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Journal of Experimental Marine Biology and Ecology 346 (2007) 36–44

Journal of EXPERIMENTAL MARINE BIOLOGY AND ECOLOGY

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Are infectious diseases really killing corals? Alternative interpretations of the experimental and ecological data

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Received 1 February 2007; received in revised form 14 February 2007; accepted 15 February 2007

Abstract

Emerging infectious diseases are a worldwide problem and are believed to play a major role in coral reef degradation. The study of coral diseases is difficult but the use of culture-independent molecular techniques has been, and will continue to be, useful in a system where a limited number of visible signs are commonly used to define a "coral disease". We propose that coral "diseases", with rare exception, are opportunistic infections secondary to exposure to physiological stress (e.g. elevated temperature) that result in reduced host resistance and unchecked growth of bacteria normally benign and non-pathogenic. These bacteria are from the environment, the host, or the coral mucus layer and become opportunistic pathogens. While difficult and time consuming, we do not advocate abandoning the study of disease-causing pathogens in corals. However, these studies should include comprehensive efforts to better understand the relationship between coral diseases and environmental changes, largely anthropogenic in nature, occurring on coral reefs around the world. These environmental insults are the cause of the physiological stress that subsequently leads to coral mortality and morbidity by many mechanisms including overwhelming infections by opportunistic pathogens.

Keywords: Bacteria; Corals; Disease

1. Introduction

The emergence of infectious disease in humans, wildlife, and important agriculture crops continues to be an area of concern and investigation (Daszak et al., 2000; Harvell et al., 2002). Many of these diseases occur as epidemics/epizootics and are associated with the effects of global climate change, range expansions of disease vectors, and other factors such as introduced species (Daszak et al. 2000; Harvell et al., 2002). Additionally, most of these diseases have a well-defined set of signs, a specific etiology and a known epidemiology or epizootiology. Marine ecosystems are not immune from the reported increases in diseases (Harvell et al., 1999), and outbreaks have been reported in a broad range of marine taxa including corals (Harvell et al. 2004; Lafferty et al., 2004; Ward and Lafferty, 2004). Here we focus our attention on incidence and impact of infectious disease on scleractinian corals.

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0022-0981/$ - see front matter © 2007 Published by Elsevier B.V.
doi:10.1016/j.jembe.2007.02.015

Corals form the structural and biological framework of some of the most diverse, productive and economically important marine ecosystems in the world. There is growing evidence that these ecosystems are now being degraded at an alarming rate as a result of the synergistic impacts of over-fishing, anthropogenically derived increases in carbon dioxide levels, warming of sea surface temperatures, eutrophication, sedimentation, and pollution (Lesser, 2004).

Coincident with the reported increase of diseases in marine systems are reports of the increased prevalence of coral diseases (Rosenberg and Ben-Haim, 2002; Sutherland et al., 2004). The number of published works on coral diseases has increased dramatically during the last ten years (Ward and Lafferty, 2004), and an ecological survey of coral diseases in the Caribbean reports that disease outbreaks are widespread (Weil et al., 2002). While an analysis of published work suggests that the prevalence of coral diseases is increasing, recent survey data do not always support these conclusions (Voss and Richardson, 2006). Coral disease prevalence in the wider Caribbean is reported to be low (3.02%), and recent surveys in Mexico show a decrease or no change in the prevalence of sea fan and coral disease (Ward et al., 2006; Weil et al., 2002). In fact, sea fan disease (aspergillosis) has been on a steady decline for over 6 years (Kim and Harvell, 2004). Only in the Florida Keys reef tract are increases in the prevalence of "coral disease" reported (Santavy et al., 2001). Here, we discuss the current state of coral disease microbiology by examining the published literature and question the conclusion that diseases of corals are caused by a primary pathogen and are infectious in nature, and suggest that they are most often a secondary phenomenon caused by opportunistic pathogens after physiological stress. This alternative interpretation does not mean that the study of putative infectious agents of diseased corals should be abandoned, but we do advocate for more comprehensive studies that emphasize studying the underlying causes responsible for the increased susceptibility of corals to opportunistic infections by microbes.

2. Coral disease microbiology

Despite the reported impact of coral disease on the mortality of corals, the etiologies of most coral diseases remain unknown (Richardson, 1998; Richardson and Aronson, 2002; Sutherland et al., 2004). Over 35 different coral disease names have been described, yet specific pathogen(s) have only been putatively identified for a handful of these (Richardson, 1998; Richardson and Aronson, 2002; Sutherland et al., 2004). One of the foundations of pathogenic microbiology is Koch's postulates (Grimes, 2006). However, this set of rules for identifying infectious agents in a variety of clinical, veterinary and wildlife settings has been difficult to apply in marine systems. One problem is that Koch's postulates do not incorporate changes in host susceptibility or pathogen virulence with changes in the environment. Another problem is the tendency to assign a group of limited visible characteristics (signs) as a "coral disease" without a detailed investigation of underlying cellular and structural characteristics as well as pathogen identification. It is therefore often difficult to be certain that the same disease has been produced in laboratory tests of Koch's postulates as was present in the environment, and this critical evidence is typically missing from studies that report new coral disease pathogens. This assumption is implicit to Koch's postulates but is often not formally stated because human diseases provide such a complex and extensive suite of symptoms that it is unlikely that one disease will be confused with another. The increasingly confusing descriptions of coral diseases are impeding our understanding of the underlying pathology involved, and our ability to identify and distinguish between primary and opportunistic pathogens that may be causing disease. Recent work (Work and Aeby, 2006) attempts to make the diagnosis of coral diseases based on visible signs less ambiguous using specific descriptions of lesions observed in the field. However, in the absence of microbiological data the rigorous description of disease signs will only have diagnostic utility when supporting epizootiological data are also available (e.g., *Diadema* die off) (Lessios et al., 1984).

