

# Chapter 19

## MARINE ALGAL TOXINS OF CONCERN AS INTENTIONAL CONTAMINANTS

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### INTRODUCTION

Paralytic Shellfish Poisoning  
Neurotoxic Shellfish Poisoning  
Amnesic Shellfish Poisoning  
Palytoxin

### SUMMARY

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## INTRODUCTION

Marine biotoxins are a problem of global distribution, estimated to cause more than 60,000 foodborne intoxications annually. In addition to human morbidity, some marine toxins may cause massive fish kills, such as those occurring during the Florida red tides. Others have been implicated in mass mortalities of birds and marine mammals. However, their presence in the environment is more often “silent,” unless detected by monitoring programs or when contaminated foodstuffs are ingested.

The long-term environmental and public health effects of chronic exposure in humans have not been extensively studied, although questions are beginning to arise about whether chronic exposures to some marine toxins, such as okadaic acid, may increase the risk of cancer through their action as tumor promoters. Intoxication syndromes from ingestion of marine toxins have long been known, primarily associated with molluscan shellfish. These syndromes include paralytic shellfish poisoning (PSP), neurotoxic shellfish poisoning (NSP), diarrhetic shellfish poisoning, amnesic shellfish poisoning (ASP), and azaspiracid poisoning. Another important marine intoxication is ciguatera fish poisoning, which is caused by ingesting contaminated finfish. Although for the most part, molluscan shellfish are the primary vectors to humans, filter feeding and other trophic transfers can result in occurrence in other seafood such as crustaceans and finfish.

With the exception of ASP, which is of diatom origin, the causative toxins all originate from marine dinoflagellates. More recently, palytoxin—a marine toxin originally described from zoanthid soft corals of the genus *Palythoa* in the Pacific Ocean, but now known to be produced by the dinoflagellate *Ostreopsis* spp—has become a potential human health problem in the Adriatic and Mediterranean seas. The toxin-producing algal species are a small fraction of the thousands of known phytoplankton species. However, under the proper environmental conditions, they can proliferate to high cell densities known as blooms. During these blooms, they may be ingested in large quantities by zooplankton, filter-feeding shellfish, and grazing or filter-feeding fishes. Through these intermediates, toxins can be vectored to humans who consume the seafood.

In general, marine algal toxins are not viewed as important biological warfare threat agents for several reasons. Marine toxins occur naturally at low concentrations in wild resources, and extraction of large quantities is difficult. Most are nonproteinaceous and, therefore, not amenable to simple cloning and expression in microbial vectors. Although some toxins can

be harvested from laboratory cultures of the toxic organism, yields are insufficient to supply the large amounts required for deployment in traditional biological warfare aerosols or munitions.

Targeting food supplies as an act of biological terrorism is a more likely scenario. The toxins occur naturally in seafood products in concentrations sufficient to cause incapacitation or death. The contaminated foodstuffs appear fresh and wholesome, and cannot be differentiated from nontoxic material except by chemical analysis, which obviates the need for isolation of large quantities of pure toxins and subsequent adulteration of the food supply. In theory, the toxic seafood needs only to be harvested and then introduced into the food supply at the desired location. Regulatory testing, if any, is typically done only at the harvester and distributor levels. The natural occurrence of these toxins in seafood may provide cover for an act of intentional bioterrorism.

In some cases, harvesting toxic seafood is difficult. In the case of ciguatoxin, contaminated fish are typically a small percentage of the catch, and levels of toxin within toxic fish tissues are extremely low. In other cases, harvesting could be easy. The United States and other countries maintain monitoring programs at the state and local levels to ensure consumer safety. On the US Gulf Coast, concentrations of toxin-producing dinoflagellate *Karenia brevis* in the water column are closely monitored. When cell numbers increase to levels suggestive of an imminent bloom, harvesting of shellfish is officially halted. The shellfish are then monitored by chemical analysis or mouse bioassay until toxin concentrations in the edible tissues fall to safe levels, at which point harvesting is allowed to resume. During the period when shellfish are toxic, information is made available through the news media and regulatory agencies to discourage recreational harvesting, and anyone could conduct surreptitious harvesting during such a time.

Of the six marine toxin syndromes, three—ciguatera fish poisoning, diarrhetic shellfish poisoning, and azaspiracid poisoning—are unlikely to be significant bioterrorism threats. Diarrhetic shellfish and azaspiracid poisoning cause mild to moderate intoxications that are self-limiting and likely to be mistaken for common gastroenteritis or bacterial food poisoning; the syndromes are unlikely to cause the sorts of disruptions sought by terrorists. Ciguatera fish poisoning can present a more serious intoxication, but toxic fish are difficult to procure. Acquiring sufficient toxin to launch a food-related bioterrorist attack of any magnitude is nearly impossible.

The three marine algal toxin syndromes with bioterrorism potential and their causative toxins (Table 19-1) are described in the following sections. In addition, a brief description of palytoxin and its physiological effects is presented. Some of these effects are of greater concern for homeland security than others. Issues that may impact or limit their potential use as weapons of bioterror will be discussed, followed by clinical aspects and treatment.

**Paralytic Shellfish Poisoning**

*Description of the Toxin*

PSP results from exposure to a family of toxins called paralytic shellfish poisons, or saxitoxins. Saxitoxin (STX) was the first known member of this family, named for the giant butter clam, *Saxidoma giganteus*, from which it was first isolated.<sup>1</sup> Later it was learned that STX is the parent compound of more than 20 derivatives of varying potency produced by marine dinoflagellates of the genera *Alexandrium* (previously *Gonyaulax*), *Pyrodinium*, and *Gymnodinium*, as well as several species of freshwater cyanobacteria. In the 1990s, STX was isolated from bacterial species associated with dinoflagellate cells, suggesting the possibility of a bacterial origin in at least some dinoflagellates.<sup>2</sup> STX also occurs in other benthic marine organisms, such as octopi and crabs, from which the ultimate source of toxin is unknown but assumed to be the food web.<sup>3</sup>

In humans, the greatest risk is associated with consumption of filter-feeding mollusks such as clams, mussels, and scallops that ingest dinoflagellate cells during bloom conditions or resting cysts from the sediment. The original toxin profiles in the dinoflagellate cells may be metabolically altered by the shellfish. Ingestion by humans results in signs and symptoms characteristic of PSP. Approximately 2,000 cases occur annually across regions of North and South America, Central and South America, Europe, Japan, Australia, Southeast Asia, and India. PSP-related fatalities have been reported in South Africa, Canada, Chile, Guatemala, and Mexico. Because of this, numerous monitoring programs are now in place worldwide, which have minimized risks and drastically reduced fatalities.<sup>4</sup> The overall mortality rate has been estimated at 15%,<sup>5</sup> although mortality is highly dependent on the quality of medical care received. Etheridge provides a review of PSP toxins from a human health perspective.<sup>4</sup>

