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Marine Mammals as Sentinel Species for Oceans and Human Health

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Abstract

The long-term consequences of climate change and potential environmental degradation are likely to include aspects of disease emergence in marine plants and animals. In turn, these emerging diseases may have epizootic potential, zoonotic implications, and a complex pathogenesis involving other cofactors such as anthropogenic contaminant burden, genetics, and immunologic dysfunction. The concept of marine sentinel organisms provides one approach to evaluating aquatic ecosystem health. Such sentinels are barometers for current or potential negative impacts on individual- and population-level animal health. In turn, using marine sentinels permits better characterization and management of impacts that ultimately affect animal and human health associated with the oceans. Marine mammals are prime sentinel species because many species have long life spans, are long-term coastal residents, feed at a high trophic level, and have unique fat stores that can serve as depots for anthropogenic toxins. Marine mammals may be exposed to environmental stressors such as chemical pollutants, harmful algal biotoxins, and emerging or resurging pathogens. Since many marine mammal species share the coastal environment with humans and consume the same food, they also may serve as effective sentinels for public health problems. Finally, marine mammals are charismatic megafauna that typically stimulate an exaggerated human behavioral response and are thus more likely to be observed.

Keywords

marine mammals, sentinel species, ecosystem health, human health

As the effects of climate change and potential environmental degradation are debated and better characterized, worldwide concern is being raised about the health of the earth's aquatic ecosystems.[40,148,206,212] The long-term consequences of environmental change on aquatic ecosystems are not well characterized but are likely to include aspects of disease emergence in aquatic plants and animals.[206] In turn, these emerging diseases may have epizootic potential, zoonotic implications, and a complex pathogenesis involving other cofactors such as anthropogenic contaminant burden, genetics, and immunologic dysfunction.[30,181] Emerging diseases have themselves become new drivers of environmental change since they can cause extinction of endangered species; alter the ratios of predators, prey, competitors, and recyclers necessary for healthy, well-functioning ecosystems; and alter habitat already threatened by the emergence of discontinuities (ie, habitat fragmentation) and climate change.[62]

Ocean health is inextricably linked to human health on a global scale as well. Connections between the health of humans, animals, and the environments in which they live are well recognized and recently have been referred to as "one health, one medicine." The "one health, one medicine" worldwide strategy for expanding interdisciplinary collaborations and communications in all aspects of health begins to address these critical relationships.

The concept of marine sentinel organisms provides one approach to evaluating aquatic ecosystem health. Such sentinels are used to gain early warnings about current or potential negative impacts on individual- and population-level animal health.[29] In turn, such warnings permit better characterization and management of these impacts that ultimately affect human and animal health associated with the oceans. Marine mammals are described as prime sentinels because many species have long life spans, are long-term coastal residents, feed at a high trophic level, and have large blubber stores that can serve as depots for anthropogenic chemicals and toxins.[7,15,29,30,110,111,154,155,184,234] Finally, marine mammals are charismatic megafauna that typically stimulate an exaggerated human behavioral response and are thus more likely to be observed.[21] Therefore, health concerns that affect these species

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may make humans more likely to pay attention to ocean health issues.

Emerging Infectious and Neoplastic Disease in Marine Mammals

Emerging and reemerging viral, bacterial, protozoal, and fungal diseases have been described in marine mammals. Additionally, complex diseases involving emerging infectious and neoplastic components have been reported, and these diseases may provide important information on aquatic ecosystem and public health.

Morbillivirus Infection

Morbillivirus infections are responsible for recent widespread epizootics and mortality in cetaceans.[129,130,131,177,225,226] A cetacean morbillivirus caused a massive epizootic that resulted in the death of an estimated 2,500 dolphins or approximately 50% of the inshore population of Atlantic bottlenose dolphins (*Tursiops truncatus*) in 1987–1988.[129] This large-scale epizootic was followed by further die-offs of bottlenose dolphins in the Gulf of Mexico in 1993 and 1994. Morbillivirus antigen and characteristic lesions were detected in tissues from both epizootics, and morbillivirus RNA was demonstrated by reverse transcription polymerase chain reaction (PCR) testing.[129,130,120,204]