We also know that many infectious diseases are polymicrobial, and are the result of perturbations in long-standing evolutionary relationships between an organism and its "normal flora" (Ruby et al., 2004). In such cases, it is difficult, if not impossible, to satisfy Koch's postulates. More confounding is the fact that many marine bacteria are viable but non-culturable and it is only with the application of culture-independent methods that the identification and enumeration of those bacteria associated with a diseased state can be resolved (Fredricks and Relman, 1996; Ritchie et al., 2001). Recognizing many of these problems, Grimes (2006) suggested a modified version of Koch's postulates (Koch's postulates-simplified) that might prove useful, when combined with culture-independent methods or a "Molecular Koch's postulates" (Fredricks and Relman, 1996; Ritchie et al., 2001), for the diagnosis of coral diseases. We also recognize that fulfilling Koch's postulates using ecologically relevant inocula provides definitive evidence of the infectious agent, but not

fulfilling these standards does not eliminate the possibility that a primary pathogen is involved. Another confounding aspect of coral microbiology is the discovery that corals harbor microbial communities not just in their outer mucus layers, but in their tissues (Ducklow and Mitchell, 1979; Klaus et al., 2005; Ritchie and Smith, 1995; Rohwer et al., 2002). These assemblages are distinct from those in the water column and can change when corals are diseased (Cooney et al., 2002; Frias-Lopez et al., 2002, 2004). The presence of these microbial consortia is likely to complicate disease diagnosis in corals and requires the characterization of the "normal flora" of corals before initiating studies aimed at isolating either primary or opportunistic disease-causing pathogens.

3. Coral diseases—a primary or opportunistic phenomenon?

To what extent are coral diseases non-specific and largely opportunistic in nature? Does the infectivity vary if the disease is caused by a primary or opportunistic pathogen? Where are the reservoirs of these putative infections, and what are the effects of physiological stress and changes in the ability to defend against primary and opportunistic pathogens? Can we first develop a simple matrix (Fig. 1) in which we place putative diseases into that is based on their signs, microbiology and epizootiology? What is currently known about the microbiology of coral diseases and the role of intrinsic (i.e. coral host) and extrinsic (i.e., environmental) factors that would help initially develop and expand this matrix?

3.1. Black-band disease

Black-band disease (BBD, Fig. 2a) was the first coral disease to be described (Garrett and Ducklow, 1975; Richardson 1998, 2004; Rützler et al., 1983). The microbiology of this disease has revealed that the infection is polymicrobial, comprising bacteria that are sulfate reducers, sulfide oxidizers and a cyanobacterium *Phormidium corallyticum* (Richardson, 2004). The prevalence of BBD is generally low on Caribbean reefs (Edmunds, 1991), but is highest during the warmest months (i.e., August and September) of the year (Voss and Richardson, 2006; Kuta and Richardson, 1996; Richardson, 2004). The recent application of culture-independent techniques has revealed that the polymicrobial communities associated with BBD are more diverse than previously described (Cooney et al., 2002; Frias-Lopez et al., 2002, 2004; Sekar et al., 2006), that *P. corallyticum*, is not detectable in some diseased corals (Frias-Lopez et al., 2004), and that more than one species of cyanobacteria are found in corals exhibiting BBD in both the Caribbean and the Indo-Pacific (Frias-Lopez et al., 2003). The most recent of these studies has also shown that several toxin-producing strains of cyanobacteria and heterotrophic bacteria are present in BBD (Sekar et al., 2006). No complete test of Koch's postulates has been satisfied, but recent data suggests that the transmission of BBD may be vector mediated via corallivorous fish (Aeby and Santavy, 2006). The experimental data of Aeby and Santavy (2006) showed a requirement for a break in the integrity of the coral tissue for an infection to occur. The microbiological data

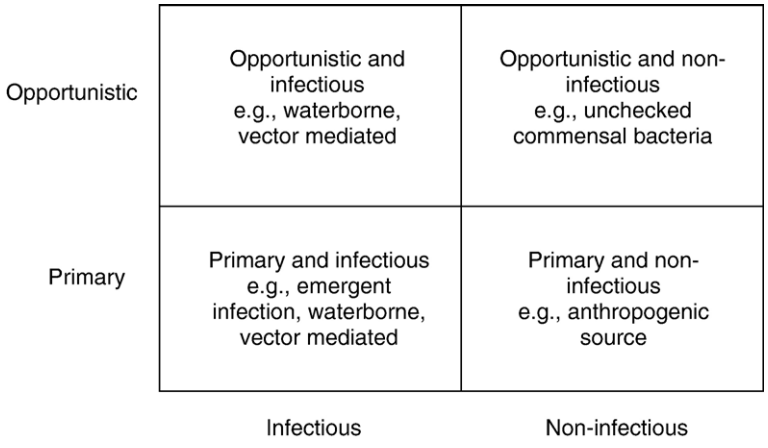

Fig. 1. Matrix of possibilities for pathogens (primary and opportunistic), and their infectivity (infectious and non-infectious) for coral diseases. The categories are not mutually exclusive and the matrix could potentially be expanded to include subtle differences in either axis. Defining where a potential pathogen resides in the matrix, using epizootiological and microbiological data as well as observed signs, will help develop more effective approaches to understand the etiology of that disease, and potential remedies.

