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Linking environmental nutrient enrichment and disease emergence in humans and wildlife

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Abstract

Worldwide increases in the numbers of human and wildlife diseases present ecologists with the challenge of understanding how large-scale environmental changes affect host-parasite interactions. One of the most profound changes to Earth's ecosystems is the alteration of global nutrient cycles, including those of phosphorus (P) and especially nitrogen (N). Alongside the obvious direct benefits of nutrient application for food production, growing evidence suggests that anthropogenic inputs of N and P can indirectly affect the abundance of infectious and noninfectious pathogens, sometimes leading to epidemic conditions. However, the mechanisms underpinning observed correlations, and how such patterns vary with disease type, have long remained conjectural. Here, we discuss recent experimental advances in this area to critically evaluate the relationship between environmental nutrient enrichment and disease. Given the inter-related nature of human and wildlife disease emergence, we include a broad range of human and wildlife examples from terrestrial, marine and freshwater ecosystems. We examine the consequences of nutrient pollution on directly transmitted, vector-borne, complex life cycle, and noninfectious pathogens, including West Nile virus, malaria, harmful algal blooms, coral reef diseases and amphibian malformations.

Our synthetic examination suggests that the effects of environmental nutrient enrichment on disease are complex and multifaceted, varying with the type of pathogen, host species and condition, attributes of the ecosystem and the degree of enrichment; some pathogens increase in abundance whereas others decline or disappear. Nevertheless, available evidence indicates that ecological changes associated with nutrient enrichment often exacerbate infection and disease caused by generalist parasites with direct or simple life cycles. Observed mechanisms include changes in host/vector density, host distribution, infection resistance, pathogen virulence or toxicity, or the direct supplementation of pathogens. Collectively, these pathogens may be particularly dangerous because they can continue to cause mortality even as their hosts decline, potentially leading to sustained

epidemics or chronic pathology. We suggest that interactions between nutrient enrichment and disease will become increasingly important in tropical and subtropical regions, where forecasted increases in nutrient application will occur in an environment rich with infectious pathogens. We emphasize the importance of careful disease management in conjunction with continued intensification of global nutrient cycles.

Keywords

eutrophication; nitrogen; zoonotic disease; harmful algal blooms; HABs; global change; host-parasite interaction

Disease emergence in humans and wildlife

Despite major advances in human medicine, infectious disease remains the largest cause of human mortality worldwide (WHO 2004). While some pathogens have been eliminated or controlled, the combination of newly emerging diseases and the resurgence of extant diseases engenders an annual human death toll of ~12 million people. New diseases such as Acquired Immunodeficiency Syndrome (AIDS), Lyme borreliosis, Ebola, Sudden Acute Respiratory Syndrome (SARS), Bovine Spongiform Encephalopathy (BSE) and Hantavirus Pulmonary Syndrome (HPS) have emerged, while significant increases in established infections such as malaria, tuberculosis, cholera and measles have also occurred. Importantly, however, this trend is not unique to human pathogens. Emergence of wildlife diseases have exhibited a similar pattern in recent decades, largely over-turning the once-dominant paradigm that disease is not an important cause of wildlife mortality (May 1988; Daszak et al. 2000; Dobson and Foufopoulos 2001). Examples are numerous and include Viral Hemorrhagic Septicemia Virus (VHSV) in fishes, colony collapse disorder in honeybees, sudden oak death in trees, mycoplasmosis in birds, toxoplasmosis in sea otters, and chytridiomycosis in amphibians (Daszak et al. 2000; Miller et al. 2002; Rizzo and Garbelotto 2003; Lips et al. 2006).

The parallel emergence of human and wildlife diseases reflects the facts that (i) each have similar etiologies involving ecological changes in the environment, and (ii) the division between medical and veterinary diseases is largely an artificial one. Most emerging diseases of humans are zoonotic, meaning they involve animal hosts or vectors at some stage of transmission (Taylor et al. 2001). Consequently, patterns of infection in humans are often linked to the levels of infection in wildlife, and a thorough understanding of disease emergence thus requires knowledge of the ecological factors that influence humans, wildlife hosts, and their interactions (NRC 2001). A growing number of examples illustrate the value of an ecological approach for understanding disease and collectively suggest that broad patterns of emergence are best understood by examining human and wildlife populations concurrently. Here we adopt such an approach to explore the relationships between environmental nutrient enrichment and disease. Recognizing the parallel and often inter-related patterns between pathogens of humans and those wildlife, we do not differentiate between medical and veterinary diseases, and interweave examples of each to broadly examine the effects of nutrients on diseases.

Changing N and P Cycles

Human activities have driven massive changes in the major biogeochemical cycles, particularly those of nitrogen (N) and phosphorus (P). For example, nitrogen (N) fixed via fossil fuel combustion, fertilizer production and through cultivation of N fixing crops now outpaces N inputs from all natural processes on the land surfaces of the planet combined (Galloway et al. 2004). Similarly, the extraction, refining and application of P fertilizer has amplified the natural P cycle by ~ 2- to 3-fold (Howarth et al. 1995). The regional variation in the acceleration of

