

Review

## Parasitic and Infectious Disease Responses to Changing Global Nutrient Cycles

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**Abstract:** Parasitic and infectious diseases (PIDs) are a significant threat to human, livestock, and wildlife health and are changing dramatically in the face of human-induced environmental changes such as those in climate and land use. In this article we explore the little-studied but potentially important response of PIDs to another major environmental change, that in the global nutrient cycles. Humans have now altered the nitrogen (N) cycle to an astonishing degree, and those changes are causing a remarkable diversity of environmental and ecological responses. Since most PIDs are strongly regulated by ecological interactions, changes in nutrients are likely to affect their dynamics in a diversity of environments. We show that while direct tests of the links between nutrients and disease are rare, there is mounting evidence that higher nutrient levels frequently lead to an increased risk of disease. This trend occurs across multiple pathogen types, including helminths, insect-vectored diseases, myxozoa, and bacterial and fungal diseases. The mechanistic responses to increased nutrients are often complex and frequently involve indirect responses that are regulated by intermediate or vector hosts involved in disease transmission. We also show that rapid changes in the N cycle of tropical regions combined with the high diversity of human PIDs in these regions will markedly increase the potential for N to alter the dynamics of disease. Finally, we stress that progress on understanding the effects of nutrients on disease ecology requires a sustained effort to conduct manipulative experiments that can reveal underlying mechanisms on a species-specific basis.

**Keywords:** parasite, infectious disease, nutrients, nitrogen, phosphorus, eutrophication

### INTRODUCTION

Despite enormous public health efforts in recent decades, parasitic and infectious diseases (PIDs) still account for

more years of human life lost than any other major health risk (WHO, 2004). Malaria alone kills over one million people each year, diarrheal diseases cause more than 2 million deaths annually, and roughly 20 million people suffer severe consequences from schistosomiasis (WHO, 2004). Similarly, PIDs are a significant and at times growing threat to domestic and wild animals (Daszak et al., 2000), and to major crop species (Power and Mitchell,

2004). Nearly all PIDs are united by a common fact: they are regulated by ecological interactions in a rapidly changing world. Effective management of disease burdens throughout the world must therefore incorporate an understanding of ecological dynamics (e.g., Dobson, 2004) and how they respond to changes in environmental conditions.

The literature is now replete with examples of how anthropogenic effects on the environment can alter human, animal, and plant diseases (e.g., Daszak et al., 2001; Patz et al., 2004). However, most such studies have concentrated on two arenas of environmental change: those in land cover and land use and those in climate. In contrast, little is known about how another major change in the global environment—those in major nutrient cycles such as nitrogen (N) and phosphorus (P)—may alter the prevalence and risk of PIDs (Johnson and Carpenter, 2007). In particular, N is an essential and often limiting nutrient in ecosystems throughout the world, and humans are increasing the amount of biologically available N at an extraordinary rate (Galloway et al., 2004; Vitousek et al., 1997). These changes are known to alter the structure and function of multiple terrestrial and aquatic ecosystems (NRC, 2000; Vitousek et al., 1997), and evidence is emerging that an increased supply of both N and P to ecosystems may also cause an increased risk of disease in humans, livestock, and wildlife.

In this article we provide an overview of the changing global nitrogen cycle, review the evidence linking nutrients and disease, and discuss the ways in which major classes of PIDs may respond to continued changes in nutrient availability. Much of our focus is on diseases of aquatic or marine ecosystems as such environments are often focal points for high nutrient loading (NRC, 2000; Vitousek et al., 1997). However, we note that many of the principles discussed apply to diseases with a sizable terrestrial component.

## DISEASE AND THE CHANGING GLOBAL NITROGEN CYCLE

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Earth's atmosphere is predominantly  $N_2$  gas, but  $N_2$  is accessible to only a subset of microorganisms that are capable of "fixing" it into forms that are then available to the rest of Earth's biota. Absent human influences, such biological N fixation is the major source of new N to ecosystems, and this flux is well below biotic demand (Cleveland et al., 1999). For this and other reasons, N limits

primary production and energy availability in many of earth's ecosystems (Vitousek and Howarth, 1991). This fact accounts for the enormous use of nitrogen fertilizers in modern agriculture.

Fertilizer creation and use, widespread cultivation of leguminous crops, and fossil fuel burning have caused the global N cycle to change dramatically in the last few decades (Galloway et al., 2004). More than half of all N fertilizer ever used in Earth's history has been applied in the past two decades (Howarth et al., 2002). In portions of North America, Europe, and Asia, atmospheric N deposition and river-borne N fluxes to the coast have risen an order of magnitude in less than a century (Boyer et al., 2002; Galloway et al., 2004; Howarth et al., 1996). Such changes are projected to continue well into the future (Galloway et al., 2004).