*Mechanism of Action*

STX and its derivatives elicit their toxic effects by interacting with the voltage-dependent sodium channels in electrically excitable cells of heart, muscle, and neural tissue. High-affinity binding to a specific binding site (denoted neurotoxin binding site 1) on sodium channels blocks ionic conductance across the membranes, thereby inhibiting nerve polarization. Although voltage-dependent sodium channels in many

**TABLE 19-1**  
**COMPARISON OF SELECTED MARINE ALGAL TOXINS**

	Paralytic Shellfish Poisoning	Neurotoxic Shellfish Poisoning	Amnesic Shellfish Poisoning
Toxin	Gonyautoxins (saxitoxin)	Brevetoxins	Domoic acid
Source	Marine dinoflagellates	<i>Karenia brevis</i>	<i>Pseudo-nitzschia</i> multiseriis
Mechanism of action	Binds to site 1 of voltage-dependent sodium channels, leading to inhibition of nerve polarization.	Binds to site 5 of voltage-dependent sodium channels and prevents channel inactivation.	Binds to kainate and AMPA subtypes of glutamate receptors in the central nervous system, leading to excitotoxic effects and cell death.
Clinical manifestations	Circumoral parasthesias that may rapidly progress to the extremities. May result in diplopia, dysarthria, and dysphagia. Progression may lead to paralysis of extremities and respiratory musculature.	Symptoms similar to paralytic shellfish poisoning, but usually milder. Nausea, diarrhea, and abdominal pain. Neurological symptoms include oral parasthesias, ataxia, myalgia, and fatigue.	Vomiting, diarrhea, and abdominal cramps, which may be followed by confusion, disorientation, and memory loss. Severe intoxications may result in seizures, coma, or death.

AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

tissues are susceptible to these toxins, pharmacokinetic considerations make the peripheral nervous system the primary target in seafood intoxications.

### *Clinical Signs and Symptoms*

**Ingestion.** Ingestion of PSP toxins results in a rapid onset (minutes to hours) complex of paresthesias, including a circumoral prickling, burning, or tingling sensation that rapidly progresses to the extremities. At low doses, these sensations may disappear in a matter of hours with no sequelae. At higher doses, numbness can spread to the trunk, and weakness, ataxia, hypertension, loss of coordination, and impaired speech may follow. Death has been known to occur in as little as 3 to 4 hours.<sup>6</sup>

A 20-year retrospective analysis of PSP documented by the Alaska Division of Public Health from 1973 to 1992 revealed 54 outbreaks involving 117 symptomatic patients.<sup>7</sup> The most common symptom in these outbreaks was paresthesia, and 73% of patients had at least one other neurological symptom. Other documented symptoms in descending order of occurrence included perioral numbness, perioral tingling, nausea, extremity numbness, extremity tingling, vomiting, weakness, ataxia, shortness of breath, dizziness, floating sensation, dry mouth, diplopia, dysarthria, diarrhea, dysphagia, and limb paralysis.<sup>7</sup>

Approximately 10 outbreak-associated PSP cases are reported to the Centers for Disease Control and Prevention each year. Thirteen cases of neurological illness associated with consumption of pufferfish containing STX caught near Titusville, Florida, occurred in 2002.<sup>8</sup> All 13 symptomatic patients reported tingling or numbness in the mouth or lips. Additionally, eight patients reported numbness or tingling of the face, 10 patients reported these symptoms in the arms, seven patients reported these symptoms in the legs, and one patient reported these symptoms in the fingertips. Six of the 13 patients experienced nausea, and four reported vomiting. Symptoms began between 30 minutes and 8 hours after ingestion, with a median of 2 hours. The illness lasted from 10 hours to 45 days, with a median of 24 hours. All of these cases resolved.

At lethal doses, paralysis of the respiratory musculature results in respiratory failure. Intoxication of a 65-year-old female in the Titusville case series is illustrative. The patient experienced perioral tingling within minutes of meal ingestion. Her symptoms worsened over the next 2 hours, and she experienced vomiting and chest pain. Emergency department evaluation noted mild tachycardia and hypertension. Over the next 4 hours, she developed an ascending paralysis, carbon dioxide retention, and a decrease in

vital capacity to less than 20% predicted for her age, which led to intubation and mechanical ventilation. She regained her reflexes and voluntary movement within 24 hours and was extubated in 72 hours.<sup>9</sup>

Children appear to be more susceptible than adults. The lethal dose for small children may be as low as 25 µg of STX equivalents, whereas that for adults may be 5 to 10 mg of STX equivalents.<sup>10</sup> In adults, clinical symptoms probably occur upon ingestion of 1- to 3-mg equivalents. Because shellfish can contain up to 10 to 20 mg equivalents per 100 grams of meat, ingestion of only a few shellfish can cause serious illness or death.<sup>10,11</sup>

Fortunately, clearance of toxin from the body is rapid. In one series of PSP outbreaks in Alaska resulting from the ingestion of mussels, serum half-life was estimated at less than 10 hours. In these victims, respiratory failure and hypertension resolved in 4 to 10 hours, and toxin was no longer detectable in the urine 20 hours postingestion.<sup>11</sup> A paper describing a 2007 outbreak in Maine evaluated the clearance of individual PSP toxin congeners from the urine.<sup>12</sup> Half-lives were shorter for the sulfated derivatives GTX (gonyautoxin) 1/4 and GTX 2/3 (5–6 h) than for the parent toxins STX and neoSTX (16–20 h), suggesting that the toxin profile in the ingested shellfish may be an important factor in recovery time.<sup>12</sup>

**Inhalation.** In mice, STX is considerably more toxic by inhalation (LD<sub>50</sub> of 2 µg/kg) or by intraperitoneal injection (LD<sub>50</sub> of 10 µg/kg) than by oral administration (LD<sub>50</sub> of 400 µg/kg).<sup>13</sup> Unlike PSP in humans, which is an oral intoxication and has a lag time to toxicity resulting from adsorption through the gastrointestinal tract, inhalation of STX can cause death in animals within minutes. At sublethal doses, symptoms in animals appear to parallel those of PSP, albeit with a more rapid onset reflective of rapid absorption through the pulmonary tissues.

### *Cause of Death*

The cause of death in human cases of STX ingestion, as well as in experiments with animal models, is respiratory failure. Postmortem examination of STX victims reveals that the most notable effects are on the respiratory system, including pulmonary congestion and edema, without abnormalities of the heart, coronary arteries, or brain.<sup>6,14</sup> In vitro, STX does not directly affect the smooth muscle of airways or large blood vessels, but in vivo axonal blockade may lead to respiratory failure and hypotension.<sup>15</sup> Intoxication with large doses of STX may lead to metabolic acidosis, cardiac dysrhythmias, and cardiogenic shock, even with correction of ventilatory failure.<sup>16</sup> For patients that survive 24 hours, the prognosis is good, regardless of respiratory support.