these nutrient cycles is remarkable. While some regions of the world such as northern Canada and Siberia have seen little if any change, other regions such as western Europe, the northeastern US, and east Asia have seen 10- to 15-fold increases in nutrient flows in rivers and in the atmospheric deposition of nitrogen (Howarth et al. 2005; Howarth 2008). Nutrient use for human enterprises has a range of effects on the Earth system, both positive and negative. For example, mineral fertilizer production and legume crop cultivation fueled the Green Revolution, significantly increasing crop yields that support growing human populations, decreasing malnutrition and enhancing economic prosperity (Sanchez 2002, Smil 2001, 2002). On the other hand, environmental N loading can cause a cascade of negative effects (*sensu* Galloway et al 2003), including declines in forest health (Schulze 1989, Aber et al. 1998), changes in species composition and losses of biodiversity (Vitousek et al 1997; Stevens et al 2004), eutrophication and loss of habitat quality in aquatic ecosystems (NRC 2000, Howarth et al. 2000; Schindler 2006; Smith et al. 2006), acidification of soils (Högberg et al. 2006) and changes to the chemistry and radiative balance of the atmosphere (IPCC 2007). P enrichment has a less diverse set of consequences, but is a major driver of aquatic eutrophication, particularly in freshwaters (Carpenter et al. 1998; Schindler 2006; Smith et al. 2006). Thus, in spite of the clear benefits to humans of the increased uses of fertilizer N and P, the widespread and increasing use of anthropogenic nutrients is also transforming the state of natural ecosystems and the myriad services and functions they provide (Vitousek et al. 1997). Here we explore the consequences of such nutrient enrichment for patterns of disease in human and wildlife populations.

Nutrient enrichment and disease

Our understanding of the effects of nutrient enrichment on patterns of disease remains limited. Direct exposure to nutrients (especially nitrate ingestion via drinking water) can cause or contribute to pathology in humans and wildlife, with examples ranging from methyoglobinemia, to reproductive problems to various cancers (Ward et al. 2005). Similarly, increases in food production associated with fertilizer usage can reduce malnutrition and enhance human health (Sanchez and Swaminathan 2005; Smith et al. 2005). Our goal here, however, is to explore the indirect effects of environmental nutrient enrichment on diseases, which are often ecologically complex and potentially far-reaching. Both theoretical and empirical studies suggest that, unlike many stressors, nutrient enrichment often enhances pathogen abundance (Lafferty 1997; Lafferty and Holt 2003; Townsend et al. 2003; McKenzie and Townsend 2007; Johnson and Carpenter 2008). Anthropogenic inputs of nutrients to the environment frequently correlate with increases in the prevalence, severity, or distribution of infectious diseases in nature (Coyner et al. 2003; Rejmankova et al. 2006; Voss and Richardson 2007; Johnson et al. 2007). Postulated mechanisms for these linkages include changes in host abundance and distribution, shifts in pathogen virulence, or changes in host susceptibility (see reviews by McKenzie and Townsend 2007; Johnson and Carpenter 2008).

However, interpretation of these correlations is often confounded by the fact that nutrient enrichment is frequently accompanied by additional forms of environmental change (e.g., land use changes, chemical pollution, changes in species composition), precluding precise identification of causal mechanisms. Moreover, levels of nutrient enrichment are infrequently measured directly, making it difficult to understand the range of enrichment values over which pathogens will be most responsive. The problem is further confounded by the tendency of nutrient enrichment to have non-linear effects on ecological response variables, including primary production, decomposition, habitat quality, food web structure, and species diversity (Dodson et al. 2000; NRC 2000; Howarth et al. 2000). Thus, extremely high nutrient inputs may induce different effects for host-pathogen interactions relative to low or moderate levels of enrichment (Johnson and Carpenter 2008).

Recent experimental research focused on the nutrient-disease linkage offers new and direct insights about the mechanisms underpinning observed field patterns. Collectively these experiments encompass a broad range of human and wildlife disease examples, including field and laboratory studies in marine, freshwater and terrestrial ecosystems. Here our goal is to highlight these recent experimental advances and use them to discuss general mechanisms linking nutrients and disease. Recognizing that the effects of nutrients will vary with the type of pathogen and its mode of transmission, we evaluate the effects of nutrient enrichment on directly transmitted diseases, vector-borne infections, complex life cycle parasites, harmful algal blooms and noninfectious diseases. By synthesizing existing information from a range of systems and transmission modes, we aim to elucidate how nutrient-mediated changes in disease levels may affect human health, economic sustainability, and wildlife conservation.

A. Direct horizontal transmission

Directly transmitted diseases are caused by parasites that require only one type of host to maintain the life cycle. They are usually transmitted via direct contact between hosts or by the spread of infective propagules (e.g., fungal spores, viral particles, eggs, cysts, etc.) in the environment. Examples include many viruses, bacteria, fungi, protists and some metazoan parasites. Nutrient enrichment is hypothesized to influence directly transmitted parasites by (i) changing the density of hosts (and therefore the parasite transmission rate), (ii) altering the duration of infectivity by hosts (e.g., by increasing host survival), or (iii) by providing additional nutrient resources to the pathogen (Johnson and Carpenter 2008). For example, Mitchell et al. (2003) examined the response of fungal foliar pathogens to experimental N deposition (as well as elevated carbon dioxide and decreased plant diversity) on 16 species of host plants, and found a significant increase in fungal disease severity in species that also displayed increased foliar N content. The correlation between foliar N and disease severity suggests that increased N availability may benefit foliar pathogens by promoting higher infection establishment rates, lesion growth (Sander and Heitfuss 1998), and increased spore production (Jensen and Munk 1997).