A second major morbillivirus epizootic killed several thousand striped dolphins (*Stenella coeruleoalba*) along the Spanish Mediterranean coast from 1990 to 1992, and more recently an epizootic occurred in 2007.[57-59,177] Historically, 2 strains of cetacean morbillivirus have been reported to infect odontocete cetacean populations worldwide: dolphin morbillivirus (DMV) and porpoise morbillivirus (PMV).[57,58,223] DMV and PMV appear to be closely related strains of a cetacean morbillivirus and are distinct from phocine distemper virus and canine distemper virus and more closely related to the ruminant morbilliviruses and measles virus.[14,10,232] Additionally, a novel morbillivirus was identified in a long-finned pilot whale (*Globicephala melas*) that died off the coast of New Jersey and may represent a third member of the cetacean morbillivirus group.[217] A central role for infection in pilot whales (*Globicephala* sp.) has been suggested on the basis of high seroprevalence in samples obtained during multiple stranding events for both *G. melas* and *G. macrorhynchus* dating back to 1982.[61] The high rates of seroprevalence and gregarious nature of the species led to the hypothesis that pilot whales may serve as reservoirs for cetacean morbilliviruses and transmit the agent to other cetaceans; however, the nature of enzootic infection in *Globicephala*, if it occurs, remains unresolved.[61]

In general, DMV infection is not considered an endemic infection, and it is speculated that a decline in herd immunity and an increase in population density will render dolphin populations susceptible to new epizootics.[33] However, evidence for chronic infection consisting of nonsuppurative encephalitis characterized by DMV antigen in the brain in the absence of other systemic involvement has been reported in striped dolphins.[59] Similarly, DMV titers and antigen persistence in the brain, in the absence of typical morbillivirus lesions or systemic involvement, have both been observed in Indo-Pacific bottlenose dolphins (*Tursiops aduncus*), further illustrating the complexity of this infection (G. D. Bossart, unpublished data). Furthermore, in an ongoing comprehensive Atlantic bottlenose dolphin health assessment program in the Indian River Lagoon (IRL), Florida, positive fluctuating morbillivirus titers and seroconversion were recently reported in this dolphin population that has strong site fidelity.[33] Seropositivity was detected in IRL dolphins less than 6 years of age as well as in dolphins that were alive during the 1987–1988 epizootic. During the study period, pathologic and immunohistochemical findings from stranded IRL dolphins did not demonstrate typical morbillivirus-associated lesions or the presence of morbillivirus antigen. The findings suggest that recurring endemic morbillivirus transmission and subclinical infections are occurring in the absence of widespread mortality in IRL dolphins. In cases of widespread cetacean morbilliviral disease, disease surveillance becomes an important component of population health and epidemiology and may provide information on population susceptibility to epizootics that can significantly impact ecosystem health and stability.

Brucellosis

Brucellosis is a zoonotic disease of terrestrial and marine mammals. *Brucella* spp. were first isolated in 1994 from tissues collected at necropsy from stranded harbor seals (*Phoca vitulina*), harbor porpoise (*Phocoena phocoena*), and common dolphins (*Delphinus delphis*) from Scotland and from an aborted fetus of a bottlenose dolphin in the United States.[63,194,195] The isolation of *Brucella* has since been described from a wide variety of marine mammals including Atlantic white-sided dolphin (*Lagenorhynchus acutus*), striped dolphin, hooded seal (*Cystophora cristata*), gray seal (*Halichoerus grypus*), Pacific harbor seal (*Phoca vitulina richardsi*), minke whale, and white beaked dolphin (*Lagenorhynchus albirostris*).[42,75,76,78,105,176] Furthermore, strong serological evidence exists to suggest that marine mammal *Brucella* infections are globally widespread among marine mammal species and have a high prevalence.[46,107,161-163,169,191,195,214,221,224] Marine mammal *Brucella* strains are distinct from the terrestrial *Brucella* species, and recently 2 new species, *B. pinnipedialis* and *B. ceti*, were described.[77] New molecular data confirm that there are significant subtypes within the newly described marine mammal *Brucella* species, which add to a body of evidence that could lead to the recognition of additional species or subspecies within this group.[47,136]