## Diagnosis

Clinicians should consider PSP patients who present with rapid onset of neurological symptoms that are sensory, cerebellar, and motor in nature and occur shortly after the consumption of seafood. Confirmatory diagnosis should rely on an analysis of body fluid samples, as well as an analysis of gastric contents or uneaten portions of recent meals. Urine, which is the primary mechanism of elimination, is used for analysis; the residence time of PSP toxins in the serum is short.<sup>12</sup> Animal studies and human intoxications both indicate toxins present in the urine for several days post-ingestion, although this time frame is dose dependent. Urine samples should be collected as soon as possible to ensure accurate analysis.

Postmortem examinations of fatally intoxicated humans have identified STX in gastric contents, body fluids (serum, urine, bile, and cerebrospinal fluid), and tissues (liver, kidney, lungs, stomach, spleen, heart, brain, adrenal glands, pancreas, and thyroid).<sup>6,14</sup> The largest concentrations of toxin existed in the gastric contents and urine.

Food or clinical samples can be evaluated by several methods. The traditional "gold standard" method is the mouse bioassay, which is an official method of the Association of Official Analytical Chemists International. High performance liquid chromatography, which is also an official method, can detect individual toxin congeners, but requires either precolumn or postcolumn derivatization of toxin mixtures for optimal detection.<sup>12,17,18</sup> Receptor binding assays based on either rat brain membranes<sup>19</sup> or purified STX binding proteins from frogs or snakes<sup>20</sup> measure total toxicity rather than individual toxin profiles. All of these have been used to detect PSP in urine and serum of intoxicated victims.<sup>11</sup> Immunoassays can detect individual toxins, but cross-reactivity among different congeners is highly variable; although useful in some situations, good correlation with analytical methods has so far been problematic. Rapid test kits are commercially available.

## Medical Management

Treatment of STX intoxication consists exclusively of supportive care. Patients may benefit from gastric lavage if ingestion is recent. Patients need to be monitored closely for 24 hours, and if signs of respiratory compromise occur, aggressive respiratory management should be instituted. Intravenous fluids should be used judiciously to maintain urine output and blood pressure. Large doses of STX or intoxication in patients with underlying medical conditions may lead to car-

diovascular abnormalities including hypotension, T-wave inversions, dysrhythmias, and cardiogenic shock. Sodium bicarbonate may be required for correction of metabolic acidosis. Vasopressor agents may be used to maintain blood pressure and perfusion of vital organs. Dobutamine may be the preferred agent; in experiments with high doses of STX given intravenously to cats, dobutamine improved recovery over dopamine.<sup>16</sup>

Research into specific treatments has examined heterologous antibody therapy and pharmacologic agents to overcome inhibition of the voltage-dependent sodium channel. However, at this time, no specific chemotherapeutic or immunotherapeutic agents exist for STX intoxication.

Because of its high potency and relative stability, STX must be considered a potential bioterrorist threat agent. Toxins are easily isolated from laboratory cultures, but production constraints would limit the scope of an aerosol attack. The more likely threat is through the food supply, with the vector being naturally contaminated fresh shellfish. Blooms of the causative organism occur annually along both the Atlantic and Pacific coasts of the United States and Canada, as well as elsewhere around the world, often in underdeveloped nations with poor screening programs. Toxins can easily reach lethal levels in filter-feeding shellfish. Depuration is slow enough that in some areas, such as George's Bank, some shellfisheries are permanently closed to harvesting. Threats to the water supply are minimal. Small-scale contamination (eg, of water coolers) is feasible, but large-scale contamination of reservoirs or even water towers is unlikely to be successful because of dilution effects coupled with the reduced potency of the oral route.

## Neurotoxic Shellfish Poisoning

### Description of the Toxin

NSP results from exposure to brevetoxins, a group of cyclic polyether toxins produced by the marine dinoflagellate *K brevis* (formerly *Ptychodiscus brevis* or *Gymnodinium breve*). Blooms of *K brevis*, with the associated discolored water and mass mortalities of inshore fish, have been described in the Gulf of Mexico since 1844.<sup>21</sup> As are paralytic shellfish poisons, brevetoxins are typically vectored to humans through shellfish; although in the case of NSP, the proximal agents are actually molluscan metabolites of the parent brevetoxins.<sup>22</sup> In addition to causing NSP, annual blooms of *K brevis* in the Gulf of Mexico can cause significant revenue losses in the tourism and seafood industries. Beachgoers can be especially affected because the unarmored dinoflagellates are easily broken up by rough

wave action, and the toxins become aerosolized into airborne water droplets, causing respiratory irritation and potentially severe bronchoconstriction in people with asthma.

Historically, NSP has been virtually nonexistent outside the Gulf of Mexico. However, an outbreak was reported in New Zealand in 1993. Blooms of another dinoflagellate, *Chattonella verruculosa*, occurred in Rehoboth Beach, Delaware, in 2000 and caused a series of localized fish kills.<sup>23</sup> Although no cases of NSP were reported, these events suggest a possible NSP range extension.

### Mechanism of Action

Brevetoxins exert their physiological effects by binding with high affinity and specificity to neurotoxin receptor site 5 on the voltage-dependent sodium channel.<sup>24</sup> Unlike STX, which inhibits the sodium channel by binding to site 1, binding of brevetoxins to site 5 prevents channel inactivation. This shifting of the voltage-dependence of channel activation leads to channel opening at lower membrane potentials<sup>25</sup> and inappropriate ionic flux. Clinical effects are typically more centrally mediated than peripherally mediated. Brevetoxins can cross the blood-brain barrier, and it hypothetically leads to injury and death of cerebellar neurons by stimulation of glutamate and aspartate release, activation of the *N*-methyl-D-aspartate (NMDA) receptor, and excitotoxic cell death.<sup>26</sup> A detailed review of the molecular pharmacology and toxicokinetics of brevetoxin can be found in Poli's *Recent Advances in Marine Biotechnology. Vol 7: Seafood Safety and Human Health.*<sup>27</sup>

### Clinical Signs and Symptoms

**Ingestion.** Symptoms of NSP are similar to that of PSP, but are usually milder. Manifesting within hours after ingestion of contaminated seafood, symptoms include nausea, diarrhea, and abdominal pain. Typical neurological symptoms are oral paresthesia, ataxia, myalgia, and fatigue. In more severe cases, tachycardia, seizures, loss of consciousness, and respiratory failure can occur. During a 1987 outbreak, 48 cases of NSP occurred in the United States. Acute symptoms documented in the outbreak included gastrointestinal (23% of cases) and neurological (39% of cases) symptoms. Symptoms occurred quickly, with a median of 3 hours to onset, and lasted up to 72 hours. Most of the victims (94%) experienced multiple symptoms, and 71% reported more than one neurological symptom.<sup>28</sup>