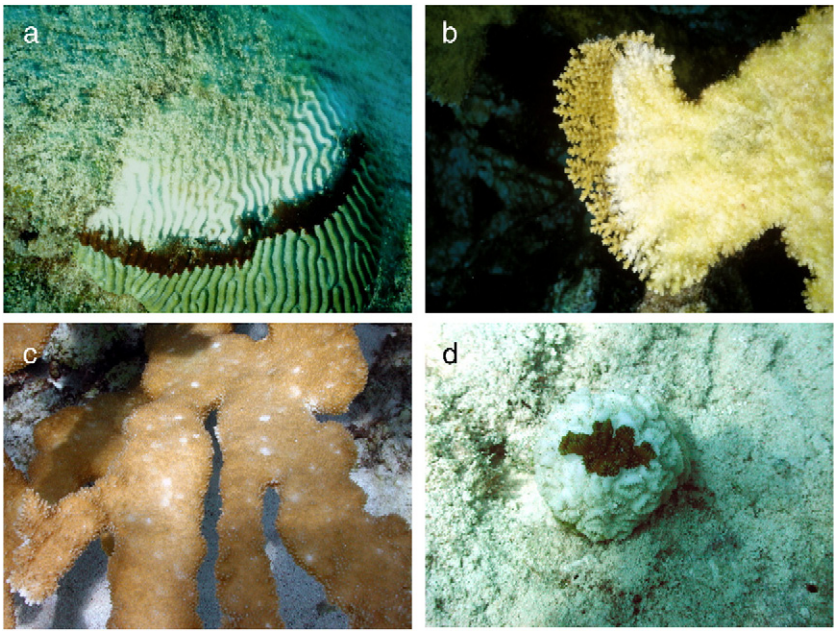

Fig. 2. Photographs of corals exhibiting external signs ascribed for common coral diseases. (a) Black-band disease on *Diploria strigosa*. (b) White-band disease on *Acropora palmata*. (c) White pox on *Acropora palmata*, and (d) White plague on *Dichocoenia stokesi*.

suggest that BBD consists of a consortium of specific functional groups of bacteria that exhibit similar signs, but with different microbial taxa, which does not support the assignment of a specific consortium as the primary pathogen of this "disease". Black-band syndrome exhibits features associated with an opportunistic infection that requires some "physical disturbance" of the coral tissue and is potentially transmitted by a vector.

3.2. White-band disease

White-band disease (WBD, Fig. 2b) affects acroporid corals and is generally believed to have caused losses of 80–98% of these formerly dominant coral species in the Caribbean (Gladfelter, 1982). Despite the widespread disappearance of acroporids during the 1980s in the Caribbean being an unprecedented event in the recent (3000–7000 y) geological record (Aronson and Precht, 2001), the pattern of disease spread in the 1980s described by Gladfelter (1982) was against the prevailing currents suggesting that it was not a transmissible agent unless it was vector mediated rather than waterborne. Acroporid corals are also affected on regional scales by extremes in seawater temperature (i.e., both cold and warm extremes) that results in a stress response (i.e., bleaching) that causes the loss of zooxanthellae and high rates of mortality (Lesser, 2004; Porter et al., 1982). These thermal events, especially the occurrence of elevated sea surface temperatures (SST), occurred increasingly during the 1970s and 1980s (Hoegh-Guldberg, 1999), exactly during the time of the greatest decreases in acroporid coral cover (Aronson and Precht, 2001).

Two forms of the disease have been reported (Type I and Type II, (Gladfelter, 1982; Ritchie et al., 2001), and no causal agent has been positively identified for either. Using molecular techniques Pantos and Bythell (2006) recently showed that several potential pathogens exist in WBD, but these pathogens are common to other diseases, including BBD and white plague-like disease (see below). Another culture-independent study by Casas et al. (2004) has shown a predominance of Rickettsiales-like bacteria in both healthy and diseased samples of *Acropora cervicornis*, *A. palamata* and *A. prolifera*. Casas et al. (2004) then show that these phylotypes were absent in archived (ethanol preserved) samples of Caribbean acroporids from as far back as 1937 suggesting it may be a new bacterium associated with acroporids but not the causative agent of WBD. There are no microbiological data directly linking WBD with the Caribbean-wide decline of *Acropora* sp. and the epizootiological data are confounded by the extent and magnitude of SST changes Caribbean wide during the timeframe of acroporid decline. Collectively, the available evidence does not provide strong evidence that WBD is caused by a primary pathogen and the alternative interpretation that WB syndrome is caused by

opportunistic pathogen (s) should be experimentally tested.