Some coral pathogens also respond positively to nutrient enrichment, perhaps through a similar mechanism. Outbreaks of disease in some coral reefs have been correlated with increases in nutrient runoff (Kim and Harvell 2002; Sutherland et al. 2004), and Bruno et al. (2003) used time-release fertilizer pellets to experimentally evaluate the effects of nutrient enrichment on naturally infected sea fans and reef-building corals *in situ*. Added nutrients nearly doubled the severity of both aspergillosis and Yellow Band Disease and the rate of host tissue loss (Bruno et al. 2003). Similarly, Voss and Richardson (2006) used a combination of field and laboratory experiments to test the effect of nutrient additions on black-band disease (BBD; Fig. 1A) in Caribbean corals. Their results also revealed the positive effects of nutrient additions on disease, with BBD progressing approximately 2.5× faster in experimentally exposed corals than in unmanipulated controls (Fig. 2A). Corresponding laboratory trials confirmed that host tissue loss increased in a dose-dependent manner with increasing nitrate (Voss and Richardson 2006).

The mechanism(s) linking accelerated pathogen spread and nutrient additions remain unclear. BBD, like YBD, is a microbial consortium of more than 50 different heterotrophic bacteria, as well as some sulfide-oxidizing bacteria and filamentous cyanobacteria (Carlton and Richardson 1995; Cooney et al. 2002), making its responses to environmental change difficult to ascertain. The causal pathway could be similar to that observed for foliar plant pathogens discussed above, whereby nutrients benefit the pathogen by directly stimulating growth and development. Given that *Aspergillus* infections are caused by a single pathogen and that Voss et al. (2007) did not find BBD community shifts in response to nutrients, the mechanism of direct resource benefits to the pathogen is most plausible. In either case, these examples from

completely different systems (grasslands and coral reefs) suggest the broad potential for nutrient enrichment to enhance the availability of resources for some pathogens, thereby facilitating their rate of spread and the resulting host pathologies.

B. Indirect transmission: vector-borne

Indirect transmission of vector-borne pathogens requires three components: a disease agent (parasite), a vector (often an arthropod such as a mosquito) and a host (Fig. 1B). While an increase in nutrient availability could conceivably affect any of these components, published research has often focused on how nutrients affect the vector, as vector abundance strongly affects overall transmission. For example, changes in land use can alter both the type of habitat and the amount of food available for larval mosquitoes, with higher food resources enhancing the production of adults and increasing disease risk (Lawler and Dritz 2005, Yanoviak et al. 2006, Munga et al. 2006). Recent work on malaria offers a particularly compelling example of the relationship between nutrient enrichment and the vector community.

Malaria has once again become a global killer, with an estimated 2 million human deaths per year, most of which involve children under the age of 5 (WHO 2004). Understanding the ecology of this disease is therefore an important public health priority. Transmission of malaria requires a protist parasite (*Plasmodium* spp.), a mosquito vector, and a human host. The presence and abundance of mosquito larvae in aquatic habitats and the resulting number of adults capable of malaria transmission are regulated by a variety of ecosystem processes operating at several organizational levels and spatial/temporal scales. Aquatic plants (both micro- and macrophytes) provide protection from predators and contribute detritus that supports the bacterial community, which, in turn, serves as food for larval mosquitoes. A change in any component within this complex structure may have a substantial impact on the mosquito population and can even lead to a replacement of one species with another. Since not all mosquito species are equally efficient in transmission of malaria, replacement of a less efficient vector with a more efficient one would increase the risk of malaria transmission.

A series of experimental and correlative studies in the malaria endemic country of Belize have revealed the mechanistic linkages among nutrient enrichments, wetland vegetation, and vector production. Oligotrophic, limestone-based wetlands of the Caribbean are strongly phosphorus (P) limited. In wetland habitats, phosphorus-enriched runoff from agricultural lands and human settlements causes a replacement of sparse macrophyte (rush) vegetation with tall dense macrophytes (cattail), with important consequences for the larval mosquito community (Pope et al. 2005; Rejmánková et al. in review). Rushes provide typical habitat for *Anopheles albimanus* larvae, whereas cattails represent a typical habitat for *A. vestitipennis*, which is a superior vector of *Plasmodium* to humans (Grieco et al. 2006). Nutrient-mediated changes in wetland plant communities can thereby lead to the replacement of *A. albimanus* by *A. vestitipennis*, increasing the risk of malaria transmission risk in the region (Achee et al. 2000). Indeed, recent spatial data on malaria incidence showed a weak but positive correlation between the distribution of cattail marshes and number of malaria cases in humans (Pope et al., unpublished data).

Other mosquito-vectored diseases may also respond positively to nutrient enrichment. For instance, following its introduction to the USA in 1999, West Nile virus has spread rapidly across North America, adapting to endemic mosquito vectors in the genus *Culex*. Experimental work has demonstrated a link between nutrient enrichment and breeding success of *Culex* mosquitoes. Reiskind and Wilson (2004) found that female *Culex restuans* oviposited more than ten times the number of egg clutches in containers with added nutrients compared to control containers. Larval survival and the mean size of emerging adults were greater in higher nutrient treatments compared with controls (Fig. 2B; Reiskind et al. 2004). Similarly, in California rice fields, Lawler and Dritz (2005) reported that nutrient enrichment through

incorporation of rice straw led to increased production of *Culex tarsalis*, another important vector of West Nile virus (Lawler and Dritz 2005). Given the importance of both *C. restuans* and *C. tarsalis* as vectors for West Nile virus in the USA, these data suggest that nutrient rich water bodies nearby to human and bird populations could increase disease risk.