Although a fatal case of NSP has never been reported, children may be more susceptible, and a fatal dose must be considered a possibility.<sup>22</sup> The toxic dose of

brevetoxins in humans has not been established. However, important information has been gleaned from a clinical outbreak. A father and two small children became ill after ingesting shellfish harvested in Sarasota Bay, Florida, in 1996. Both children were hospitalized with severe symptoms, including seizures. Brevetoxin metabolites were detected in urine collected 3 hours postingestion. With supportive care, symptoms resolved in 48 to 72 hours, and no brevetoxin was detectable in the urine 4 days later.<sup>22</sup> Mass chromatography of serum samples taken immediately after the family checked into the hospital demonstrated ion masses suggestive of brevetoxin metabolites, although these compounds were never isolated. The amount of toxin ingested was not determined, although the father, who had milder symptoms and was released from the hospital after treatment, reported eating "several" shellfish. The number eaten by the children (ages 2 and 3) was unknown.

The toxicity of brevetoxins in mice is well established. LD<sub>50</sub> values range from 100 to 200 µg/kg after intravenous or intraperitoneal administration for PbTx-2 and PbTx-3, the two most common congeners. Oral toxicity is lower: 500 and 6,600 µg/kg for PbTx-3 and PbTx-2, respectively.<sup>29</sup> Animal models indicate brevetoxin is excreted primarily in the bile, although urinary elimination is also significant. Toxin elimination is largely complete after 72 hours, although residues may remain in lipid-rich tissues for extended periods.<sup>30</sup>

**Inhalation.** Respiratory exposure may occur with brevetoxins associated with harmful algal blooms or "red tides." As the bloom progresses, the toxins are excreted and released by disruption of the dinoflagellate cells. Bubble-mediated transport of these toxins leads to accumulation on the sea surface; the toxins are released into the air by the bursting bubbles. The toxins are then incorporated into the marine aerosol by on-shore winds and breaking surf, leading to respiratory symptoms in humans and other animals. Sea foam may also serve as a source of toxin and result in symptoms if it is ingested or inhaled. During harmful algal blooms, the on-shore concentration of aerosolized toxins varies along beach locations by wind speed and direction, surf conditions, and exposure locations on the beach. Concentrations of the toxin are highest near the surf zone.<sup>31</sup>

Systemic toxicity from inhalation is a possibility. Distribution studies of intratracheal instillation of brevetoxin in rats have shown that the toxin is rapidly cleared from the lung, and more than 80% is distributed throughout the body. Twenty percent of the initial toxin concentration was present in several organs for 7 days.<sup>32</sup>

## Diagnosis

Brevetoxin intoxication should be suspected clinically when patients present with gastrointestinal symptoms and neurological symptoms occurring shortly after ingesting shellfish. Although these symptoms may be similar to those of STX intoxication, they do not progress to paralysis. Epidemiological evaluation of cases may identify additional cases during an outbreak and allow for public health measures, including surveillance, to be put into place.

Human cases are typically self-limiting, with improvement in 1 to 3 days, but symptoms may be more severe in young persons, elderly persons, or those with underlying medical conditions. Evaluation of biological samples should include urine as well as any uneaten shellfish from the meal. Toxins in clinical samples can be detected by liquid chromatography mass spectrometry receptor-binding assays, or immunoassay. Because metabolic conversion of parent toxins occurs in shellfish and the metabolites are apparently less active at the sodium channel, it appears that immunoassays are better screening tools. However, secondary metabolism in humans has yet to be fully investigated.

## Medical Management

No specific therapy exists for NSP. If the ingestion is recent, treatment may include removal of unabsorbed material from the gastrointestinal tract or binding of residual unabsorbed toxin with activated charcoal. Supportive care, consisting of intravenous fluids, is the mainstay of therapy. Although brevetoxin has not been implicated in human fatalities, symptoms of NSP may overlap with symptoms of STX and thus warrant observation for developing paralysis and respiratory failure. Aggressive respiratory management may be required in severe cases.

Pulmonary symptoms resulting from inhalation of marine aerosols typically resolve upon removal from the environment, but may require treatment for reactive airway disease, including nebulized albuterol and anticholinergics to reverse bronchoconstriction. Mast cell release of histamine may be countered with the use of antihistamines. Mast cell stabilizers, such as cromolyn, may be used prophylactically in susceptible persons exposed to marine aerosols during red tide events.

No antitoxins for NSP are available. However, experiments with an anti-brevetoxin immunoglobulin G showed that treatment before exposure blocked nearly all neurological symptoms.<sup>33</sup> Additional research into pharmacologic agents should be pursued. Two brevetoxin derivatives that function as brevetoxin antagonists but do not exhibit pharmacologic properties have been identified. Other agents that compete with

brevetoxin binding for the sodium channel include gambierol, gambieric acid, and brevenal.<sup>34,35</sup> Future research with these agents may assist in developing adequate therapeutics.

Brevetoxins are likely to have only moderate potential as agents of bioterror. Although unlikely to cause mortality in adults, oral intoxication can be severe and require hospitalization. Disruption of a local event, inundation of medical facilities by the “worried well,” and societal overreaction possibly leading to economic disruption of local industry are the most likely repercussions. *K. brevis* is easily cultured and produces toxins well in culture. Unpublished animal experiments suggest brevetoxins may be 10-fold to 100-fold more potent by aerosol—versus oral—exposure. Thus, small-scale aerosol attacks are technically feasible, although isolation and dissemination of toxins would be difficult for nonexperts.

## Amnesic Shellfish Poisoning

### Description of the Toxin

ASP was defined after an outbreak of mussel poisoning in Prince Edward Island, Canada, in 1987. More than 100 people became ill with an odd cluster of symptoms, and three died. Canadian researchers quickly isolated the causative agent and identified it as domoic acid.<sup>36</sup> Domoic acid, which was previously known as a compound tested and rejected as a potential insecticide, is a common ingredient in Japanese rural folk medicine. Domoic acid was originally isolated from the marine red algae *Chondria* spp, and researchers were surprised to discover that the diatom *Pseudo-nitzschia pungens f multiseriis* (now *Pseudo-nitzschia multiseriis*) was the causative organism. ASP remains the first and only known seafood toxin produced by a diatom.