The resultant environmental effects are diverse and at times severe. They include eutrophication of coastal marine and some freshwater ecosystems, increases in atmospheric pollutants such as tropospheric ozone ( $O_3$ ), contributions to climate change, soil and water acidification, shifts in species composition, and losses of biodiversity (Vitousek et al., 1997). Thus, management of a changing N cycle is becoming a significant policy issue (Mosier et al., 2002) as nations struggle with balancing human need for fertilizer and crop production with the environmental damages created by high N inputs.

A changing N cycle can also affect human health well beyond the obvious benefits of increased crop production (Townsend et al., 2003). Some of these connections are well recognized, e.g., anthropogenic N can fuel high levels of ozone and other components of air pollution, but many other potential links remain poorly studied, especially those mediated by ecological interactions. However, because rising N inputs can promote a broad suite of ecological changes, they are likely to influence the dynamics of parasitic and infectious diseases (Mitchell et al., 2003; Townsend et al., 2003, 2007). For example, vector-borne pathogens that cause malaria and schistosomiasis involve intermediate hosts (mosquitoes and snails) whose growth and reproduction depend on primary producers in their respective environments. Where N additions cause greater plant growth and/or changes in plant species composition, the density of these intermediate hosts is also likely to be affected, with cascading consequences for the risk of disease. Moreover, increased N loading to the environment often occurs in tandem with that of phosphorus; in freshwater ecosystems in particular, a combined increase in both

N and P is highly likely to drive eutrophication and associated significant ecological change.

Direct tests of how nutrient additions alter the dynamics of disease are rare (Bruno et al. 2003; Johnson et al., 2007; Voss and Richardson, 2006). However, a few theoretical treatments of eutrophication, along with a number of observational studies summarized in the next section, provide some guidance for considering the potential effects of changing nutrient cycles on PIDs. For example, Lafferty (1997) reviewed parasitic responses to a suite of environmental changes and found that in 11 of 12 cases, eutrophication caused an increase in parasite abundance. In all likelihood the positive association was a product of increased resources for growth and reproduction of the intermediate hosts, to an extent that outweighed any direct (e.g., low O<sub>2</sub>) or indirect (e.g., predation) changes that may also have occurred. This suggestion is supported by modeling studies of environmental stress and disease in which higher resource availability in eutrophic conditions led to higher host densities and increased disease transmission efficiency (Lafferty and Holt 2003). Marcogliese (2001) suggested that eutrophication will lead to an increase in generalist vs. specialist parasites and to an increase in overall parasite abundance, up to the point at which water quality declines so severely that anoxic conditions are widespread. At this extreme, when poor water quality leads to host mortality and decreased host density, disease may decrease as a result of the inability of the pathogen to transmit to new susceptible hosts. Alternatively, if poor water quality does not have a significant effect on host mortality but instead lowers host immune function, an increase in disease levels may result due to higher host susceptibility.

Of course, the multiple ways in which a pathogen may respond to changing conditions (e.g., Lafferty and Holt, 2003), especially ones like increased N or P that can have ecosystem-level consequences, means that rising nutrient inputs will not always increase disease prevalence. Rather, the net result will be a balance between the direct effects of the change on the pathogen itself and a large potential array of indirect effects mediated through other species that affect its fitness. In theory, increased nutrient availability could cause responses in disease that run the entire spectrum from strongly negative to strongly positive. An example from *Aedes albopictus* mosquitoes—carriers of several human viruses, including dengue and Cache Valley fever—illustrates the difficulty in making broad generalizations. Comiskey et al. (1999) showed that low-nutrient habitats led to significantly higher mosquito mortality from

ascogregarine parasite infections, but that in high-nutrient conditions, parasitism reduced female mosquito reproductive output. Thus, changing nutrient availability affects *Aedes* survival and fitness in complex ways involving parasitism of the mosquito, which in turn will alter the risk to hosts of contracting PIDs vectored by *Aedes albopictus*.

That said, past reviews by Lafferty (1997) and Townsend et al. (2003), along with the evidence described below, suggest a worrisome trend in which the majority of associations between increased nutrients and disease are positive. Because direct, experimental tests are virtually nonexistent, it remains unclear if this trend is simply a bias in what associations have been reported (i.e., negative and neutral responses go undocumented), or if it truly represents a common response to eutrophication. In this article we review the existing evidence and outline probable ways in which major pathogen classes may respond to increased nutrient availability. Finally, we discuss future potential changes in the links between nutrients and disease, with an emphasis on the PID-rich equatorial latitudes.