For both West Nile virus and malaria, nutrient enrichment enhanced production of the necessary mosquito vector, thereby increasing potential disease risk. However, mosquito species have diverse habitat requirements for breeding and larval development, and it is probable that, in other cases, competent disease vectors will respond negatively to nutrient enrichment, underscoring the need for more experimental studies that address species-specific ecological responses. Moreover, the importance of understanding nutrient-mosquito interactions extends beyond malaria and West Nile virus; other widespread tropical diseases vectored by mosquitoes include dengue fever, yellow fever, and Bancroftian filariasis, and almost no studies have addressed the relative risk of these diseases with respect to land use change and nutrient enrichment.

C. Indirect transmission: complex life cycle

Parasites with complex life cycles require multiple hosts to complete their life cycles and reproduce, frequently alternating between free-living infectious stages (e.g., cercariae, zoospores, miracidia) and endoparasitic forms. These life cycles are common to many helminths, such as trematodes (flatworms), cestodes (tapeworms), nematodes (roundworms), acanthocephalans (spiny-headed worms), as well as some myxozoans and chytridiomycetes. Importantly, because infection must progress sequentially among hosts, the parasites cannot generally reinfect the same hosts, as might occur with a virus living inside its host. As a result, the number of parasites in a host – which determines the risk of pathology – is a function of how many times the host has been independently infected (intensity-dependent pathology). Because complex life cycle parasites are sensitive to changes in the distribution and/or abundance of all required hosts, predicting the effects of environmental change on infections is often challenging (Lafferty and Holt 2003). Depending upon the parasite's specificity, the loss of even one host species can effectively eliminate the parasite from the system, even when the remaining hosts persist. Field data suggest that many complex life cycle parasites (especially trematodes) increase in abundance with low to moderate levels of eutrophication (Lafferty 1997; Johnson and Carpenter 2008). This often occurs because of (i) increases in intermediate host density following nutrient mediated changes in primary and secondary production and (ii) an increased ability of hosts to withstand infection under nutrient-rich conditions (i.e., decrease in parasite-induced mortality). Many of these parasites depend on invertebrate intermediate hosts, such as snails, worms and crustaceans, which can respond quickly and strongly to nutrient inputs (Zander and Reimer 2002; Johnson and Carpenter 2008). The resulting increase in infection can enhance disease and pathology in some host species.

Because of the difficulties inherent in manipulating complex life cycle parasites, experimental research involving >1 host species or parasite stage in the life cycle are rare. However, a recent combination of field surveys and experiments suggest a link between aquatic eutrophication and infection by the digenetic trematode *Ribeiroia ondatrae*. *Ribeiroia* uses freshwater snails as first intermediate hosts, larval amphibians as second intermediate hosts, and birds as definitive hosts (Johnson et al. 2004). In amphibians, *Ribeiroia* infection can cause high frequencies (>50%) of severe limb malformations, including missing, misshapen and extra limbs (Fig. 1C; Johnson et al. 1999, 2002; Sessions and Ruth 1990). Such deformities, which are considered a major detriment to amphibian survival, are widely suspected to have increased in recent decades (Johnson et al. 2003), but the reasons for the apparent increase remain speculative. Previous field surveys suggested a link between wetlands with deformed

amphibians and nutrient runoff from agricultural fertilizers, cattle grazing, and urbanization (Johnson et al. 2002; Johnson and Chase 2004). Johnson and Chase (2004) hypothesized that, by stimulating algae growth in wetland habitats, nutrient runoff enhanced the population of herbivorous snails, providing greater intermediate host availability for *Ribeiroia*.

Johnson et al. (2007) tested this hypothesis by manipulating nutrient inputs into a series of outdoor mesocosms stocked with snails, larval amphibians, and parasites. Eutrophication indirectly increased infection through changes in the aquatic food web. Experimentally elevated nutrient levels led to an increase in periphytic algal growth, which enhanced growth and reproduction of snail hosts (*Planorbella trivolvis*). Higher snail densities increased the likelihood that hatching parasites (miracidia) successfully found a snail host, thereby leading to a larger number of infected snails. Infected snails from the high nutrient condition also produced, on average, twice as many parasites per 24 hr relative to snails in low the nutrient treatment, likely as a result of higher food (algae) availability and lower mortality (Johnson et al. 2007). The combination of more infected snails and a greater per snail release of parasites led to a 3- to 5-fold increase in amphibian infection (Fig. 2C), which is a direct predictor of disease risk (Johnson et al. 2007). Other experiments have demonstrated similar increases in parasite production in response to food quantity and quality (Keas and Esch 1997; Sandland and Minchella 2003).