Compared with the reported high global seroprevalence of marine mammal *Brucella* spp. infection, clinical disease does not appear to be common. In one study, minke whales (*Balaenoptera acutorostrata*) and Bryde's whales (*Balaenoptera edeni*) in the western North Pacific were reported to have chronic purulent or granulomatous orchitis associated with positive *Brucella* antibody titers.[169] Two cases of *Brucella* placentitis and abortion

have been reported in captive Atlantic bottlenose dolphins.[149] Neurobrucellosis recently was reported in striped dolphins and was characterized by lymphoplasmacytic and histiocytic nonsuppurative meningoencephalitis.[84,95] Dolphins with neurobrucellosis typically are PCR, serologically, and immunohistochemically positive to *Brucella* spp and *Brucella ceti* and may be isolated from cerebrospinal fluid. In dolphins, *B. ceti* has tropism for placental and fetal tissues. Vertical transmission and the possibility of horizontal transmission to newborns have been postulated.[95] Thus, bacteria may be shed as in *Brucella*-infected domestic livestock. Moreover, the localization of the bacteria in particular organs suggests the possibility of transmission through sexual intercourse and may ensure the prevalence of both clinical and latent infections.[95] It appears that striped dolphins constitute a highly susceptible host and a potential reservoir for *B. ceti* transmission.[84,95,158] Marine mammal *Brucella* strains are capable of infecting humans and livestock and thus represent an important zoonotic consideration despite the observation that human clinical disease does not appear to be common.[174,207,235] Notably, in one review, none of the 3 human patients infected with marine mammal brucellosis had direct contact with marine mammals, although all had consumed raw seafood.[235] These findings suggest that more extensive studies of the presence and distribution of marine mammal *Brucella* genotypes are needed before the zoonotic significance can be evaluated. Additionally, global surveillance is required to fully understand the distribution, ecology, and genetic relatedness of *Brucella* isolates from marine mammals that become valuable sentinels for evaluating the aquatic health impacts of this infectious agent.

Leptospirosis

Leptospirosis is a zoonotic disease infecting a broad range of mammalian hosts and is reemerging globally.[12] California sea lions (*Zalophus californianus*) have experienced recurrent outbreaks of leptospirosis since 1970, and the infection is thought to be enzootic.[1,142,228] Leptospirosis, primarily caused by *L. interrogans* serovar Pomona, is known to cause abortions and renal disease in California sea lions with clinicopathologic features similar to domestic animals.[56,87] Histologically, a lymphoplasmacytic interstitial nephritis with tubular necrosis is present with the spirochete identified in the renal tubular epithelium and free in the lumina. In newborns and aborted fetuses, the disease is characterized by subcutaneous hemorrhage and hyphema.[142,228]

Recent research to elucidate the epidemiology of leptospirosis in California sea lions demonstrated that the disease is enzootic but also occurs in outbreaks of acute disease every 4–5 years.[133] The latter findings call into question the apparent contradiction between maintenance hosts of leptospirosis, which experience chronic but largely asymptomatic infections, and accidental hosts, which suffer acute illness or death as a result of disease spillover from reservoir species. Furthermore, environmental risk factors for sea lion leptospirosis may include exposure to dogs and dog parks or factors associated with them.[167] The sea lion/leptospirosis system raises questions regarding the accepted view of the epidemiology of this important zoonosis, especially since leptospirosis has resurged in humans and domestic dogs in California.[4,144]

Protozoal Infection

Protozoal infection is a major cause of mortality among southern sea otters (*Enhydra lutris nereis*). Infections with protozoal pathogens *Toxoplasma gondii* and *Sarcocystis neurona* were the cause of death in approximately 25% of the freshly dead sea otters examined from 1998 to 2001.[121,122] Introduced and invasive terrestrial mammals including domestic cats and opossums are the respective definitive hosts for these protozoa. Oocysts from cat feces wash into seawater, where they can survive for at least 24 months and serve as a source of infection via transport hosts.[128] A seroprevalence analysis showed *T. gondii* infection in 52% of beached sea otters and 38% in live sea otters sampled along the California coast, with a clear association between proximity of freshwater inputs into the ocean and infection.[147] Southern sea otters consume a wide variety of benthic marine invertebrates; their daily food consumption is equivalent to 25–35% of their body weight.[111] In the laboratory, filter feeding sea otter prey species such as blue mussels (*Mytilis* spp.) accumulate *T. gondii* oocysts that remain infective for weeks.[8] As nearshore predators, otters serve as sentinels of protozoal pathogen flow into the marine environment since they share the same environment and consume some of the same foods as humans such as mussels, clams, and crabs.[111,146] Eating improperly prepared seafood containing oocysts may result in human toxoplasmosis, which is a potentially fatal infection in immunocompromised patients and a well-documented cause of serious fetal malformations.[37,60] Investigation into the processes promoting protozoal infections in sea otters provides a better understanding of terrestrial parasite flow and the emergence of disease at the interface between wildlife, domestic animals, and humans.[44,68,146]