## OBSERVATIONS TO DATE

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Studies that consider the relationship between anthropogenic sources of nitrogen (N) and phosphorus (P) and infectious disease are summarized in Table 1. The parasites and pathogens encompassed in these 34 studies include helminths, protozoans, bacteria, viruses, fungi, and myxozoans, totaling 41 different species that infect humans and wildlife in six of the seven continents. There are additional studies that address links between nutrients and plant pathogens (cf. Mitchell et al., 2003), but because the dynamics of plant infections are typically different from those of humans and animals, here we restrict our discussion to the latter classes. The data and conclusions represented in Table 1 range from field observations to experimental manipulations, to modeling, to largely anecdotal accounts. Collectively, 51 of 55 (93%) of these parasite or pathogen observations demonstrate a positive relationship with increasing nutrients.

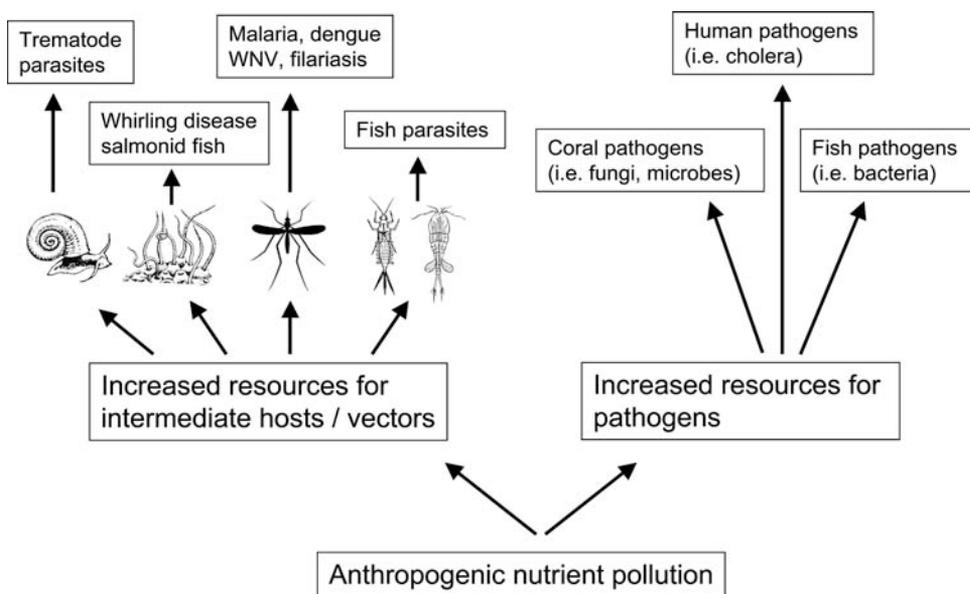
The diversity of pathogen types suggests many mechanistic pathways by which nutrients may stimulate a disease response. A parasite or pathogen may respond to nutrients directly or an intermediate/vector host may respond to nutrients, mediating the overall disease response. Thus, diseases with a “direct” mechanistic response are those that do not require an intermediate or vector host. However, we