In addition to these controlled experiments, results from various unplanned “natural” experiments further support links between nutrient enrichment and elevated infection by complex life cycle parasites. For example, Coyner et al. (2003) found a strong association between sewage treatment runoff and infection by the nematode *Eustrongylides ignotus*, which can increase nestling mortality in wading birds. Inputs of N and P were positively correlated with the density of first intermediate hosts (a tubificid worm) and with infection in second intermediate hosts (mosquitofish). Following diversion of the sewage and a corresponding reduction in nutrient concentrations, infections in mosquitofish declined from 54% in 1990 to 0% in 1998 (Coyner et al. 2003, see also Weisberg et al. 1986; Muzzall 1999 for additional examples). Similarly, sewage inputs into Gull Lake, Michigan, were linked to a four-fold increase in infection of mayflies by the trematode *Crepidostomum cooperi* (Marcogliese et al. 1990). Deep-water hypoxia caused by nutrient-mediated eutrophication of the lake altered the distribution of oxygen-sensitive mayflies, forcing them into shallower water and into closer proximity with sphaeriid clams, which are the first intermediate hosts of *Crepidostomum*. After the lake’s sewage system was improved in 1984, infection prevalence in mayflies declined by 70% within 5 years (Marcogliese et al. 1990), presumably owing to the movement of mayflies into deeper water.

E. Noninfectious diseases

Finally, environmental nutrient enrichment can influence levels of noninfectious diseases. Noninfectious disease represents a broad category of health conditions ranging from cancer to hypoxia; etiological factors can include chemical exposure, temperature, oxygen availability and especially biotoxins produced algae, plants, fungi and bacteria. Unlike with infectious diseases, the dynamics of “pathogens” responsible for noninfectious diseases may have limited or no dependency on the dynamics of the species experiencing pathology. Some allergic diseases, for example, have exhibited substantial increases in recent decades, and currently affect millions of peoples in developed countries (e.g., Sly 1999). High pollen counts cause hayfever, allergenic rhinitis, and allergenic asthma, and for those already suffering from other pulmonary ailments, these pollen-induced responses can be especially serious (NIH 1993). Pollen counts have increased in multiple highly populated regions (e.g. Clot 2003; Spijksma et al. 2003), for reasons that may be related climate change, shifts in species composition, and increased atmospheric CO₂ (Wayne et al. 2002). However, while little is known about the

broad-scale relationships between excess nutrients and pollen production, evidence suggests that N enrichment can stimulate pollen production (Lau et al. 1995). While such effects are likely to vary between species, some evidence suggests that in many weedy species, pollen production frequently increases following nutrient enrichment. For example, N fertilization caused substantial increases in pollen production of ragweed, one of the most problematic sources of allergenic pollen, (Townsend et al. 2003). In addition, recent evidence suggests that pollen grains in polluted atmospheres – to which reactive N is a big contributor – displayed an altered surface structure and chemistry that led to enhanced allergenicity (Majd et al. 2005). Taken as a whole, the potential for nutrient loading to alter pollen counts and/or their effects seems clear, and an area ripe for further experimental study.

Increased inputs of nutrients into aquatic ecosystems can also cause pronounced changes in Harmful Algal Blooms (HABs), which are proliferations of algae and cyanobacteria that can cause massive fish kills, marine mammal kills, contaminate seafood or drinking water with toxins, or alter ecosystems in ways that are detrimental (Glibert and Pitcher 2001, Backer and McGillicuddy 2006). Algae produce a wide range of toxins (Table 1) which may accumulate in predators and organisms higher in the food web, ultimately affecting humans when seafood is consumed, when toxin-laden aerosols are inhaled, or when contaminated water is consumed. Toxic syndromes include paralytic shellfish poisoning, amnesic, diarrhetic, neurotoxic and cyanotoxic, among others. Evidence is also mounting that HABs can elicit subtle effects on fish and wildlife (Fig. 1D). For example, domoic acid, a neurotoxin produced by the diatom *Pseudo nitzschia* spp., has been shown to induce seizure and memory loss in laboratory animals (Tiedeken and Ramsdell 2007), saxitoxin from paralytic shellfish toxin producing dinoflagellates have been shown to cause reproductive dysfunction in whales (e.g. Doucette et al. 2006), and toxic dinoflagellates have been associated with embryonic deformities in oysters (Glibert et al. 2007a). In addition, aerosolized red tide toxins can exacerbate respiratory symptoms among asthmatics (Milian et al. 2007). Exposure to peptide toxins produced by cyanobacteria have also been suggested as contributing to increased rates of liver cancer in populations consuming water from nutrient rich lakes (Grosse et al. 2006).

Throughout many parts of the world, marine and freshwater HABs are increasing in geographic extent, in duration of occurrences, in numbers of toxins and toxic species identified, in numbers of fisheries affected, and in economic costs (Anderson 1989, Hallegraeff 1993, Anderson et al. 2002, Glibert et al. 2005b). While many factors likely influence these increases, nutrient runoff in freshwater and marine ecosystems is likely an important contributor (NRC 2000; Smith et al. 2006). As is the case with emerging pathogens, the evidence linking proliferation of many HABs with nutrients is on the one hand compelling, while at the same time, complex and multifaceted (Anderson et al. 2002, Glibert et al. 2005b, 2008, Glibert and Burkholder 2006, Heisler et al. 2008). Nutrient availability sets the upper limit to the algal biomass production in aquatic ecosystems, but the rate of loading, the form and relative composition of nutrients, as well as numerous other physical and ecological interactions interact to determine whether a HAB actually proliferates. Establishing cause and effect relationships is further complicated by the fact that most studies are undertaken after a bloom is underway, and thus many of the nutrients are already incorporated into algal biomass. In such cases, ambient nutrient concentrations may be low because they have been immobilized by the biota, leading to a potentially erroneous conclusion that nutrients are not associated with the phenomenon. In coastal marine ecosystems, concentrations of inorganic N and P are very poor indicators of nutrients inputs and availability precisely because of rapid uptake by blooms (NRC 2000). Clear dose-response relationships between nutrient loading and HABs are more commonly observed in freshwater systems than in marine and estuarine systems, perhaps due to the large spatial scale involved and the increased role of physical flushing in marine and coastal systems.