Mycotic Disease

The emergence of lobomycosis was recently reported in dolphins along Florida's Atlantic coast and in North Carolina.[26,29,189,198] Lobomycosis is a rare chronic mycotic disease of the skin and subcutaneous tissues caused by a yeast-like organism known as *Lacazia loboi*.[17] Dolphins and humans are the only species known to be naturally susceptible to infection with *Lacazia loboi*. The clinicopathologic manifestations of lobomycosis in humans and dolphins are similar and consist of focal to locally extensive verrucoid to nodular lesions that typically progress slowly over the course of years without involvement of internal organs. The tissue response consists of multifocal dermal granulomas. Within granulomas, *Lacazia* can be demonstrated as yeast-like organisms, 6–12 μm in diameter with thick, refractile walls, arranged singly or in chains connected by tube-like bridges.[17,189] The organism has not been cultured to date in vitro; therefore, diagnosis depends on identification of the characteristic yeast-like cells in tissue or exudates.

The IRL is an endemic area for the lobomycosis in dolphins with a prevalence of 10–12%.[189] Recent research indicates that the disease is associated with humoral and cell-mediated immunosuppression.[17,188] The spatial distribution of lobomycosis within the IRL suggests that environmental factors contribute to the expression of the disease.[159] Mercury levels in dolphin tissues in the IRL are high and may play a role in the disruption of immune function, increasing susceptibility to opportunistic infections.[188,208,209] Limited evidence exists to suggest that lobomycosis may be transferred from infected animals to people.[189] However, the high prevalence of lobomycosis in the dolphin population of a Florida coastal region, which is used extensively for recreational purposes, raises concerns for zoonotic or common source transmission. Thus, from several perspectives, lobomycosis in bottlenose dolphins represents an animal sentinel of environmental and ecosystem change, with particular implications for human health in populations inhabiting coastal environments.

Viral Disease

Diseases with complex multifactorial etiologies associated with novel viral infections are being characterized in marine mammals. For example, approximately 20% of sexually mature stranded California sea lions have urogenital cancer, which often metastasizes and is associated with a novel gammaherpesvirus, designated otarine herpesvirus-1 (OtHV-1).[38,39,118,132] Other cofactors potentially involved in the pathogenesis of urogenital carcinoma in sea lions include exposure to anthropogenic contaminants that persist in the sea lions' feeding grounds and genetic factors, specifically inbred sea lions and those with a specific MHC genotype.[2,35,238]

Recently, sexually transmitted orogenital papillomatosis that occasionally undergoes transformation to metastatic squamous cell carcinoma was found to be frequently associated with a novel herpesvirus and newly sequenced papillomaviruses (TtPV-1, TtPV-2) in Atlantic bottlenose dolphins.[28,32,183,185-187] The dolphin disease is associated with immunologic perturbations and, in some instances, with high levels of anthropogenic contaminants, including mercury and infection with immunosuppressive cetacean morbilliviruses.[32,33,208,209] Cutaneous papillomatosis associated with another novel papillomavirus (TmPV-1) was documented in Florida manatees (*Trichechus manatus latirostris*) with virally productive papillomas associated with immunosuppression.[23,182] In manatees, it is thought that cutaneous papillomas are caused by activation of latent infection and reinoculation from active infection with concurrent immunologic suppression as a cofactor in disease pathogenesis.[23] Because related papillomaviruses are associated with human disease, including cervical cancer, dolphins and manatees may be good models for understanding oncogenesis mechanisms in humans. These combined data suggest that interactions occur among genes, anthropogenic toxins, immunologic factors, and/or oncogenic viruses in these common marine mammals that share a coastal environment with humans.[2,29,188,238]

Antibiotic Resistant Bacteria

Other confirmed or suspected infectious disease agents have been reported in marine mammals that may have ecosystem or human health implications.[19,94,135,165,166,230,226] One significant concern to public health authorities is the emergence of antibiotic-resistant species of bacteria among animals and humans. Widespread evidence of antibiotic-resistant bacteria was recently described in northern elephant seals (*Mirounga angustirostris*) and bottlenose dolphins, the latter as part of health assessment studies from the coastal waters of Charleston (CHS), South Carolina, and the IRL.[85,201,202,211] Direct release of resistant bacterial species and/or unused antimicrobial agents into the aquatic environment appears to affect these dolphin populations. Twenty-five percent of *Escherichia coli* fecal isolates from IRL and CHS dolphins demonstrated resistance to 1 or more antibiotics. Disturbingly, a small number of methicillin-resistant also were reported from dolphins. The results suggest that the transfer of resistance from humans or domestic animals may occur or that antibiotics are reaching the marine environment, creating selective genetic adaptation.[85,201,202] Thus, from an aquatic perspective, dolphins appear to be prime sentinels for this important public health problem.