**Table 1.** Studies that address the relationship between parasites or pathogens and nutrients

Location	Disease response to + nutrients	Intermediate/ vector host	Type of data	Reference
Antarctica	Increase	Amphipod	Field	Moser and Cowen, 1991
Antarctica	Increase	Decapod	Field	Moser and Cowen, 1991
Antarctica	Increase	Copepod	Field	Moser and Cowen, 1991
Antarctica	Increase	Snail	Field	Moser and Cowen, 1991
Antarctica	Decrease	Snail	Field	Moser and Cowen, 1991
Michigan, USA	Increase	Mayfly	Field	Marcogliese et al., 1990
Michigan, USA	Increase	Snail	Field	Lindblade, 1998
Midwest, USA	Increase	Snail	Anecdotal	Levy and Folstad, 1969
Brazil	Increase	Snail	Anecdotal	de Oliveira and Krau, 1970
Brazil	Decrease	Snail	Anecdotal	Thomas, 1995
North America	Increase	Snail	Field	Johnson and Chase, 2004
North America	Increase	Snail	Experimental	Johnson et al., 2007
North America	Increase	Snail	Model	McKenzie, 2005
Southeast USA	Increase	Snail	Anecdotal	Overstreet and Curran, 2004
Costa Rica	Decrease	Fingernail Clam	Field	McKenzie, 2007
Costa Rica	Decrease	Snail	Field	McKenzie, 2007
Costa Rica	Increase	Snail	Field	McKenzie, 2007
Costa Rica	Increase	Snail	Field	McKenzie, 2007
Costa Rica	Increase	Snail	Field	McKenzie, 2007
Costa Rica	Increase	None	Field	McKenzie, 2007
Costa Rica	Increase	Mosquito	Field	McKenzie, 2007
Costa Rica	Increase	Unknown	Field	McKenzie, 2007
Midwest USA	Increase	Bryozoans	Field/ Anecdotal	Okamura et al., 2001
Western USA	Increase	Oligochaetes	Anecdotal	Hedrick et al., 1998
Western USA	Increase	Oligochaetes	Field	Krueger et al., 2006
Eastern USA	Increase	Oligochaetes	Field	Kaesler et al., 2006
Kenya	Increase	Mosquito	Field/ Anecdotal	Munga et al., 2006
Tanzania	Increase	Mosquito	Field/ Anecdotal	Sattler et al., 2005
Mexico	Increase	Mosquito	Field/ Anecdotal	Rejmankova et al., 1991
Taiwan	Increase	Mosquito	Field/ Anecdotal	Teng et al., 1998
Brazil	Increase	Mosquito	Anecdotal	Vasconcelos et al., 1997
North America	Increase	Mosquito	Exp't/ Anecdotal	Reiskind and Wilson, 2004
North America	Increase	Mosquito	Exp't/ Anecdotal	Reiskind et al., 2004
coastal USA	Increase	None	Anecdotal	Burkholder et al., 1997
Kuwait Bay	Increase	None	Field/ Anecdotal	Heil et al., 2001
Italy lakes	Increase	None	Anecdotal	Grimaldi, 1991
Florida Keys	Increase	None	Field/ Anecdotal	Kim and Harvell, 2002
Caribbean	Increase	None	Field/ Experimental	Bruno et al., 2003
Caribbean	Increase	None	Field/ Experimental	Bruno et al., 2003
Florida Keys	Increase	None	Field	Kuta and Richardson, 2002
Caribbean	Increase	None	Field/ Experimental	Voss and Richardson, 2006
Caribbean	Increase	None	Field/ Anecdotal	Kaczmarek et al., 2005
Caribbean	Increase	None	Field/ Anecdotal	Kaczmarek et al., 2005
Japan	Increase	None	Anecdotal	Kusuda, 1992
Japan	Increase	None	Anecdotal	Kusuda, 1992
Japan	Increase	None	Anecdotal	Kusuda, 1992
Japan	Increase	None	Anecdotal	Kusuda, 1992

**Table 1.** Continued

Location	Disease response to + nutrients	Intermediate/ vector host	Type of data	Reference
Japan	Increase	None	Anecdotal	Kusuda, 1992
Japan	Increase	None	Anecdotal	Kusuda, 1992
Japan	Increase	None	Anecdotal	Kusuda, 1992
Japan	Increase	None	Anecdotal	Kusuda, 1992
Japan	Increase	None	Anecdotal	Kusuda, 1992
Kuwait Bay	Increase	None	Field/ Anecdotal	Glibert et al., 2002
Bangladesh	Increase	None	Anecdotal	Epstein, 1993
India, Bangladesh, SA	Increase	None	Anecdotal	Colwell and Huq, 2001

**Figure 1.** Conceptual diagram of mechanisms by which parasites and pathogens may respond positively to increased nutrient availability.

note that for most of the pathogens listed in Table 1 that do not have an intermediate or vector host, it remains unknown if the disease agent is directly limited by available nutrients or if other processes are involved. Diseases with a “mediated” mechanistic response are those that require an intermediate or vector host. This intermediate or vector host response is typically either an increase in population density as a result of increased primary productivity, or a decrease in population due to some disturbance related to nutrient addition, though direct nutrient limitation of hosts (e.g., of mosquito larval growth) may occur in some situations. Regardless of the mechanism, changes in intermediate host/vector density result in changes in transmission success of the parasite or pathogen (Anderson and May, 1978; Arneberg et al., 1998; Dobson, 1990).

In general, the helminths, insect-vector diseases, and myxozoans are categorized as mediated responders because

of their reliance on intermediate hosts, while the bacterial and fungal pathogens are categorized as direct responders (Fig. 1). We stress, however, that despite the diversity in pathogens and modes of response, a remarkably consistent trend emerges from Table 1, in which nutrient additions are nearly always associated with a greater risk of disease. In the following sections, we examine the mechanisms proposed for each major group of parasites and pathogens listed in Table 1 and identify the gaps in understanding the relationship between nutrient pollution and infectious disease.