3.3. White pox

Populations of the elkhorn coral *Acropora palmata* have been afflicted with a disease called white pox (WP, Fig. 2c) first described from corals in the Florida Keys where the mortality of *A. palmata* has been reported to be in excess of 70% of affected colonies (Patterson et al., 2002). The putative pathogen of WP is the enteric bacterium *Serratia marcescens* (Patterson et al., 2002). Despite the apparent fulfillment of Koch's postulates the sample sizes in these experiments are small and were accomplished using an inoculum of questionable ecological significance (10^9 CFU ml^{-1} absorbed onto calcium carbonate sediment) (Patterson et al., 2002). In the context of this experimental inoculum, Lipp et al. (2002) surveyed the enteric bacteria from the surface mucous layer of several species of coral in the Florida Keys. They found a maximum number of 10 CFU ml^{-1}, and most corals harbored concentrations of enteric bacteria less than this. While a contagion model provides strong epizootiological evidence that WP is an infectious disease (Patterson et al., 2002), it is also well known that *S. marcescens* is an opportunistic pathogen and common in marine habitats impacted by sewage, as is the case in the Florida Keys (Patterson et al., 2002). Additionally, during the period of time when the study ws conducted, and where the data for the contagion model were obtained (1996–2000), the SST records for the Florida Keys regions experienced warming above the maximum mean monthly SST or above the coral bleaching threshold SST for 2–4 months every year during the summer (http://coralreefwatch.noaa.gov). Patterson et al. (2002) also report reduced disease activity in the winter months when SST is lower and below the thresholds described above. Additionally, all the sites are within ~130 n.m. It was reported that the spread of WP within reefs and between reefs took approximately one year. Compared to other marine epizootics with known pathogens this is a remarkably slow rate of transmission even for an open oceanic system of sessile hosts (McCallum et al., 2003). Given these perspectives, we feel that the identification of *S. marcescens* as the causative agent responsible for WP is tenuous and requires further corroboration. Additionally, the epizootiological data suggest an agent of low transmissibility if a primary infectious agent is involved. More interesting to us would be the question of differential host susceptibility to opportunistic pathogens after exposure to environmental stress. It is evident that whether we are discussing WBD or WP, acroporids are not as resilient in the face of environmental perturbation compared to other species on the same reef, and we do not yet know why.

3.4. White plague

White plague (WPl, Fig. 2d) disease was first described during the late 1970s in corals from the Caribbean and Indo-Pacific. It is now known as a group of three diseases that are all characterized by similar disease signs (WPl 1, WPl 2 and WPl 3) (Richardson et al., 1998; Ward et al., 2006). WPl 2 was first described from an epizootic in the Florida Keys that affected the coral *Dichocoenia stokesi* (Richardson et al., 1998) with the bacterium *Aurantimonas coralicida* described as the pathogen responsible (Denner et al., 2003; Richardson et al., 1998). There has been no identification of the causative agents, if any, of WPl 1 and WPl 3, and *A. coralicida* is not associated with white plague-like disease reported for *Montastraea annularis* (Pantos et al., 2003). The temperature dependence of *A. coralicida* (optimal growth between 30°C and 35°C, Remily and Richardson, 2006) suggests that this is an opportunistic infection following environmental stress (i.e., thermal stress). The observation of similar signs for all of the putative WPl diseases (Sutherland et al., 2004), despite the fulfillment of Koch's postulates for WPl 2, is also problematic from a diagnostic perspective. A recent description of another putative agent for a disease with similar signs and etiology from Eilat, Israel (Thompson et al., 2006) further complicates our understanding of this phenomenon. The lack of host specificity, the occurrence of similar sets of signs with different microbial communities in different oceans, and the lack of fulfillment of Koch's postulates for most cases of disease with similar signs does not support a specific diagnosis of WPl disease, and is more consistent with an opportunistic infection following environmental stress.

3.5. Aspergillosis

In the Caribbean, the sea fan *Gorgonia ventalina* has experienced widespread mortality owing to aspergillosis (Sutherland et al., 2004). Aspergillosis has a well-defined set of signs and the fungus *Aspergillus sydowii* has been shown by Koch's postulates to be the causative agent (Smith et al., 1996) which can appropriately be described as an emergent infectious disease (Harvell et al., 1999). The virulence of *A. sydowii* increases with increasing water temperature (Alker et al., 2001), and long-term studies on populations of sea fans affected by aspergillosis have provided a good understanding of the epizootiology of a fungal disease and its effects on sea

fan populations, both spatially and temporally, in a marine ecosystem (Kim and Harvell, 2004). Aspergillosis of sea fans has declined in prevalence from 31% in 1997 to 5.9% in 2003 in the Florida Keys, which probably reflects a reduction in the number of susceptible individuals left on the reef coupled with the diminished number of sea fans left in the most affected areas. Interestingly, although aspergillosis has had a dramatic impact on sea fan populations in the Florida Keys, which may reflect the sea fan proximity to sources of the pathogen, populations in other locations (e.g. Little Cayman Island) remain largely unaffected (M.P.L., personal observation).