Anthropogenic Chemicals

Marine mammals are exposed to a variety of persistent organohalogen compounds (POCs) and inorganic pollutants that bioaccumulate in marine ecosystems, resulting in high tissue contaminant concentrations. In particular, marine mammals from coastal regions associated with dense human populations and greater industrial and agricultural activities have high tissue concentrations of POCs.[6,64,101,171-173] In addition to being apex predators, small cetaceans have several anatomic and life-history features that contribute to the accumulation of lipophilic pollutants, which may increase susceptibility to other anthropogenic stressors.[64] Cetacean species have extensive fat stores that accumulate high levels of POCs. During periods of fasting, starvation, lactation, or other physiological demands, these contaminants may be mobilized, which may redistribute traditional contaminants as well as emerging chemicals of concern. The redistribution of these contaminants may affect adult and perinatal health. Furthermore, the lower capacity for degradation of these chemicals in these species exacerbates toxic effects.[16,215]

High levels of contaminants documented in marine mammals include legacy chemicals such as the organochlorine pesticides including dichlorodiphenylethanes (ie, DDTs), dieldrin, chlordanes, hexachlorocyclohexanes (HCHs), polychlorinated dioxins, dibenzofurans, and polychlorinated biphenyls (PCBs)[64,86,93,115,116,151,153,164] and emerging compounds such as polybrominated diphenyl ethers (PBDEs),[64,65,103,112,116,143,222] perfluorinated chemicals (PFCs),[34,64,117] hexabromocyclododecanes, and polybrominated dimethoxybiphenyls.[113,231,240] Hydroxylated PCBs and PBDEs were reported in various tissues

of beluga whales, bottlenose dolphins, and killer whales (*Orcinus orca*).[11,102,143]

In particular, the widespread coastal distribution of bottlenose dolphins and their role as apex predators support their relevance as important sentinel species for biomonitoring spatial and temporal trends in contaminants.[29,64,66,67,184,210,234] Interestingly, in a novel POC risk assessment model, marine mammals also have been used as sentinel species for Arctic ecosystem and public health.[97-100,123,134,236] The accumulation of POCs in Native populations from Arctic subsistence communities has raised questions concerning the suitability of terrestrial and marine wildlife from this region for human consumption.[100,168,199,200] For Arctic residents dependent upon marine resources, a clear human connection exists with marine mammal health since Arctic marine mammal species consume similar prey and many marine mammal species are themselves consumed by indigenous peoples.

Persistent organohalogen compounds are resistant to environmental degradation and persist for long periods, becoming widely distributed geographically and accumulating in the fatty tissue of humans and wildlife. The associations of adverse health effects with POCs in marine mammals have been arguably linked to increased infectious disease susceptibility,[5,91,108,109,196,197] immunosuppression,[43,51,54,55,156,157,196] reproductive impairment,[3,43,190,109] endocrine disruption,[73,74,106,175,213,216] and neoplasia.[43,138,140,160,238] In toxicology testing in laboratory species, convincing evidence exists for the toxicopathologic effects of many of these contaminants on endocrine, neurologic, reproductive, developmental, immunologic, and cellular systems.[13,41,45,53,67,79,104,125,126,170,193,229]

Beluga whales (*Delphinapterus leucas*) from the St. Lawrence estuary are one of the most extensively and consistently studied groups of free-ranging marine mammals in relation to POCs and other contaminants and the development of neoplasia.[50,92,137,140,141,160] Beluga whales from the St. Lawrence region develop a wide variety of neoplasms, many of which are of similar types to those seen in domestic species and in humans.[48,49,139,140,160] Exposure to carcinogenic contaminants such as POCs in the food chain is a speculated cause of the high prevalence of neoplasia in this population of whales.[50,92,137,140]