Since the 1987 outbreak, several toxic species of diatoms have been found around the world and are now the subject of many regional monitoring programs. Domoic acid is seasonally widespread along the US Pacific Coast and the Gulf of Mexico. It has also been found in New Zealand, Mexico, Denmark, Spain, Portugal, Scotland, Japan, and Korea. Although amounts of domoic acid in shellfish occasionally reach levels sufficient to stimulate harvesting bans, no further human cases have been reported, reflecting the efficacy of monitoring programs. However, the toxicity of domoic acid remains evident in biotic events.

In 1991, numerous cormorants and pelicans died after feeding on anchovies (a filter-feeding fish) during a bloom of *Pseudo-nitzschia australis* in Monterey Bay, California. High levels of domoic acid were detected in the gut contents of the anchovies. Later that year, after

the bloom moved northward along the coast, razor clams and Dungeness crabs became toxic off the Washington and Oregon coasts. Several cases of human intoxication apparently followed ingestion of razor clams, although a definitive link was not found.<sup>37</sup> More than 400 sea lions died and numerous others became ill in 1998 after ingesting anchovies feeding in a bloom of *P australis*, again in Monterey Bay.<sup>38</sup> Domoic acid was detected in both the anchovies and feces from the sea lions.<sup>39</sup> These events suggest that periodic blooms of domoic acid-producing *Pseudo-nitzschia* on the western coast of the United States may cause significant toxicity in seafood items.

### Mechanism of Action

Domoic acid is a neuroexcitatory amino acid structurally related to kainic acid. As such, it binds to the kainate and AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) subtypes of the glutamate receptor in the central nervous system, which subsequently elicits nonsensitizing or very slowly sensitizing currents,<sup>40</sup> causes a protracted influx of cations into the neurons, and stimulates a variety of intracellular events leading to cell death.<sup>41</sup> This effect may be potentiated by synergism with the excitotoxic effects from high glutamate and aspartate levels found naturally in mussel tissue.<sup>42</sup> The kainate and AMPA receptors are present in high densities in the hippocampus, a portion of the brain associated with learning and memory processing. Mice injected with domoic acid develop working memory deficits.<sup>43</sup> Neuropathological studies of four human fatalities revealed neuronal necrosis or loss with astrogliosis, mainly affecting the hippocampus and the amygdaloid nucleus.<sup>44</sup> Developing and aging brains show higher susceptibility to domoic acid, and thus define susceptible subpopulations.

### Clinical Signs and Symptoms

**Ingestion.** The 1987 Prince Edward Island outbreak provided information on the clinical effects of domoic acid ingestion in humans.<sup>45</sup> The outbreak occurred during November and December, with 250 reports of illness related to mussel consumption (107 of these reports met the classic case definition). All but seven of the patients reported gastrointestinal symptoms ranging from mild abdominal discomfort to severe emesis requiring intravenous hydration. Forty-three percent of patients reported headache, frequently characterized as incapacitating, and 25% reported memory loss, primarily affecting short-term memory.

At higher doses, confusion, disorientation, and memory loss can occur. Severe intoxications can produce seizures, coma, and death. Nineteen of the

patients required hospitalization for between 4 and 101 days, with a median hospital stay of 37.5 days. Twelve patients required care in an intensive care unit. The intensive care patients displayed severe neurological dysfunction, including coma, mutism, seizures, and purposeless chewing and facial grimacing.<sup>45</sup> Severe neurological manifestations, which were more common in elderly persons, included confusion, disorientation, altered states of arousal ranging from agitation to somnolence or coma, anterograde memory disorder, seizures, and myoclonus. Although mean verbal and performance IQ scores were average and language tests did not reveal abnormalities, severe memory deficits included difficulty with initial learning of verbal and visuospatial material, with extremely poor recall. Some of the more severely affected patients also had retrograde amnesia that extended to several years before ingestion of the contaminated mussels.<sup>44</sup> Nine of the intensive care patients required intubation for airway control resulting from profuse secretions, and seven of them suffered unstable blood pressures or cardiac dysrhythmias. Three patients died during their hospitalization.<sup>45</sup>

Symptoms of intoxication occur after a latency period of a few hours. In mild cases, the gastrointestinal symptoms of vomiting, diarrhea, and abdominal cramps occurred within 24 hours. The time from ingestion of the mussels to symptom onset ranged from 15 minutes to 38 hours, with a median of 5.5 hours.<sup>45</sup> In a study of 14 patients who developed severe neurological manifestations, 13 developed gastrointestinal symptoms between 1 and 10 hours after ingestion, and all of the patients became confused and disoriented 1.5 to 48 hours postingestion. Maximal neurological deficits were seen 4 hours after mussel ingestion in the least affected patients and up to 72 hours postingestion in those patients who became unresponsive.<sup>44</sup> All the patients who developed severe neurological symptoms were older than 65 or had preexisting medical conditions such as diabetes or renal failure that altered their renal clearance.

**Inhalation.** No natural cases of domoic acid inhalation exist, and no experimental models have evaluated an aerosol exposure to this toxin. It may be assumed that the toxin would be absorbed through the pulmonary tissues leading to systemic symptoms comparable to other exposure routes, although no data confirm this theory.

### Diagnosis

Diagnosis should be suspected by the clinical presentation after ingestion of filter feeding seafood. Patients may have mild symptoms that resolve spontaneously

or may present with more severe signs of neurotoxicity, including confusion, altered mental status, or seizures. Symptomatic patients typically are older than 65 or have underlying medical conditions that affect renal clearance.<sup>45</sup> Initial evaluation of these patients should include standard protocols for patients with altered mental status, including toxicological screens to rule out more common intoxicants, especially illicit substances. Other diagnostic tests can be used to rule out other clinical causes of the symptoms including imaging with computed tomography scans, which does not show abnormality related to domoic acid intoxication, and monitoring of brain activity with electroencephalography. Of the 12 patients that were admitted to the intensive care unit during the 1987 outbreak, electroencephalograms showed that nine had generalized slow-wave activity and two had localized epileptogenic activity.<sup>45</sup> Positron emission tomography scanning of four patients with varying degrees of illness revealed a correlation between glucose metabolism in the hippocampus and amygdala with memory scores.<sup>44</sup>

Based primarily on levels measured in Canadian shellfish after the 1987 outbreak, mild symptoms in humans may appear after ingestion of approximately 1 mg/kg of domoic acid, and severe symptoms may follow ingestion of 2 to 4 mg/kg. The official regulatory testing method uses analytical high performance liquid chromatography, although both immunological methods and a simple, inexpensive thin-layer chromatography method are available.<sup>46–48</sup> No evidence of domoic acid metabolism by rodents or primates exists, as shown by recovery in an unchanged form from the urine or feces.<sup>49</sup> Samples to be included for definitive testing include serum, feces, urine, and any uneaten portions of the suspected meal.