4. Resistance to coral disease

Other than generalized studies on coral resistance to stress and injury there is comparatively little known about the mechanisms employed by corals to resist pathogens (Sutherland et al., 2004; Mullen et al., 2004) and their relationship to changes in the environment. Corals have a suite of properties that provide resistance to microbial invasion. These include mucous; its production, biochemical properties and microbial flora (Ritchie, 2006; Sutherland et al., 2004; Mullen et al., 2004), and a cellular immune response that isolates and limits the spread of pathogens that have infected coral tissues (Sutherland et al., 2004; Mullen et al., 2004). Cellular defenses include wandering amoebocytes that phagocytize microbial invaders (Sutherland et al., 2004; Mullen et al., 2004), and chemical defenses in the form of antimicrobials (Sutherland et al., 2004; Mullen et al., 2004; Ward et al., 2007). While the majority of these antimicrobials have been observed in soft corals (Kelman et al., 2006), recent data has shown that hard corals can also release antimicrobials after exposure to stress (Geffen and Rosenberg, 2005). It is reasonable to hypothesize that the ability to maintain a multi-layered defense system against potential pathogens could be compromised by environmental stress and lead to a range of opportunistic infections. The more interesting question is whether corals can acquire resistance either through survival and reproduction of resistant genotypes, or through some sort of immunological memory which corals have demonstrated for allorecognition (Mullen et al., 2004; Sutherland et al., 2004), but not for disease resistance. One bacterial infection of corals, the infection of *Oculina patagonica* by *Vibrio shiloi* Rosenberg and Ben-Haim, 2002), has not been observed since 2004 (Reshef et al., 2006). *V. shiloi* is no longer present in either healthy or bleached coral samples, and has recently been presented as an example of a coral developing resistance to infection by changing the composition and abundances of its microbial communities (Reshef et al., 2006). Other putative infectious

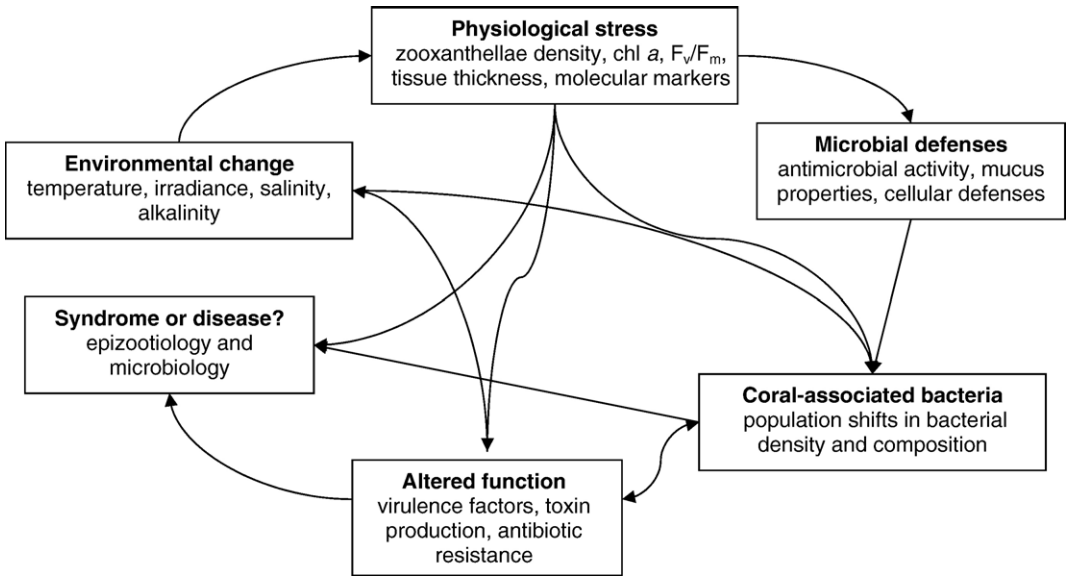

Fig. 3. Approach to coral disease microbiology. Most current "coral diseases" begin with changes in the environment and subsequent physiological stress by the coral. The host may, or may not, exhibit various defense mechanisms (e.g. antimicrobials) in response to physiological stress which then becomes a determining factor in the ability of coral associated bacteria or a primary pathogen to invade, multiply, produce various virulence factors and cause disease. Until a definitive pathogen can be shown to cause a coral disease all disease-like maladies should be called syndromes. The use of clear definitions and approaches to coral diseases, and an approach to diagnosis that includes investigating the underlying causes for physiological stress and disease resistance in corals, will improve our abilities to diagnose and distinguish between primary and opportunistic infections.

diseases of corals such as WPl 2 have undergone a similar decrease in prevalence (Richardson, 1998) either by increased host resistance, decreased pathogen virulence, or a decrease in susceptible hosts.

5. Where do we go from here?

We suggest that the relationship between a specific pathogen and the best described coral diseases is tenuous and highlights the potential importance of compromised coral health states and opportunistic infections as drivers of coral disease. While this may appear obvious, the concepts of runaway bacterial growth caused by elevated temperature, nutrients or dissolved organics are not always included in the definition of coral diseases (Fig. 3). In addition to the physiological stress that corals undergo when exposed to increases in seawater temperature (Lesser, 2004), many bacteria increase the expression of virulence genes and antibiotic resistance when exposed to elevated temperatures (Martínez and Baquero, 2002). The changing pathogenicity of commensal bacteria into opportunistic pathogens may also involve the expression of virulence factors, changes in the local environment, and competition with other bacterial populations that normally prevent infections (Martínez and Baquero, 2002). These opportunistic pathogens are not the result of the evolution of an infectious species with a particular host and are therefore not "emergent pathogens" (Martínez and Baquero, 2002). With these concepts in mind it is instructive that in 1982, Segel and Ducklow (1982) proposed a model for the response of a coral to pollution stress, in which the coral produces excess mucus that, in turn, leads to increased microbial growth, oxygen depletion and the death of the coral tissue due to toxin accumulation (e.g. hydrogen sulfide), and direct bacterial consumption. This model implies that there is a critical stress level that, if exceeded, leads to explosive bacterial activity and coral mortality. More recent studies have shown that some coral diseases are linked to bacterial overgrowth driven by direct and indirect contact with algae (Nugues et al., 2004; Smith et al., 2006), increased inorganic nutrients (Bruno et al. 2003) and increased dissolved organic carbon (Kuntz et al., 2005) supporting this model of opportunistic coral infections.