Heavy metal levels have often been measured from the blood of marine mammals, but the significance of the levels found is not fully understood. High levels of mercury have been reported in dolphins from the Gulf and Atlantic coasts of Florida and Australia.[127,208,209,237] For example, the IRL dolphin population has the highest mean concentrations of mercury in blood and skin from the limited set of studies of free-ranging bottlenose dolphins reported to date. The concentrations of mercury found in IRL dolphins exceeded the EPA benchmark of mercury in cord blood for humans.[208,209] Correlations between mercury and selenium have been reported in many marine mammal species, and the ability of marine mammals to withstand large concentrations of mercury is believed to be partly due to this protective pairing with selenium.[127,237] Further studies are required to explore the effects of mercury on these marine mammal populations as well as the potential implications for humans that inhabit the same coastal ecosystems.

The interactions of mercury and selenium may play a role in the cardiomyopathy (CMP) reported in pygmy sperm whales (*Kogia breviceps*) and dwarf sperm whales (*Kogia sima*). The disease in *Kogia* spp. has been described primarily in stranded adult male whales from the southeastern Atlantic Ocean, but it also occurs in Pacific Ocean whales.[18,31] More than half of documented adult *Kogia* spp. strandings exhibit signs of chronic progressive idiopathic CMP or some state of myocardial degeneration. The cause of this complex disorder remains unknown. However, factors speculated to contribute to the development of CMP in these species include genetics, infectious agents, contaminants, biotoxins, and dietary intake (vitamins, selenium, mercury, and prooxidants).[31] In a recent age-controlled study of *K. breviceps*, both mercury and selenium concentrations increased with animal age and progression of CMP (C. E. Bryan, personal communication). Whales with CMP had greater overall protein oxidation, and selenium protein patterns were different between animals with no myocardial lesions and those with CMP, suggesting that selenium protein expression is altered with the disease state in pygmy sperm whales. The latter studies increased knowledge of CMP in pygmy and dwarf sperm whales and may also provide complementary information benefiting other affected species.

Using marine mammals as sentinels may provide important clues about the cumulative and synergistic effects of the mixture of the aforementioned contaminants, which is an emerging issue that requires attention.[150,153,172] Marine mammals are exposed to a wide admixture of legacy POCs and PCBs, emerging contaminants such as PBDEs and PFCs, their metabolites and/or degradation products, heavy metals, and natural marine biotoxins associated with harmful algal blooms (see below). The significance of these multiple co-exposures is still unclear, but the potential exists for additive and/or synergistic effects on the immunologic, neurologic, endocrine, and reproductive systems of not only marine mammals but also humans who inhabit the same coastal ecosystems.

Harmful Algal Blooms

Harmful algal blooms (HABs), and the potent neurotoxins they produce, have been associated with mass mortalities of dolphins, sea lions, southern sea otters, Florida manatees, Mediterranean monk seals (*Monachus monachus*), gray whales (*Eschrichtius robustus*), and humpback whales (*Megaptera novaeangliae*).[22,24,71,72,80,88,111,220] The range of biotoxins produced by HABs is extensive, and these toxins directly or indirectly affect human health. Biotoxins associated with HABs include brevetoxins, the cause of neurotoxic shellfish poisoning; saxitoxins, the cause of paralytic shellfish poisoning; okadaic acid, the cause of diarrheic shellfish poisoning; domoic acid, the cause of amnesic shellfish poisoning; and others.[124,227] The HAB problem is significant, is growing worldwide, and poses a major threat to human and ecosystem health.[81,119] The global pandemic of HABs has been

interpreted as a reflection of ecosystem instability and a threat to public health.[62] Thus, marine mammals appear to be good sentinels for the ecosystem and public health effects of HABs.[20,29]