### Medical Management

Treatment for intoxication with domoic acid is supportive care. For patients who present early after ingesting the meal, gastric lavage or cathartics may decrease toxin amounts absorbed systemically. A key issue with this intoxication is the maintenance of renal clearance; hydration or other measures may also be required. Additionally, severe intoxications may cause alterations in hemodynamic functions, requiring pharmacologic interventions to maintain perfusion. In the 1987 outbreak, some severely intoxicated patients developed substantial respiratory secretions requiring intubation. Patients should be monitored for seizure activity that may require anticonvulsants. Studies in mice have shown that sodium valproate, nimodipine, and pyridoxine suppress domoic acid-induced spike and wave activity on an electroencephalogram.<sup>50</sup>

No specific therapy exists for domoic acid intoxications. Research has revealed that competitive and noncompetitive NMDA receptor antagonists reduce the excitable amino acid cascade that leads to brain lesions.<sup>51</sup> Additionally, NMDA receptor antagonists have also been shown to antagonize domoic acid toxicity.<sup>51</sup>

Domoic acid should be considered a legitimate—if moderate—bioterrorist threat agent. Toxic shellfish are available, and ingestion elicits symptoms that can be life threatening. Although mass casualties are not likely, mortality can occur, and the frightening nature of the symptoms in survivors may cause the disruption sought by an aggressor.

## Palytoxin

### Description of the Toxin

Palytoxins are a group of complex marine natural products originally isolated from zoanthid soft corals of the genus *Palythoa*. The structure of the first palytoxin was elucidated in 1981<sup>52,53</sup> when first described by Moore and Scheuer in 1971.<sup>54</sup> Palytoxins are complex hemiketals with molecular weights of approximately 2,600 to 2,700 g/mol, and containing cyclic ethers, 64 chiral centers, and multiple hydroxyl groups. The original palytoxin from *Palythoa toxica* contains a continuous chain of 115 carbon atoms, making it unique among known natural products.<sup>55</sup> Since that discovery, a family of palytoxins has emerged, including congeners from *Palythoa tuberculosa* and *Palythoa margaritae* in Japan, and *Palythoa caribaeorum* from Puerto Rico. In addition, a palytoxin-like compound was isolated from the sea anemone *Radianthus macrodactylus* from the Seychelles,<sup>56</sup> and two analogs have been isolated from the red alga *Chondria armata*, which also produces domoic acid.<sup>57</sup> More recently, dinoflagellates of the genus *Ostreopsis* have been shown to produce a variety of palytoxin analogs, including ostreocins and ovatoxins (from *Ostreopsis ovata* and *Ostreopsis siamensis*) and macarenotoxins from *Ostreopsis mascarenensis*.<sup>55</sup> Finally, both palytoxin and one of the newly described palytoxin analogs, 42-hydroxy-palytoxin, have been identified in a marine cyanobacterium of the genus *Trichodesmium* in New Caledonia, raising the possibility of additional food–web sources.<sup>58</sup>

In this chapter, all congeners, including ovatoxins-a–f, ostreocins, and palytoxins are collectively referred to as “palytoxins.” In many of the references cited, the compounds referred to as “palytoxin” were not highly purified, or only compared to a chromatographically derived palytoxin standard. It is very likely that many

were actually mixtures of palytoxin analogs, which have only recently been described and are difficult to separate.

Palytoxins are some of the most potent nonproteinaceous toxins known. Intravenous LD<sub>50</sub> values (in µg/kg) range from 0.025 (rabbits), 0.033 (dogs), 0.078 (monkeys), 0.089 (rats), and 0.11 (guinea pigs). Of the animal models tested, mice are the least susceptible at 0.15 µg/kg to 0.45 µg/kg, depending on the investigator and the origin of the toxin.<sup>59,60</sup> Potency is somewhat less by other routes. The lowest potency seems to be by the oral route, with LD<sub>50</sub> values for palytoxin and ostreocin-D in the range of 500 µg/kg to 1,000 µg/kg in mice.<sup>61-64</sup>

In spite of the rather unimpressive oral toxicity values in mice, fatal human intoxications from palytoxins have been reported since the 1700s, primarily from grazing or filter feeding species of fish in the Atlantic and Pacific oceans and the Caribbean Sea.<sup>65</sup> Palytoxins are now thought to be the causative agent in the often fatal syndrome formerly known as clupeotoxism, which results from the ingestion of filter feeding fish of the family *Clupeidae* (herrings and sardines) and *Engraulidae* (anchovies) among others.<sup>66</sup> They have also been implicated in several fatal cases of poisoning from various species of xanthid crabs in the Philippines.<sup>66</sup> Palytoxins are known to bioaccumulate in important seafood species such as mussels, sea urchins, and cephalopods (octopus and squid), suggesting a real possibility of human intoxication from the ingestion of seafood.<sup>67,68</sup> Deeds and Schwartz<sup>55</sup> provide an excellent review of human intoxication from seafood.

More recently, palytoxins have begun to cause problems in the Mediterranean and Adriatic seas, probably as a result of the introduction of *O ovata* into these waters. Several instances of respiratory symptoms associated with blooms of *Ostreopsis* were reported in the early years of the 21st century along the coasts of Italy, Spain, and France (reviewed in Del Favero et al<sup>69</sup>). The most striking of these occurred in 2005, when more than 200 beachgoers near Genoa, Italy, experienced respiratory symptoms of bronchoconstriction, dyspnea, cough, and rhinorrhea. Of these 200, 20 beachgoers experienced symptoms severe enough to warrant extended hospitalization and intensive care. These symptoms occurred during a bloom of *O ovata* near the coast.<sup>70,71</sup> Symptoms peaked during the peak of the bloom and dissipated with the bloom. Cell samples of *O ovata* collected during the bloom tested positive for palytoxins by high performance liquid chromatography and mass spectrometry.<sup>72</sup> Similar testing from subsequent events has resulted in the identification of new palytoxin analogs, including ovatoxin-a, which may predominate in these blooms.<sup>73</sup> Blooms of *O*

*ovata* now regularly occur in the Mediterranean and Adriatic seas,<sup>69</sup> raising important questions regarding public health, seafood safety, and the potential for the accumulation of large amounts of toxins through dinoflagellate culture. More importantly, the intoxication of beachgoers during periods of little wind from dinoflagellate blooms in the water column suggests high aerosol potency. Thus, aerosol toxicology studies of palytoxin are clearly warranted.