## DISCUSSION

### Trematode Parasites

Among the helminth parasites studied with regard to environmental nutrient addition, the trematodes are per-

haps the most well known. Trematode parasites infect every class of marine and freshwater vertebrate. They include important human diseases like schistosomiasis, lung flukes, and liver flukes as well as parasites that threaten livestock and wildlife (i.e., *Ribeiroia ondatrae* in amphibians). All trematode life cycles involve a first intermediate molluscan host, where the parasite reproduces asexually to release free-swimming stages called cercariae that seek the next appropriate host in the life cycle. The dynamics of trematode life cycles are therefore heavily dependent upon the distribution of snail hosts in aquatic systems. In general, when snail hosts are densely populated, parasitic stages introduced from infected final hosts (miracidia) have an easier time locating snails to infect, thereby creating a higher proportion of infected snails relative to a system where snails are sparse. A higher number of infected snails can cause a manifold increase in cercariae production, since the parasites reproduce asexually in snails. The subsequent host to the snail in the trematode life cycle is challenged with far more infective cercariae when conditions allow snail and parasite populations to be densely packed.

Nutrients come into play in trematode life cycles by affecting snail populations (i.e., an intermediate host-mediated mechanism). Many snails consume primary producers and therefore nutrients can trigger a bottom-up effect whereby increased algal growth provides more available food. Recent experimental work (Johnson et al., 2007) suggests that planorbid snails in nutrient-rich environments enjoy increased growth in a number of ways: individuals grow faster and larger individuals are able to produce significantly more trematode cercariae at a faster rate. These multiple responses set the stage for increased trematode transmission. *Ribeiroia ondatrae* exemplifies the potential response of trematode diseases to rising nutrient inputs (Johnson and Chase, 2004). This trematode species has gained attention because it causes severe limb malformations in its amphibian hosts (Johnson et al., 1999; Sessions and Ruth, 1990). It appears to be growing more abundant across North America in recent decades (Johnson et al., 2003); at some locations the parasite now infects more than 80% of the amphibians (Johnson and Sutherland, 2003). The *R. ondatrae* life cycle has multiple secondary intermediate hosts (freshwater fishes and amphibians) and definitive hosts (birds and rodents), but the first intermediate host is consistently a planorbid snail (Beaver, 1939; Johnson et al., 2004). In addition, eutrophic systems may further exacerbate the disease problem by attracting final hosts (birds), since the productivity of those

systems frequently offers abundant prey species. Infected final hosts moving among water bodies can continually introduce the parasite to new locations, acting as a positive feedback loop at the landscape level. Model analyses by McKenzie (2005) predict that nutrient enrichment will outpace even negative feedbacks such as snail castration at high infection levels over a wide range of nutrient and parasite inputs.

Diplostomoid trematodes echo the mechanism of the *R. ondatrae* model but have received almost no attention in this context. For example, *Bolbophorus damnificus*, named for its devilish impact it has on the catfish industry (Overstreet et al. 2002), utilizes the same planorbid snail hosts as *R. ondatrae* (and some physid and lymnaeid species), but infects catfish as the second intermediate host and fish-eating birds as the final host (Overstreet and Curran, 2004). The artificial pond environments of catfish farms create supreme conditions for massive trematode infections. Fingerling catfish are densely packed and are given pellet food by the truckload. Between the pellet food and the fish excrement, most ponds are very nutrient rich and many are highly eutrophic. High primary productivity causes high snail densities and the abundant catfish attract a suite of fish-eating birds. Thus, all three hosts involved in the diplostomoid trematode life cycle are densely packed in the rearing ponds. Parasite-induced losses to some catfish farms have been catastrophic and occasionally resulted in farm closure (Overstreet and Curran, 2004). Attempted methods of parasite management focus on bird and/or snail control via chemical methods (i.e., copper sulfate) or introduction of predators (Venable et al., 2000), but none has considered controlling nutrient levels to limit snail growth.

Finally, although schistosomiasis is a widespread and debilitating human disease, there has been surprisingly little study of the ecological factors that influence the distribution and abundance of its intermediate snail hosts. Yet, the examples above suggest that disease risk may be higher in nutrient-rich environments. Three species of *Schistosoma* that infect humans use several different snails, including species of *Biomphalaria*, *Bulinus*, and *Oncomelania*. We know little about the responses of these snail species to nutrient additions. However, *Biomphalaria* belongs to the planorbid snails, which demonstrate strong positive responses to nutrient additions (Johnson and Chase, 2004), and “bird schistosomes” that cause swimmer’s itch in humans are known to be more abundant in eutrophic waters (Levy and Folstad, 1969; Lindblade, 1998). Furthermore,

Southgate (1997) observed an increase in schistosomiasis infection following the building of dams in Senegal, associated with the creation of suitable habitat for snails in agricultural areas, although the role of nutrients was not specifically discussed. Surprisingly, Thomas (1995) suggests that eutrophication may serve as a control for schistosomiasis based on a study demonstrating that European snail species (that do not transmit schistosomes) decline when a eutrophic system reaches the point of anoxia (Thomas and Daldorph, 1994). However, this result is likely a consequence of conditions that represent a “final endpoint” of eutrophication, where anoxia can become a dominant control (e.g., Marcogliese, 2001). In most cases, increased nutrients are likely to increase primary producer growth, and thereby favor higher snail densities. As such, DeOliveira and Krau (1970) suggested that eutrophic conditions will favor schistosome-transmitting snails in Brazil. Taken as a whole, an examination of trematode ecology suggests that nutrient additions should frequently increase disease risks.