Domoic Acid

Domoic acid (DA) is a neurotoxin produced by diatoms of the genus *Pseudo-nitzschia*, which targets the limbic system. This toxin causes excitotoxicity and damage to neuronal pathways responsible for the learning and recall of sequences underlying spatial memory as well as restraining seizure-prone circuitry associated with temporal lobe epilepsy.[89,179] A unique hallmark of DA intoxication in humans is loss of short-term memory, thus the term amnesic shellfish poisoning. Recurrent outbreaks of DA poisoning along the California coast have caused stranding of several thousand sea lions, and DA is now viewed as a major cause of reproductive failure.[36,52,83,89,203] The primary peracute microscopic lesions of DA toxicity in adult sea lions are microvesicular hydropic degeneration within the neuropil of the hippocampus, amygdala, pyriform lobe, and other limbic structures. Acutely, ischemic neuronal necrosis develops and is particularly apparent in the granular cells of the dentate gyrus and the pyramidal cells within the hippocampus cornu ammonis (CA) sectors CA4, CA3, and CA1. Chronically, gliosis, mild nonsuppurative inflammation, and loss of laminar organization in affected areas are found.[205] Myocardial necrosis and edema have also been reported.[88] Histopathologic findings associated with abortion and premature birth include systemic and localized inflammation and bacterial infections of amniotic origin, placental abruption, and brain edema.[83] A degenerative cardiomyopathy associated with exposure to DA, which is beyond central neurologic disease, represents another recently reported syndrome in California sea lions and may contribute to morbidity and mortality.[239] Furthermore, it has been suggested that DA intoxication may be potentiated by organochlorine burden.[219]

Recent observations have defined a chronic disease in juvenile California sea lions characterized by epilepsy and unusual behaviors.[82] This emerging chronic juvenile sea lion disease has been proposed to result from in utero toxicity to DA.[180] Research suggests that sublethal DA doses may progress to chronic epileptic disease similar to temporal lobe epilepsy in humans[178] and that magnetic imaging the hippocampus of sea lions exposed to DA may be a useful antemortem diagnostic technique.[152] Acute high-dose DA intoxication may lead to sudden death but those animals that survive the initial bout of seizures may develop neurological disease with behavioral changes and increased severity of spontaneous seizures in the absence of the DA diatom blooms. Thus, sea lions may provide important information on how marine mammals and other species, including humans, respond to DA intoxication including the possible association with epilepsy. Additionally, since sea lion strandings in California appear to be a very sensitive indicator of DA in the marine environment, it has recently been suggested that their monitoring be included in public health surveillance plans.[52]

Domoic acid also may affect southern sea otters, gray whales (*Eschrichtius robustus*), and pygmy and dwarf sperm whales. In 2003, an unusual mortality event was declared in southern sea otters by the US Fish and Wildlife Service and NOAA/National Marine Fisheries Service. Blooms of *Pseudo-nitzschia australis* were associated with this event.[111] In 2000, an abnormally high number of gray whales were stranded in California, and these strandings were associated with *Pseudo-nitzchia australis* blooms and high tissue levels as of DA.[227] Finally, DA was recently detected in urine and fecal samples recovered from pygmy sperm whales and dwarf sperm whales stranding along the US Atlantic coast from 1997 to 2008.[69] Although blooms of *Pseudo-nitzschia* are associated with repeated large-scale marine mammal mortalities on the west coast of the United States, there is no documented history of similar blooms on the southeast US coast, and there were no observed *Pseudo-nitzschia* blooms in the region associated with any of the *Kogia* spp. strandings. Since myocardial damage is a feature of DA toxicity in sea lions and DA intoxication has been identified as a risk factor for myocarditis and dilated CMP in southern sea otters, an association may exist between this toxin and the *Kogia* cardiomyopathy described above.[89,122,239] Toxin accumulation in these pelagic whale species may be an indication of harmful algal bloom activity in offshore areas not currently being monitored and thus reflect shifts in ecosystem health that deserve further investigation.

Brevetoxins

Recent, and often unprecedented, endangered Florida manatee and Atlantic bottlenose dolphin epizootics have been associated with potent marine neurotoxins known as brevetoxins, which are produced by the ''red tide'' dinoflagellate *Karenia brevis.*[20,24,70] Brevetoxins are known to kill large numbers of fish and cause illness in humans who ingest toxic filter-feeding shellfish (neurotoxic shellfish poisoning) or inhale toxic aerosols. The pathogenesis of brevetoxicosis is suspected to involve direct inhalation of toxins (in manatees) or ingestion of toxins in food sources (in manatees and dolphins).[20,25,27] At least 149 manatees died in an unprecedented epizootic along the southwest coast of Florida, and a detailed pathologic investigation was conducted.[20] At about the same time, a bloom of *K. brevis* was present in the same area. Brevetoxins were isolated in quantities from 2- to 15- fold above control levels in stomach contents, liver, kidney, and lung from dead manatees using a synaptosomal binding assay. Grossly, severe nasopharyngeal, pulmonary, hepatic, renal, and cerebral congestion was present in all cases. Nasopharyngeal and pulmonary edema and hemorrhage were also seen. Consistent microscopic lesions consisted of severe catarrhal rhinitis, pulmonary hemorrhage and edema, multiorgan hemosiderosis, and nonsuppurative leptomeningitis. Immunohistochemical staining using a polyclonal primary antibody to brevetoxin (GAB) showed intense positive staining of lymphocytes and macrophages in the lung, liver, and secondary lymphoid tissues. Lymphocytes and macrophages associated with the inflammatory lesions of the