Nutrients can stimulate or enhance a HAB species in several ways (Anderson et al. 2002). Nutrients may enhance the production of all species in relatively equal proportion, or may stimulate a species or group of species disproportionately. There are many examples demonstrating increases in HABs following nutrient enrichment. In the Gulf of Mexico, the sedimentary record of potentially toxic diatoms (*Pseudo-nitzschia* spp.) has increased in parallel with increased nitrate loading over the past several decades (Turner and Rabalais, 1991, Parson et al. 2002). Similarly, blooms of toxic HABs off the coast of China have expanded in recent years in geographic extent (km² to tens of km²), duration (days to months), and in harmful impacts. These changes are strongly correlated to increases in fertilizer use over the past two decades (Fig. 2D; Anderson et al 2002, Zhou 2003, Li et al in review). Moreover, the Baltic Sea, Aegan Sea, Northern Adriatic and Black Seas have all experienced increased HAB occurrences in relation to nutrient loading (e.g. Larsson et al. 1985, Bodeau 1993, Moncheva et al. 2001, Heisler et al. 2008).

Changes in the type of nutrients or their relative proportions can also influence the frequency and severity of HABs. Off the coast of Germany, time series analysis of nutrient concentrations over several decades has revealed that a 4-fold increase in the ratio of nitrogen: silicate (N:Si) coincided with an increase in the HAB *Phaeocystis* (Radach et al. 1990). The specific forms of available N and P, particularly with respect to organic nutrients, also play an important role in the nutrition of many HABs (Glibert and Legrand 2006). For example, blooms of the HAB species *Aureococcus anophagefferens*, which have been linked to reductions in shellfish reproduction (Tracey 1988, Gallagher et al. 1989), correlate with increases in organic compared to inorganic loading (LaRoche et al. 1997, Glibert et al. 2007b). Other work has shown that nutrient availability or composition may even alter the toxin content of individual species without altering their total abundance. For the diatom *Pseudo nitzschia australis*, the form of N influences both the growth rate as well as the toxin content. Cells grown on urea, for example, had higher levels of the toxin, domoic acid, relative to those grown on nitrate or ammonium (Armstrong-Howard et al. 2007). Similarly, the toxin content of urea-grown cells of the dinoflagellate *Alexandrium tamarense*, which causes paralytic shellfish poisoning, was significantly higher than cells grown on nitrate (Leong et al. 2004).

Summary of Nutrients and Disease

While the effects of nutrients vary with enrichment levels, the types of host and pathogen, and the characteristics of the ecosystem, the above examples illustrate that eutrophication can have important indirect effects on human and wildlife diseases. Recent experiments have shed new light on the mechanisms underpinning the observed links between nutrient enrichment and disease. Depending on the mode of transmission, these mechanisms may affect the pathogen, the host, or their interaction, and include changes in the density or distribution of suitable hosts/vectors, alterations in physical habitat, increases in parasite production, selection for more virulent or toxic pathogens, and the provisioning of pathogens with supplemental resources.

It is important to note that the effects of nutrient enrichment vary among pathogens and do not always elicit higher disease risk; exacerbation of a broad suite of diseases does appear possible, but the decline or elimination of others is also possible. Moreover, increases in parasite species richness or abundance do not always reflect an increase in disease risk, as disease is also a function of the host's response to infection. Current evidence suggests that nutrient inputs will favor generalist or opportunistic pathogens with direct or simple life cycles. Importantly, however, because these pathogens are generalists with little dependency on the dynamics of any one host species, they may cause sustained epidemics or host extirpations without suffering a reduction in transmission. Noninfectious diseases such as HABs, pollen-allergies, and avian botulism represent the extreme position in this gradient in that the dynamics of the "pathogen" (e.g., a harmful alga) are completely divorced from the species experiencing

pathology. Thus, declines in “hosts” do not necessarily lead to declines in the pathogen. Parasites with complex life cycles that depend on multiple, interacting species within a community to complete transmission are often more sensitive to environmental disturbance, as losses in any one host can reduce or eliminate the infection cycle (see Hudson et al. 2006). However, if intermediate hosts are tolerant of (or thrive under) elevated nutrient conditions, such as some hypoxia-tolerant snails and tubificid worms, infection and pathology can respond positively to inputs of N and P. Such situations can lead to increased disease within other hosts in the life cycle (e.g., amphibian malformations).