### Insect-vectoring Disease

The diversity of parasites and pathogens transmitted by insect vectors includes protozoans (i.e., malaria, leishmaniasis, trypanosomes), viral pathogens (i.e., dengue, West Nile), and filarial worms (i.e., Bancroftian filariasis, river blindness). The variety of potential mechanistic responses of this category of diseases to increased nutrients is perhaps the most complex and devoid of clear predictions. Very few studies have directly tested the effects of nutrients on insect-vectoring diseases, though several others did provide some correlative insight (Table 1). In a rare direct test, higher nutrient levels enhanced survival of larval *Culex* mosquitoes involved in West Nile virus transmission (Reiskind et al., 2004) and increased odds of oviposition by adult females (Reiskind and Wilson, 2004). Other studies have addressed (but not manipulated) the relationship between nutrients and the vector itself in field conditions, and from there drew implications about disease responses (Comiskey et al., 1999; Gimnig et al., 2002; Pope et al., 2005). Many more studies have addressed the positive relationship between land use change and mosquito-vectoring diseases (i.e., Afrane et al., 2005; Munga et al., 2006; Norris, 2004; Tadei et al., 1998; Vasconcelos et al., 1997), some of which postulate that increased nutrients following land conversion may support greater larval vector development. For example, Pope et al. (2005) examined two

sympatric species of *Anopheles* mosquitoes and their respective breeding habitats at the landscape scale in Belize. They found that one of the species, *A. vestitipennis*, breeds in marshes dominated by a particular macrophyte (*Typhus domingensis*) and that *Typhus* productivity increases in areas that receive agricultural nutrient runoff, whereas the marshes preferred by the other *Anopheles* species do not respond to the nutrient runoff. They conclude that nutrient runoff will lead to increased malaria transmitted by *A. vestitipennis*. Other studies suggest that some mosquito larvae may benefit from increased nutrients via increased algal food (i.e., *A. gambiae* in Kenya; Gimnig, 2002; Munga, 2006). However, many other environmental factors influence larval mosquito development and adult feeding behavior, such as temperature (Afrane, 2005), pH (Tadei et al., 1998), and turbidity (Sattler et al., 2005), all of which can be related to changes associated with land use and nutrient addition. This area is ripe for experimental work aimed at identifying the relative importance of these and other factors. Some vector species appear to be heavily dependent on specific breeding sites and associated macrophytes (e.g., Pope et al., 2005), while others appear to be less specific about their requirements (e.g., Sattler et al., 2005), and both types may respond to changing nutrient inputs to the environment.

Beyond malarial mosquitoes, there are many other insect vectors and diseases that likely respond to land use changes and perhaps to the increasing trend of nutrient pollution. For example, mosquitoes are also vectors of *Wuchereria bancrofti*, the filarial nematode that causes elephantiasis in humans. A related filarial parasite of amphibians transmitted by *Culex* mosquitoes was more abundant in frog hosts from clear-cut cattle pasture areas relative to forest in Costa Rica (McKenzie, 2007). Tsetse flies, the vector for trypanosomiasis, appear to respond to land use changes in West Africa (de La Rocque et al., 2001; Fournet et al., 2000). Their populations decrease in riverine habitat near crop fields but increase near cattle fields and increased human activity (de La Rocque et al., 2001); in either case, the mechanisms behind the population shifts are unclear. The role of nutrients in the dynamics of diseases transmitted by these and other insect-vectoring diseases (i.e., leishmaniasis, river blindness) remains largely unexplored. Because insects are notoriously specific regarding microhabitat requirements, we should expect that their responses to changing nutrient regimes will vary accordingly and we again underscore the importance of appreciating the unique relationships between different

insect vectors, diseases, and nutrient-driven changes to their environment.