6. Concluding remarks

It is not hard to imagine a scenario whereby exposure to environmental disturbance triggers physiological and biochemical responses in corals that promote changes in previously benign components of the coral's normal surface mucus layer and tissue-associated microbial communities. We argue here that the most parsimonious interpretation of the available scientific evidence is that most common coral "diseases" are a result of opportunistic, non-specific bacteria that exploit the compromised health state of the coral after exposure to environmental stressors (e.g. temperature stress) and produce a variety of virulence factors that promote progression of the disease lesion. We believe that much of the data supporting the involvement of primary infectious pathogens can be interpreted alternatively as opportunistic infections secondary to stress, and that the role of primary infections in the current declines of coral reefs is minimal. Absence of proof for primary infections, however, does not automatically prove the alternative hypothesis. Additionally, in the absence of a known pathogen, we support previous suggestions that all putative diseases should be called syndromes. Some may disagree with this and use disease and syndrome synonymously. However, we believe it would be useful to make a clear distinction between the two at this time as part of a more rigorous approach to diagnosis. Global patterns of warming and other environmental stressors are likely to increase the virulence of opportunistic pathogens and the susceptibility of corals to infections. We believe that studies on coral disease should always include understanding how the environment influences coral health in order to develop the scientific rationale for implementing management practices aimed at ameliorating the regional and global-scale anthropogenic impacts that are driving the declining health of coral reefs worldwide.

Acknowledgements

This article grew out of discussions among several members of the Coral Reef Targeted Research (CRTR) Program Bleaching Working Group (http://www.gefcoral.org). This paper was improved by comments from Marc Slattery and Deb Gochfeld and five anonymous reviewers. Coral disease photographs were supplied by Deb Gochfeld and John Bythell. **[SS]**

References

Aeby, G.S., Santavy, D.L., 2006. Factors affecting susceptibility of the coral *Montastraea faveolata* to black-band disease. Mar. Ecol. Prog. Ser. 318, 103–110.

Alker, A.P., Smith, G.W., Kim, K., 2001. Characterization of *Aspergillus sydowii* (Thom et Church), a fungal pathogen of Caribbean sea fan corals. Hydrobiologia 460, 105–111.

Aronson, R.B., Precht, W.F., 2001. White-band disease and the changing face of Caribbean coral reefs. Hydrobiologia 460, 25–38.

Bruno, J.F., Peters, L.E., Harvell, C.D., Hettinger, A., 2003. Nutrient enrichment can increase the severity of coral diseases. Ecol. Lett. 6, 1056–1061.

Casas, V., Kline, D.I., Wegley, L., Yanan, Y., Breitbart, M., Rowher, F., 2004. Widespread association of a Rikettsiales-like bacterium with reef-building corals. Environ. Microbiol. 6, 1137–1148.

Cooney, R.P., Pantos, O., Le Tissier, M.D.A., Barer, M.R., O'Donell, A.G.O., Bythell, J.C., 2002. Characterization of the bacterial consortium associated with black band disease in coral using molecular microbiological techniques. Environ. Microbiol. 4, 401–413.

Daszak, P., Cunningham, A.A., Hyatt, A.D., 2000. Emerging infectious diseases of wildlife-threats to biodiversity and human health. Science 287, 443–449.

Denner, E.B.M., Smith, G.W., Busse, H.-J., Schumann, P., Nartz, T., Polson, S.W., Lubitz, W., Richardson, L.L., 2003. *Aurantimonas coralicida* gen. nov. sp. nov., the causative agent of white plague type II on Caribbean scleractinian corals. Int. J. Syst. Evol. Microbiol. 53, 1115–1122.

Ducklow, H.W., Mitchell, R., 1979. Bacterial populations and adaptations in the mucus layers on living corals. Limnol. Oceanogr. 24, 715–725.

Edmunds, P.J., 1991. Extent and effect of black band disease on a Caribbean reef. Coral Reefs 10, 161–165.

Fredricks, D.N., Relman, D.A., 1996. Sequence-based identification of microbial pathogens: a reconsideration of Koch's postulates. Clin. Microbiol. 9, 18–33.

Frias-Lopez, J., Zerkle, A.L., Bonheyo, G.T., Fouke, B.W., 2002. Partitioning of bacterial communities between seawater and healthy, black band diseased, and dead coral surfaces. Appl. Environ. Microbiol. 68, 2214–2228.

Frias-Lopez, J., Bonheyo, G.T., Fouke, B.W., 2003. Cyanobacteria associated with coral black band disease in Caribbean and Indo-Pacific reefs. Appl. Environ. Microbiol. 69, 2409–2413.

Frias-Lopez, J., Klaus, J.S., Bonheyo, G.T., Fouke, B.W., 2004. Bacterial community associated with black band disease in corals. Appl. Environ. Microbiol. 70, 5955–5962.

Geffen, Y., Rosenberg, E., 2005. Stress-induced rapid release if antimicrobials by scleractinian corals. Mar. Biol. 146, 931–935.