nasal mucosa and meninges were also positive for brevetoxin. These findings implicated brevetoxicosis as a component of and the likely primary cause of the epizootic.[20] It was postulated that the route of brevetoxin exposure was inhalation of aerosolized toxins causing the upper respiratory inflammation and dissemination of toxin via macrophages and lymphocytes, ultimately resulting in acute agonal cardiovascular collapse. A chronic hemolytic process was also postulated resulting in the widespread hemosiderosis since similar changes have been reported in birds and fish exposed to brevetoxins. Additionally, retrospective histopathologic and immunohistochemical studies demonstrated that other manatee epizootics were likely due to the incidental ingestion of filter-feeding ascidians that contained brevetoxins.

Manatees from Florida's coastlines have frequent potential brevetoxin exposure because red tide blooms are common in these areas. Important new data indicate that brevetoxin vectors such as seagrasses can result in delayed or remote manatee exposure, causing intoxication in the absence of toxin-producing dinoflagelates.[71] Thus, unexpected toxin vectors may account for manatee deaths long after or remote from a dinoflagellate bloom. Therefore, manatee mortality resulting from brevetoxicosis may not necessarily be acute but may occur after chronic inhalation and/or ingestion.[20,24] Immunohistochemical studies of manatee tissues with interleukin-1β–converting enzyme showed positive staining with a cellular tropism similar to GAB.[20,24] The data suggested that brevetoxicosis might initiate the release of inflammatory mediators that culminate in fatal toxic shock. Additionally, prolonged nonlethal toxin exposure may compromise normal immunologic responses, predisposing manatees exposed to brevetoxins to opportunistic disease.[233] Interestingly, the inhalational route of brevetoxin exposure in manatees is shared with humans, making manatees an important sentinel species for this emerging health problem. Increases in human pulmonary emergency room visits are temporally related to red tide and can have significant human health and economic impact.[9,96,119]

Over the past 20 years, investigations into marine mammal mortality events have provided insight into the ecosystem events, vectors, clinical signs, and pathologic effects of HAB biotoxin exposure. Compelling evidence supports the involvement of saxitoxins, DA, and brevetoxins in marine mammal morbidity and mortality.[20,72,80,89] However, confirmation that these toxins are sole etiologic agents for disease remains problematic because the peracute, acute, and chronic biotoxin effects in marine mammals are unknown. Additionally, it is likely these toxins are involved in multifactorial disease involving infectious agents, immunologic perturbations, and other pathologic processes that makes interpretation challenging.

Conclusion

In the past 20 years, dedicated marine mammal research has resulted in an increase in reporting of marine mammal disease.[90] At the same time, the appearance of true emerging and reemerging diseases in marine mammals is also suggested historically and by the scientific literature. This phenomenon may be related to complex factors such as climate change, toxins, and immunosuppression, with coastal marine mammals particularly at risk since many inhabit an environment more affected by human activity.[29,226] Potential increased environmental pressure on marine mammals may provoke more frequent epizootics, help disseminate possible zoonotic pathogens, and increase the prevalence and severity of infectious illnesses worldwide. Marine mammals are useful sentinels for emerging and reemerging infectious and neoplastic disease, the effects of anthropogenic toxins, and the impacts of the global pandemic of harmful algal blooms. Many of these diseases have direct public health implications, whereas others may be indicative of an environmental distress syndrome. To this end, marine mammals are proving to be good sentinels for ocean and human health given their many unique natural attributes. Marine mammal research will undoubtedly expand as new species are evaluated and better tools to assess health are developed. This approach provides a new avenue for better understanding the interface between evolving ecosystem and public health issues.[29] Ultimately, it is in our own best interest to investigate all wildlife health patterns that could potentially affect our own well-being since three-fourths of all emerging infectious diseases of humans are zoonotic, most originate in wildlife, and their incidence is increasing.[114,145,192,218]

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The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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