### Myxozoans

Myxozoans infect marine and freshwater fishes; they are microscopic metazoan animals related to jellyfishes (Sidall, 1995) and are most well known because of *Myxobolus cerebralis*, the agent that causes whirling disease in salmonid fishes. Whirling disease affects spinal development and behavior in fish and mortality from it is often very high. The disease is believed to be native to salmonids in Eurasia but has been spread to regions around the world with intensive salmonid aquaculture, especially in Europe and the western United States (Halliday, 1976). Only since the 1980s has the life cycle of *M. cerebralis* been discovered to involve oligochaetes (*Tubifex* worms) as an intermediate host (Wolf and Markiw, 1984). Another pathogenic myxozoan that causes proliferative kidney disease in fishes, *Tetracapsula bryosalmonae*, uses bryozoans as the intermediate host (Feist et al., 2001). These pathogens are transferring from aquaculture environments to the wild and are responsible for massive die-offs of wild trout populations in the western U.S. (Hedrick et al., 1998; Vincent, 1996). The rearing conditions for salmonid aquaculture involve densely stocked fishes in nutrient-rich pens where the intermediate hosts thrive. Krueger et al. (2006) demonstrated that fishes are at a greater risk to contract whirling disease in areas with a higher density of intermediate hosts and further argue that preferred habitat of the tubificid worms may be enhanced in productive (high nutrient) streams. Furthermore, Kaeser et al. (2006) found *Tubifex* worms to be highly associated with point sources of organic matter enrichment in Pennsylvania water bodies. The relationship between eutrophic environments and the intermediate hosts of pathogenic myxozoans requires more study, but they appear to be another parasite that is influenced by bottom-up effects.

### Bacteria and Fungi

Bacterial and fungal pathogens that may be responsive to environmental changes are astonishingly diverse (Daszak et al., 2001; Patz et al., 2004). Several environmentally harbored bacterial diseases pose significant risks; notable examples include cholera, tuberculosis, lyme disease, and plague. In addition, both bacterial and fungal diseases can produce significant morbidity and mortality in livestock

and wildlife (Daszak et al., 2000; McCallum and Dobson, 1995).

Bacteria and fungi display a remarkable range of physiologic growth strategies, including both autotrophy and heterotrophy; thus, the effects of available nutrients on their growth and reproduction will vary depending on their means of acquiring energy. In addition, as with nearly all other organisms in the environment, the abundance of a given microbial species will be controlled by its energy sources, its competitors, and a range of potential predators. Moreover, especially for heterotrophs, energy availability may be strongly linked to the growth of primary producers. Thus, as with the insect-vectored diseases, microbial pathogen responses to nutrient enrichment are likely to span the range from negative to positive.

Studies of *Vibrio* bacteria exemplify the potential complexity and show possible modes of response. *Vibrio* are a taxonomically diverse genus of heterotrophic bacteria that are common in marine environments and responsible for a number of human and wildlife diseases, including cholera and shellfish poisoning in humans (Epstein, 1993) and vibriosis in several fish species (Kusuda, 1992). In the case of cholera, the bacteria display a strong association with marine plankton, and therefore factors that cause increases in plankton primary productivity can also increase the prevalence of *V. cholerae*. Thus, nitrogen-based eutrophication of coastal regions (NRC, 2000) has been linked to increased cholera risks (Colwell and Huq, 2001; Epstein, 1993), likely via an indirect response to plankton dynamics.

However, recent studies of microbial coral infections (Bruno et al., 2003; Voss and Richardson, 2006) suggest that direct N and/or P limitation of bacterial proliferation may also occur. These studies represent two of the few manipulative tests of how nutrient levels affect disease and demonstrated that N and P additions increased the incidence of yellow and black band disease in Caribbean corals. Nutrients also were associated with a higher incidence of the fungal disease aspergillosis in Caribbean sea fans (Kim and Harvell, 2002) as well as black band disease in brain corals (Kuta and Richardson, 2002).

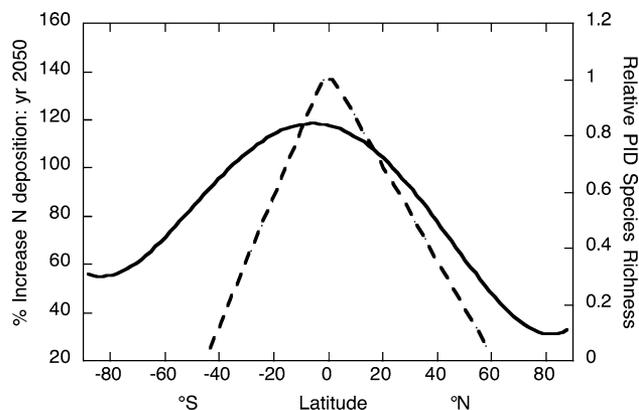
## THE FUTURE OF NUTRIENTS AND DISEASE

While numerous studies suggest rising nutrient inputs can increase disease prevalence, PID responses to such changes are likely to be complex and variable and include situations in which the risk of disease declines. However, we contend