Although many of the examples discussed here focus on wildlife diseases, we argue that the same patterns, interactions and controls are relevant for understanding the effects of nutrient enrichment on many zoonotic human diseases. For example, as discussed for malaria and WNV, nutrient runoff into freshwater habitats can increase mosquito oviposition, larval growth rate, and/or alter the vector community to favor disease transmission in humans. While vector abundance is an important predictor of disease transmission, more work is needed to definitively link nutrient inputs with infection incidence in humans from endemic areas. Similarly, in addition to affecting wildlife, HABs can cause significant disease in humans and costly economic losses. Collectively, there are >60,000 incidents of human exposure to algal toxins annually in the USA, resulting in ~ 6500 deaths (Hoagland et al. 2002). Costs associated with public health, shellfish recalls, and decreased tourism approach US \$50 million annually. (Hubbard et al. 2004). Finally, complex life cycle parasites of medical and veterinary importance may be influenced by changing nutrient levels. In livestock, the ruminant liver fluke (*Fasciola hepatica*) has caused >2 billion in livestock industry losses (Boray and Munro 1998). Infected snail hosts respond strongly to food quality and quantity, altering the output of infectious parasites by nearly 7-fold over starved snails (Kendall 1949). Infections by some schistosomes (human blood flukes), which continue to afflict 200 million people in Africa and Asia, have also been associated with increased algal growth and organic nitrogen in wetland habitats (Garcia 1972). Considering the strong response of *Ribeiroia* infection to elevated nutrient conditions and the ecological parallels between the life cycles of *Ribeiroia* and *Schistosoma*, these results may have important epidemiological implications.

A Look to the Future

Many diseases that affect both humans and wildlife have increased in incidence or severity in recent decades, frequently resulting from changes in the ecological interactions among a pathogen, its hosts, and the environment in which they co-occur (Daszak et al. 2000). The importance of incorporating ecology into the study of parasites and emerging diseases has been emphasized with increasing urgency in recent years (National Research Council 2001). In their synthesis of the Grand Challenges in Environmental Sciences, the National Research Council (2001) listed infectious disease as one of the eight most pressing environmental issues, advocating a “systems-level” approach to understanding disease emergence. Nevertheless, the ecology of zoonotic diseases is often remarkably complex, thus rendering predictions of their responses to anthropogenic change notably difficult (Daszak et al. 2000, Patz et al. 2004). Such challenges are exacerbated by the fact that human-induced changes to the environment rarely occur in isolation; for example, nutrient loading to surface waters is nearly always combined with substantial land use changes in the surrounding watersheds, with concomitant shifts in species abundances. Thus, parsing out the potential effects of a single factor such as nutrient loading is often a tall order, one which typically requires controlled, mechanistic studies to begin the construction of more prognostic models. For example, limited evidence has linked cholera to coastal eutrophication and seasonal plankton blooms. The bacterium responsible, *Vibrio cholerae*, can become concentrated in fishes, shellfishes, and especially in biofilms on the surface of crustacean zooplankton (Epstein 1993; Colwell 1996). However, patterns of human behavior, ocean temperature and circulation also influence infection dynamics, making

it difficult to identify the relative importance of nutrient inputs (Colwell and Huq 2001; Cottingham et al. 2003).

Here, we have summarized a few experimental studies that focused on nutrient effects, but they remain rare and are thus a priority in advancing our ability to forecast the future of both human and wildlife infectious disease (McKenzie and Townsend 2007; Johnson and Carpenter 2008). Based on the evidence to date, we expect that environmental nutrient enrichment will remain an important factor in the etiology of human and wildlife diseases for decades to come. Although awareness and technological innovations have slowed the problem in some regions, ongoing patterns of atmospheric deposition of reactive nitrogen, losses of wetland and riparian areas, increasing use of fertilizers in developing nations, growing livestock populations, and an increasing human population all suggest that eutrophication will continue to expand (Millennium Ecosystem Assessment 2005). Moreover, even if the contributing drivers are reversed, eutrophication tends to be a persistent condition because of internal recycling of nutrients (e.g., Carpenter 2005; Smith et al. 2006).

In addition, the disease-related outcomes of nutrient enrichment are likely to exhibit pronounced regional variation. Our growing understanding of spatial and temporal patterns in both emerging infectious diseases (e.g. Jones et al. 2008) and in rapidly changing nutrient cycles (Galloway et al. 2004) allows a focus on regionally targeted efforts that may pose the greatest risks. For example, in heavily industrialized regions such as the United States, Europe and parts of Asia, anthropogenic inputs of N and P to the environment have been exceptionally high for decades, resulting in ecosystems already demonstrating significant change in response to such disturbance. From the perspective of human infectious diseases, the overall risk of nutrient disease interactions may be lower in these temperate regions, simply because the diversity of infectious diseases responsive to nutrients is likely lower than that in tropical regions. However, a warming climate and global transport systems continue to increase the potential for a suite of “tropical” diseases to expand into higher latitude zones (Patz and Olson 2006). Noninfectious diseases, including HABs and pollen-based allergies, are already intensifying in temperate regions with ongoing nutrient deposition. In the short term, however, some of the most pressing threats from elevated nutrients may be to wildlife: in heavily industrialized temperate regions many critical habitats are already greatly reduced in size and subject to a suite of other disturbances from invasive species to acidic precipitation; here, increased disease prevalence from nutrient loading may further challenge conservation efforts.

Conservation challenges are also rising in tropical regions, as in recent decades they have exhibited the most dramatic increases in land clearing and industrialization. Such changes, as they already have in higher latitudes, are causing rapid increases in the loading of excess N and P to the environment; over the next 50 years, it is the tropical latitudes that will see the most significant increases in fertilizer use and atmospheric deposition of N (Galloway et al. 2004). At the same time, these regions are fraught with hunger, malnutrition and massive public health challenges from a range of infectious diseases (WHO 2004; Sanchez et al. 2007). As discussed above, some of the major plagues of low latitudes show worrisome signs of elevated risk in more eutrophic conditions; examples include both malaria and schistosomiasis. Taken as a whole, the intersection of a high diversity of human parasitic and infectious diseases (Guernier et al. 2004) with rapid changes in the environment, including those to nutrient cycles, suggests that some of the greatest nutrient-driven risks to humans from infectious diseases are likely to be in low latitude countries (Fig. 3; McKenzie and Townsend 2007). In a recent analysis of global trends in emerging infectious diseases, Jones et al. (2008) emphasize both the risks and challenges of the tropics, by pointing out that not only are such zones a likely hotspot for emerging diseases of humans and wildlife, but are also typified by poor health infrastructures and limited reporting of disease outbreaks (Fig. 3).