### Mechanism of Action

The well-accepted, oft-cited mechanism of action of palytoxin is through interference of the Na<sup>+</sup>/K<sup>+</sup>-ATPase ionic pump, converting it to a nonspecific ion pore and altering the internal ionic concentration of susceptible cells.<sup>60,61</sup> Binding of palytoxin to the pump causes an immediate influx of Na<sup>+</sup>, which triggers an influx of K<sup>+</sup> and Ca<sup>++</sup>. This interference with intracellular ionic homeostasis, especially the increase in intracellular Ca<sup>++</sup>, entrains a variety of toxic cell responses. Although inhibition of many of the toxic effects by ouabain supports this as the primary source of the pathophysiology of palytoxins, significant evidence from both in vivo and in vitro models indicate ancillary mechanisms as well (see the review by Munday<sup>60</sup>). Tubaro et al<sup>62</sup> provides a review of the in vitro and in vivo biological effects of palytoxin.

### Clinical Signs and Symptoms

**Ingestion.** Manifestations of palytoxin intoxication by ingestion typically involve malaise, nausea, vomiting and diarrhea, a bitter or metallic taste in the mouth, myalgia and cramps, numbness or tingling in the extremities, bradycardia, and dyspnea. Renal failure has occurred in severe cases, probably secondary to the myoglobinemia associated with skeletal muscle damage. Human oral intoxications by palytoxins are reviewed in Yasumoto and Murata,<sup>57</sup> Deeds and Schwartz,<sup>55</sup> and Tubaro et al.<sup>74</sup> However, the example of a fatal intoxication occurring after the ingestion of a crab, *Demania reynaudii*, in the Philippines is illustrative.

In November 1984, at around noon, a man cooked a crab caught in a net off Tanjay Town in the province of Negros Oriental, Philippines.<sup>66</sup> Within minutes of partially ingesting the crab, he experienced dizziness, fatigue, nausea, and a metallic taste in his mouth. Later he experienced diarrhea. When a dog died that had eaten the remainder of his crab, the man requested transport to a local hospital. During the trip, he experienced fatigue, numbness in the extremities, restlessness, and vomiting. Upon admission at about

5:45, he complained of restlessness, muscle cramps, and vomiting. He died at 3:14 the next morning, approximately 15 hours postingestion.

Clinical records revealed alternating periods of normal heart rate and severe bradycardia (30 beats/min), rapid and shallow respiration, cyanosis around the mouth and in the hands, and renal failure (anuria).<sup>66</sup> Administration of atropine, diphenhydramine, pethidine, and adrenaline was ineffective. The causative agent was determined to be palytoxin based on the dose/survival time relationship in the mouse bioassay and the chromatographic characteristics of the extracted toxin, both of which were identical to those of a palytoxin standard.

**Inhalation.** Although *O siamensis* is well known around Japan, Australia, New Zealand, and the Mediterranean, *O ovata* has only recently become established in the Mediterranean/Adriatic. The first blooms occurred in 2003, and now have become regular events. Blooms associated with respiratory effects in humans occurred in 2003 and 2004 in Italy, and they have been reported in Spain, France, Croatia, Tunisia, Greece, and Algeria since that time.<sup>75</sup>

The most complete description of aerosol exposure to palytoxin is a Genoa event in 2005. In late July, during a period of warm weather with little wind and calm seas, a large bloom of *O ovata* occurred along the coastline. Concomitantly, a total of 209 beachgoers were afflicted with a complex of symptoms that included fever (64%), sore throat (50%), cough (40%), dyspnea (39%), headache (32%), nausea (24%), rhinorrhea (21%), lacrimation (16%), vomiting (10%), and dermatitis (5%).<sup>71</sup> Although no deaths occurred, 20 people were hospitalized, some for as long as 3 days. Mean onset of symptoms was 4.5 hours (range 30 min–23 h). Laboratory analyses were available for 82 patients, including all those hospitalized. Of these, 46% had leukocytosis (mean white cell count was 13,900/mm<sup>3</sup>) and 40% had neutrophilia (mean 82%); transaminases, gamma-glutamyl transpeptidase, creatinine, and sedimentation rate values were normal. Chest X-rays and electrocardiogram values were normal.

**Dermal.** Dermal exposure to palytoxins can occur with exposure to water containing blooms of *Ostreopsis*, although this seems to be a minor hazard. For example, in the Genoa bloom event of 2005, only 5% of patients reported a mild dermatitis.<sup>71</sup> However, in describing bloom occurrences along the French Mediterranean coast, Tichadou et al reported skin irritation as the most common sign in people exposed to cells in the water column.<sup>75</sup> At low cell numbers, erythema resolved rapidly after exposure. At higher cell numbers, clinical findings included pruritis of exposed skin, conjunctivitis, rhinorrhea, and oral irritation.

**Exposure Through Home Aquaria.** A more serious dermal issue can occur through the home aquarium trade. Colonies of zoanthid corals are popular aquarium decorations. They readily propagate and provide a colorful marine backdrop to other species. Home aquarists are usually cognizant of the potential toxicity of zoanthid corals and handle them with gloves when cleaning aquaria or dividing colonies. Occasionally, however, intoxications occur. In one case, a 25-year-old woman handled a zoanthid coral without gloves in her home aquarium.<sup>76</sup> She noted a metallic taste in her mouth within minutes, followed by perioral paresthesias and hives on her torso and extremities. The next day she noted edema of the upper lip without airway compromise. By the second day, the paresthesia had resolved, but she experienced increasing edema, erythema, and pruritis in both hands. In addition, a bilateral urticarial rash was noted on her upper arms, thighs, abdomen, upper chest, and back. Symptoms improved after treatment with intravenous diphenhydramine, methylprednisolone, and lorazepam.

In another instance of aquarium dermal intoxication, a 32-year-old man was admitted to the emergency department 20 hours after cutting three fingers on his right hand on a zoanthid colony while cleaning his aquarium.<sup>77</sup> Within 2 hours, he exhibited shivering, myalgia, and general weakness of the extremities. After 16 hours, he collapsed with dizziness, speech disturbances, and glassy eyes. Upon hospital admission, swelling and erythema around the cuts were noted, which spread over his whole arm over the next 20 hours. An electrocardiogram detected incomplete left bundle block. Bloodwork was normal, with the exception of slightly elevated levels of creatine kinase, lactate dehydrogenase, and C-reactive protein. He was treated with infusion of physiological fluids. Electrocardiogram changes receded in 24 hours, but paresthesias, weakness, and myalgia persisted for 48 hours until discharge.

Several cases of pulmonary exposure to palytoxin have occurred during the aquaria cleaning using boiling water<sup>78</sup> or otherwise handling *Palythoa*.<sup>79</sup> Bernasconi et al<sup>79</sup> reported on three individuals handling *Palythoa* in a new aquarium to which sea salt had been added, which produced some foam and mist and resulted in pulmonary effects consisting of a restrictive ventilatory pattern with significant hypoxia. Bernasconi et al<sup>79</sup> also reported on an entire family that became ill after a professional aquarium cleaner poured boiling water on a *Palytoxin*-encrusted coral fragment. The cleaner, along with four members of the family elsewhere in the room, reported to the emergency department complaining of respiratory symptoms. All patients developed a low-grade fever, increased white cell

count, and elevated creatine phosphokinase during their hospital stay. The intoxication of other people not directly involved with the aquarium cleaning process strongly suggests extremely high potency of the aerosolized toxic material.