Garrett, P., Ducklow, H., 1975. Coral diseases in Bermuda. Nature 253, 349–350.

Gladfelter, W.B., 1982. White-band disease in *Acropora palmate*—implications for the structure and growth of shallow reefs. Bull. Mar. Sci. 32, 639–643.

Grimes, D.J., 2006. Koch's postulates—then and now. Microbe 1, 223–228.

Harvell, C.D., Kim, K., Burkholder, J.M., Colwell, R.R., Epstein, P.R., Grimes, D.J., Hofmann, E.E., Lipp, E.K., Osterhaus, A.D.M.E., Overstreet, R.M., Porter, J.W., Smith, G.W., Vasta, G.R., 1999. Emerging marine diseases−climate links and anthropogenic factors. Science 285, 1505–1510.

Harvell, C.D., Mitchell, C.E., Ward, J.R., Altizer, S., Dobson, A.P., Ostfeld, R.S., Samuel, M.D., 2002. Climate warming and disease risks for terrestrial and marine biota. Science 296, 2158–2162.

Harvell, C.D., Aronson, R., Baron, N., Connell, J., Dobson, A., Ellner, S., Gerber, L., Kim, K., Kuris, A., McCallum, H., Lafferty, K., McKay, B., Porter, J., Pascual, M., Smithe, G., Sutherland, K., Ward, J., 2004. The rising tide of ocean diseases: unsolved problems and research priorities. Front. Ecol. Environ. 2, 375–382.

Hoegh-Guldberg, O., 1999. Climate change, coral bleaching and the future of the world's coral reefs. Mar. Freshw. Res. 50, 839–866.

Kelman, D., Kashman, Y., Rosenberg, E., Kushmaro, A., Loya, Y., 2006. Antimicrobial activity of Red Sea corals. Mar. Biol. 149, 357–363.

Kim, K., Harvell, C.D., 2004. The rise and fall of a six-year coral-fungal epizootic. Am. Nat. 164, S52–S63.

Klaus, J.S., Frias-Lopez, J., Bonheyo, G.T., Heikoop, J.M., Fouke, B.W., 2005. Bacterial communities inhabiting the healthy tissues of two Caribbean corals: interspecific and spatial variation. Coral Reefs 24, 129–137.

Kuta, K.G., Richardson, L.L., 1996. Abundance and distribution of black band disease on coral reefs in the northern Florida Keys. Coral Reefs 15, 219–223.

Kuntz, N.M., Kline, D.I., Sandin, S.A., Rohwer, F., 2005. Pathologies and mortality rates caused by organic carbon and nutrient stressors in three Caribbean coral species. Mar. Ecol. Prog. Ser. 294, 173–180.

Lafferty, K.D., Porter, J.W., Ford, S.E., 2004. Are diseases increasing in the ocean? Ann. Rev. Ecolog. Syst. 35, 31–54.

Lesser, M.P., 2004. Experimental biology of coral reef ecosystems. J. Exp. Biol. Ecol. 300, 217–252.

Lessios, H.R., Robertson, D.R., Cubit, J.D., 1984. Spread of *Diadema* mass mortality through the Caribbean. Science 226, 335–337.

Lipp, E.K., Jarrell, J.L., Griffin, D.W., Lukasik, J., Jacukiewicz, J., Rose, J.B., 2002. Preliminary evidence for human fecal contamination in corals from the Florida Keys, USA. Mar. Pollut. Bull. 44, 666–670.

Martínez, J.L., Baquero, F., 2002. Interactions among strategies associated with bacterial infection, pathogenecity, epidemicity, and antibiotic resistance. Clin. Microbiol. Rev. 15, 647–679.

McCallum, H., Harvell, D., Dobson, A., 2003. Rates of spread of marine pathogens. Ecol. Lett. 6, 1062–1067.

Mullen, K.M., Peters, E.P., Harvell, C.D., 2004. Coral resistance to disease. In: Rosenberg, E., Loya, Y. (Eds.), Coral Health and Disease. Springer-Verlag, pp. 377–399.

Nugues, M.M., Smith, G.W., van Hooidonk, R.J., Seabra, M.I., Bak, R.P.M., 2004. Algal contact as a trigger for coral disease. Ecol. Lett. 7, 919–923.

Pantos, O., Cooney, R.P., Le Tissier, M.D.A., Barer, M.R., O'Donell, A.G., Bythell, J.C., 2003. The bacterial ecology of a plague-like disease affecting the Caribbean coral *Montastraea annularis*. Environ. Microbiol. 5, 370–382.

Pantos, O., Bythell, J.C., 2006. Bacterial community structure associated with white band disease in the elkhorn coral *Acopora palmata* determined using culture-independent 16S rRNA techniques. Dis. Aquat. Org. 69, 79–88.

Patterson, K.L., Porter, J.W., Ritchie, K.B., Polson, S.W., Mueller, E., Peters, E.C., Santavy, D.L., Smith, G.W., 2002. The etiology of white pox, a lethal disease of the Caribbean coral, *Acropora palmata*. Proc. Natl. Acad. Sci. 99, 8725–8730.

Porter, J.W., Battey, J.F., Smith, G.J., 1982. Perturbation and change in coral reef communities. Proc. Natl. Acad. Sci. 79, 1678–1681.

Remily, E.R., Richardson, L.L., 2006. Ecological physiology of a coral pathogen and the coral reef environment. Microb. Ecol. 51, 345–352.

