transitional Society,” a book that shares lessons learned in his collaborations in northeast Brazil. The New England Journal of Medicine calls it a “must for any healthcare professional planning to work in developing areas.”

DR. GUERRANT’S DECLARATION OF INTERDEPENDENCE

Dick Guerrant’s passion for the transcendence of global health as a unifying human value stems from his first plane trip to the Congo as a third year medical student at UVA. This passion fuels and drives him forward even today.

In his recent Keynote Address in Global Health at the University of Pennsylvania entitled “A Declaration of Interdependence,” he urges those working in global health to redefine “self” and to recognize that we are all defined by and dependent on the health and well-being of others. Dr. Guerrant sees us on the cusp of major evolutionary change. Where we once evolved thanks to our aggression, our best hope now is the reverse—to work together, caring about others.

“His Declaration of Interdependence illustrates how Dick Guerrant exemplifies in character, work, and influence the principles and ideals of the University of Virginia founder, Thomas Jefferson.”

– William A. Petri, Jr., MD, PhD