Without question, increases in fertilizer application and food production in these regions will likely have substantially positive effects on human health by reducing malnutrition and improving quality of life. However, a significant concern lies with the unintended side effects of such efforts: will increases in the alteration of environmental nutrient concentrations incur and increased risk of disease? A parallel can be found with the widespread construction of large dams in Africa during the mid 20th century. While dams provided valuable benefits in the form of hydroelectric power, flood control, and a reliable source of water, they also caused dramatic increases in human schistosomiasis by creating ideal transmission environments, sometimes with devastating consequences for human health (e.g., Jordan et al. 1980). These concerns are once again moving to the forefront with the completion of the Three Gorges Super Dam in China, a region with widespread infections by *Schistosoma japonicum*. Thus, ecologists, epidemiologists, and agronomists are collectively challenged to determine (1) under what conditions will nutrient enrichment enhance disease risk and (2) through what strategies can agricultural intensification be accompanied by careful management of disease-related outcomes?

Thus, while a better understanding of links between nutrients and disease is needed on a global basis, we emphasize its importance in tropical and subtropical Africa, Asia and Latin America. All three continents contain regions experiencing explosive growth and development, while still contending with rampant poverty, widespread environmental damage and a huge disease burden. Sub-Saharan Africa is particularly afflicted by both poverty and disease, making it a global priority for aggressive action to improve human welfare through agricultural and infrastructural development (Sanchez et al. 2007). Here and elsewhere in the tropics, as such development proceeds, there are urgent needs for region-specific management plans that can incorporate knowledge of ecosystem processes, including their effects on disease.

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Figure 1.

Representative diseases or hosts that respond to nutrient enrichment. A. Black Band Disease (BBD), a directly transmitted disease, in reef-building corals (photo courtesy USGS); B. Vector-borne pathogens, such as malaria and West Nile Virus, may be enhanced with nutrient enrichment owing to changes in mosquito production or larval habitat; C. Complex life cycle parasites, including the trematode (*Ribeiroia ondatrae*) that causes limb deformities in amphibians, can increase in abundance or pathology due to changes in intermediate host abundance or parasite production (photo courtesy P. Johnson); D. Noninfectious diseases such as Harmful Algal Blooms (HABs) may directly or indirectly cause a broad range of pathologies in human and wildlife populations (photo courtesy P. Glibert).

Figure 2.

Select examples of how nutrient enrichment affects different types of disease conditions. A. Effects of experimental nutrient addition on black band disease in reef-building corals in the Bahamas; (Source: Voss and Richardson 2006); B. Influence of total nutrients (nutrient concentration multiplied by water volume) on survival of larval mosquitoes (*Culex restuans*); (Source: Reiskind et al. 2004); C. Experimental nutrient additions (N and P) indirectly increased *Ribeiroia* infection in larval amphibians through changes in infected snail abundance and per capita parasite release; (Source: Johnson et al. 2007); D. Trends in nitrogen fertilizer use (solid line) and the number of red tides (dashed line) reported for Chinese coastal waters through the mid-1990's; (Sources: Smil (2001) for fertilizer use and Zhang (1994) for red tide abundance; reprinted from Glibert and Burkholder (2006)).

Figure 3. Geographic distribution of (A) estimated global patterns in total nitrogen deposition for 2005 (in $\text{mg N m}^{-2} \text{y}^{-1}$) and (B) global distribution of the estimated risk of emerging infectious disease event. Relative risk scaled from low values (green) to high values (red). Panel (A) Adapted from Galloway et al. (2008) and panel (B) from Jones et al. (2008).

Table 1

Illness	Major Vector	Symptoms
Amnesic Shellfish poisoning	Domoic acid from <i>Pseudonitzschia</i> sp. in Shellfish	Short-term memory loss; vomiting, cramps
Diarrhetic shellfish poisoning	Okadaic acid from <i>Dinophysis</i> sp. in shellfish	Diarrhea, vomiting, cramping
Neurotoxic shellfish poisoning	Brevetoxin from <i>Karenia</i> sp. in shellfish, aerosolized toxins	Nausea, diarrhea, Respiratory distress, Eye irritation
Paralytic shellfish poisoning	Saxitoxin from <i>Alexandrium</i> sp. and other species in shellfish	Numbness around lips and mouth; Respiratory paralysis; Death
Cyanotoxin poisoning	Microcystins and other toxins from <i>Microcystis</i> and other cyanobacteria in water	Skin irritation; Respiratory irritation; Tumor-promotion; Liver cancer, failure
Ciguatera fish poisoning	Gambiertoxins/ciguatoxins from <i>Gambierdiscus</i> sp. that accumulate in reef fish	Gastrointestinal distress; Numbness around mouth, reversal of hot and cold sensations; Hypotension