that the coming decades will bring a marked increase in the *potential* for nutrients, especially N, to affect parasitic and infectious diseases for two major reasons. First, changes in the N cycle have not been—and will not be—globally uniform (Galloway et al., 2004). Historically, the most dramatic changes have occurred in three Northern Hemisphere regions that combine a long history of industrial activity with intensive agricultural practices; these are (1) much of the United States and portions of Canada, (2) western Europe, and (3) temperate to subtropical portions of eastern Asia. However, the global pattern is beginning to shift, as the most dramatic recent changes have occurred in tropical and subtropical regions. For example, soybean agriculture has exploded in Brazil over the last decade, leading to rapid increases in regional N deposition and nutrient loading to aquatic ecosystems (Martinelli et al., 2006). Similar increases are occurring throughout tropical and subtropical portions of Asia and Central America. These recent trends, combined with population and industrial growth projections for much of the developing world, lead to the prediction that the greatest relative changes in the N cycle over the next 50 years will occur largely in tropical and subtropical regions (Dentener, 2006; Galloway et al., 2004).

Second, it is these same regions that harbor the greatest diversity of human PIDs (Guernier et al., 2004), including those that currently cause the majority of PID-related human deaths (WHO, 2004). To illustrate the growing future potential for N to influence disease, we compared latitudinal patterns in PID species richness (Guernier et al., 2004) to modeled predictions of total N deposition (Dentener et al., 2006). The latter is a good index of regional changes in the N cycle and of potential impacts on ecological systems because N deposition sources are both agricultural and industrial, and higher deposition can occur even in systems that otherwise receive relatively minimal human disturbance. Figure 2 shows that the far greater human PID diversity in equatorial latitudes is likely to interact with substantial increases in N deposition over the next 50 years. Moreover, unlike temperate latitudes, terrestrial ecosystems in the tropics are often relatively N rich, even in a pristine state; thus, as additional, human-generated N enters these landscapes, they may show much more rapid and sizable N losses to aquatic realms (Matson et al., 1999) where a number of important diseases are harbored.

It is only with direct, experimental tests that we can begin to derive predictions that are useful in a management context. Moreover, predictions of N and/or P effects on



**Figure 2.** Relative increase in nitrogen deposition between 1993 and 2050 (solid line) vs. latitudinal patterns in parasitic and infectious disease (PID) species richness (dashed lines). The N deposition line is an interpolated pattern from modeled projections by Dentener (2006), while the PID line is adapted from Guernier et al. (2004).

disease are further challenged by the fact that they will typically occur in tandem with other significant environmental changes. For example, the tropics are home to substantial current and future changes in land use and land cover, a disturbance that is known to cause increased potential for a suite of human and animal diseases (Patz et al., 2004). Likewise, we are very likely already experiencing human-induced climate change, even in tropical regions (IPCC, 2007); shifts in climate can alter the distribution and abundance of many environmentally harbored diseases (Marcogliese, 2001; Patz and Olson, 2006; Shope, 1991) and will affect entire ecosystems in ways that will interact with responses to increased N. Rising N availability throughout the world may also, in some instances, favor species invasions (Sala et al., 2000), and, regardless of the drivers, the spread of invasive organisms is a global-scale change that can both include and affect pathogens (Daszak et al., 2000; Torchin et al., 2003). Thus, while changes in the N cycle are notably large, they are but one of several significant alterations of the global environment; therefore, assessments of the effects of N on disease cannot reasonably be done in isolation.

## CONCLUSIONS

Anthropogenic changes to the global nutrient cycles, especially the N cycle, are already without parallel in Earth's history and will continue to increase in the foreseeable future. We know that human creation and use of fixed N (1) has substantial health benefits via increased food pro-

duction but (2) leads to a widespread and growing litany of environmental problems. The unwanted consequences also include risks for human health, some of which are well known but others of which remain poorly understood. The latter certainly applies to the responses of parasitic and infectious diseases.

Above all, to resolve current uncertainties we need controlled, manipulative experiments that can clearly identify the mechanisms by which a given pathogen may respond to altered nutrient availability. Only a very small number exist that test links between nutrients and disease (Bruno et al., 2003; Johnson et al., 2007; Mitchell et al., 2003; Voss and Richardson 2006). Not all pathogens will readily lend themselves to such experiments, but model systems exist that span the range of major pathogen classes. In addition, even in the absence of manipulative tests, correlation-based studies can benefit greatly from collection of data that are most indicative of ecosystem nutrient status.

Finally, there is much that society could do to change the future course of N creation and use. Examples include improved technologies for reducing N emissions during fossil fuel burning (Moomaw, 2002), precision agricultural and economic incentives to reduce fertilizer use and pollution (Matson et al., 1998), shifts in human dietary preferences (Howarth et al., 2002), and even changes in cultural practices that tend to lead to overuse of fertilizers without benefits to crop production. Taken as a whole, it is clearly possible to substantially reduce the negative and unwanted consequences of anthropogenic N while still maximizing its benefits to society.

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