### Diagnosis

Context is key to the clinical diagnosis of the known palytoxin intoxication syndromes. Palytoxin poisoning should be suspected in patients who present with rapid onset of respiratory distress and tonic muscle contractions soon after eating grazing fish species (especially sardines, but also other fish such as herring, anchovies, etc), and especially during warm summer months.<sup>80</sup> Essentially the same high fatality syndrome is described in cases of xanthid crab ingestion. Cases have been described only in Caribbean, African coastal, and Indo-Pacific waters. The complication of rhabdomyolysis, with creatine kinase levels peaking at about 24 to 36 hours after symptom onset, would also be an important later clue if the diagnosis has not yet been made.<sup>55,81</sup> Paresthesias and numbness, as well as gastrointestinal symptoms, also occur in the other seafood toxidromes, but absence of frank paresis or paralysis—which has not been described with palytoxins—may be a relative discriminator from PSP. Other palytoxin intoxication syndromes differ from fish poisoning in varying degrees according to the route of exposure: dermal exposure, as with marine aquarium hobbyists, can be expected to produce local and systemic skin manifestations as described above; inhalational exposure near an algal bloom is known to produce respiratory distress and a mild dermatitis, but also fever (in a majority of cases) and conjunctivitis (in a minority). Gastrointestinal symptoms were also reported in a significant minority of inhalational cases, and low-grade fever was reported in most of the aquarium hobbyists.

Definitive laboratory identification of palytoxins in seafood can be accomplished with rapid and sensitive hemolysis neutralization assays,<sup>82</sup> but the relative rarity of these syndromes does not make the licensing or widespread commercial availability of these tests likely in the foreseeable future. A number of other investiga-

tional methods of detection (including immunoassays and a fluorescence polarization) have been described in the literature.<sup>62</sup>

### Medical Management

No specific therapy exists for palytoxin intoxications. For exposures restricted to contact with intact skin/mucosa only (eg, beachgoers exposed to algal blooms), experience indicates that nonsteroidal anti-inflammatory drugs are effective and that the condition is self-limited.<sup>75</sup> For recent ingestions, however, gastric emptying procedures, implemented as early as possible, are highly desirable and may be undertaken even with uncertainty as to the specific seafood-related toxin involved. Supportive care and the amelioration of symptoms are then the basis of treatment, with aggressive hydration via infusion of intravenous fluids being the primacy focus in significant intoxications where avoidance of rhabdomyolysis-induced renal failure is the goal. Palytoxin(s) have been implicated in a number of human fatalities involving ingestion of tropical fishes, with one author estimating a case fatality rate—based on an admittedly limited number of cases—of 45%.<sup>80</sup> Cardiac conduction disorders and heart failure (with consequent hypotension), as well as renal failure, appear to be important mechanisms in these patients.<sup>80,83</sup>

As with other toxic marine aerosols, the respiratory symptoms associated with inhalation would be expected to rapidly diminish upon vacating the contaminated site, but severe intoxications by this route may require standard treatment for reactive airway disease (nebulized albuterol, anticholinergics, antihistamines).<sup>78</sup> Aggressive treatment in an intensive care facility may prove necessary, and—although not validated—administration of steroids,<sup>79</sup> antihistamines, or benzodiazepines<sup>76</sup> have proved helpful and may be tried.

Given the apparent potency of exposures to aerosols, as well as the lethality associated with ingestions, palytoxins seem to have potential as bioterrorism agents. The large numbers sickened (more than 200 individuals) in the 2005 Genoa event (20% of whom were hospitalized) indicate these possibilities.

## SUMMARY

Exposure to marine algal toxins may occur via ingestion or delivery as an aerosol at the tactical level. Although the toxins may be highly lethal, extracting and weaponizing them is relatively difficult because of the relatively small amounts of toxins typically produced by the source organ-

isms. Such toxins may be more suitable for causing incapacitation or death among small groups or for assassinations. The toxins presented in this chapter are diverse in structure and mode of action. Proper diagnosis and care represent a daunting challenge for physicians.

STX, brevetoxins, and domoic acid are marine algal toxins associated with human illness in natural outbreaks related to harmful algal blooms. STX blocks ionic conductance of the voltage-dependent sodium channels, leading to neurological symptoms (parasthesias and paralysis) as well as respiratory distress and cardiovascular instability. Treatment includes respiratory support and intensive cardiovascular management. Anti-STX serum and antibodies have shown promise in animal models, but such reagents are unavailable for human use. Brevetoxins inhibit sodium channel inactivation, leading to depolarization of membranes. Brevetoxin symptoms are similar to those of STX but are usually milder and lack paralysis. Although naturally acquired cases typically resolve spontaneously in 1 to 3 days, patients should be carefully observed and may require aggressive airway management. Domoic acid is a neuroexcitatory amino acid that kills cells within the central nervous system, particularly in the hippocampus, which is associated with learning and memory. Patients with domoic acid intoxication develop gastrointestinal symptoms and neurological symptoms, including anterograde memory loss and myoclonus. Severe intoxications may lead to convulsions and death. Medical management of domoic acid intoxications includes monitoring of

hemodynamic status and pharmacological treatment of seizures.

Palytoxins derive from both dinoflagellate blooms or from the polyps of soft corals of the genus *Palythoa*. Their primary mechanism of action is to bind to the Na<sup>+</sup>/K<sup>+</sup>-ATPase, converting it to a nonselective cationic pore and interfering with intracellular ionic homeostasis. Oral intoxication can lead to malaise, vomiting and diarrhea, a bitter or metallic taste in the mouth, muscle aches and cramps, numbness or tingling in the extremities, bradycardia, and dyspnea. Renal failure resulting from myoglobinemia secondary to rhabdomyolysis can occur. Inhalation exposure can lead to respiratory symptoms such as fever, sore throat, cough, dyspnea, headache, nausea/vomiting, rhinorrhea, lacrimation, and dermatitis. An underappreciated exposure mechanism is through the home aquarium trade, whereby several incidences of inhalational or dermal intoxication have occurred through the handling or disinfection of *Palythoa* polyps. Treatment of palytoxin intoxication, which is nonspecific, is based on the route of exposure. The apparent extreme aerosol toxicity of palytoxins, as suggested by several incidences of beachgoers being intoxicated during near-shore blooms of *O. ovata*, makes it critical for further investigation of the aerosol toxicology of these compounds.

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