Reshef, L., Koren, O., Loya, Y., Zilber-Rosenberg, I., Rosenberg, E., 2006. The coral probiotic hypothesis. Environ. Microbiol. 8, 2068–2073.

Richardson, L.S., 1998. Coral diseases: what is really known? Trends Ecol. Evol. 13, 438–443.

Richardson, L.L., 2004. Black band disease. In: Rosenberg, E., Loya, Y. (Eds.), Coral Health and Disease. Springer-Verlag, pp. 325–336.

Richardson, L.L., Aronson, R.B., 2002. Infectious diseases of reef corals. Proc. 9th Int. Coral Reef Symp., vol. 2, pp. 1225–1230.

Richardson, L.L., Goldberg, W.M., Kuta, K.G., Aronson, R.B., Smith, G.W., Ritchie, K.B., Halas, J.C., Feingold, J.S., Miller,

S.L., 1998. Florida's mystery coral-killer identified. Nature 392, 557–558.

Ritchie, K.B., Smith, G.W., 1995. Preferential carbon utilization by surface bacterial communities from water mass, normal, and white-band diseased *Acropora cervicornis*. Mol. Mar. Biol. Biotechnol. 4, 345–352.

Ritchie, K.B., Polson, S.W., Smith, G.W., 2001. Microbial disease causation in marine invertebrates: problems, practices, and future prospects. Hydrobiologia 460, 131–139.

Ritchie, K.B., 2006. Regulation of microbial populations by coral surface mucus and mucus-associated bacteria. Mar. Ecol. Prog. Ser. 322, 1–14.

Rohwer, F., Seguritan, V., Azam, F., Knowlton, N., 2002. Diversity and distribution of coral-associated bacteria. Mar. Ecol. Prog. Ser. 243, 1–10.

Rosenberg, E., Ben-Haim, Y., 2002. Microbial diseases of corals and global warming. Environ. Microbiol. 4, 318–326.

Ruby, E., Henderson, B., McFall-Ngai, M., 2004. We get by with a little help from our (little) friends. Science 303, 1305–1307.

Rützler, K., Santavy, D.L., Antonius, A., 1983. The black band disease of Atlantic reef corals. III. Distribution, ecology, and development. P.S.Z.N.I. Mar. Ecol. 4, 329–358.

Santavy, D.L., Mueller, E., Peters, E.C., MacLaughlin, L., Portwe, J.W., Patterson, K.L., Campbell, J., 2001. Quantitative assessment of coral diseases in the Florida Keys: strategy and methodology. Hydrobiologia 460, 39–52.

Segel, L.A., Ducklow, H.W., 1982. A theoretical investigation into the influence of sublethal stresses on coral-bacterial ecosystem dynamics. Bull. Mar. Sci. 32, 919–935.

Sekar, R., Millis, D.K., Remily, E.R., Voss, J.D., Richardson, L.L., 2006. Microbial communities in the surface mucopolysaccharide layer and the blank band microbial mat of black band-diseased *Siderastrea siderea*. Appl. Environ. Microbiol. 72, 5963–5973.

Smith, G.W., Ives, L.D., Nagelkerken, I.A., Ritchie, K.B., 1996. Caribbean sea-fan mortalities. Nature 383, 487.

Smith, J.E., Morrigan, S., Edwards, R.A., Obura, D., Pantos, O., Sala, E., Sandin, S.A., Smriga, S., Hatay, M., Rohwer, F.L., 2006. Indirect effects of algae on coral: algae-mediated, microbe-induced coral mortality. Ecol. Lett. 9, 835–845.

Sutherland, K.P., Porter, J.W., Torres, C., 2004. Disease and immunity in Caribbean and Indo-Pacific zooxanthellate corals. Mar. Ecol. Prog. Ser. 266, 273–302.

Thompson, F.L., Barash, Y., Sawabe, T., Sharon, G., Swings, J., Rosenberg, E., 2006. *Thalassomonas loyana* sp. nov., a causative agent of the white plague-like disease of corals on the Eilat coral reef. Int. J. Syst. Evol. Microbiol. 56, 365–368.

Voss, J.D., Richardson, L.L., 2006. Coral diseases near Lee Stocking Island, Bahamas: patterns and potential drivers. Dis. Aquat. Org. 69, 33–40.

Ward, J.R., Lafferty, K.D., 2004. The elusive baseline of marine diseases: are diseases in ocean ecosystems increasing? PLoS Biol. 2, 542–547.

Ward, J.R., Rypien, K.L., Bruno, J.F., Harvell, C.D., Jordan-Dahlgren, E., Mullen, K.M., Rodríguez-Martinez, R.E., Sánchez, J., Smith, G., 2006. Coral diversity and disease in Mexico. Dis. Aquat. Org. 69, 23–31.

Ward, J.R., Kiho, K., Harvell, C.D., 2007. Temperature affects coral disease resistance and pathogen growth. Mar. Ecol. Prog. Ser. 329, 115–121.

Weil, E., Urreiztieta, I., Garzón-Ferreira, J., 2002. Geographic variability in the incidence of coral and octocoral diseases in the wider Caribbean. Proc. 9th Int. Coral Reef Symp., vol. 2, pp. 1231–1237.

Work, T.M., Aeby, G.S., 2006. Systematically describing gross lesions in corals. Dis. Aquat. Org. 70, 155–160.