FIGURE 73-106 Giant clams. **A,** Giant clam with diver. **B,** Giant clam mantle (*Tridacna* sp.) obtains its coloration from algae used for photosynthesis. *(**A** courtesy Howard Hall; **B** copyright 2000 Norbert Wu: norbertwu.com.)*

FIGURE 73-107 Mantle of the giant clam. *(Copyright Stephen Frink.)*

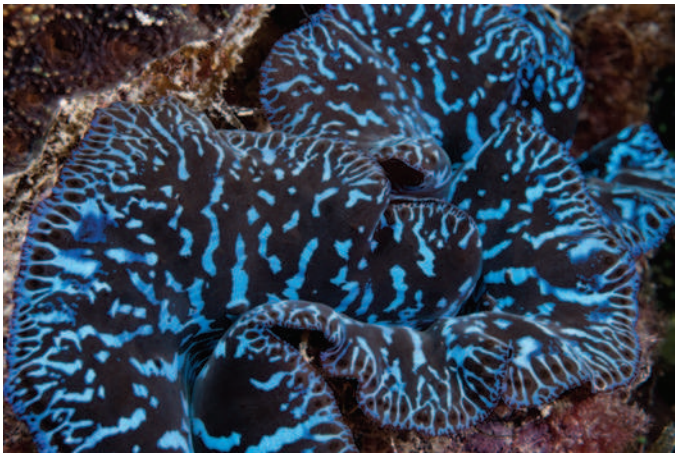

FIGURE 73-108 Colorful mantle of the giant clam. *(Copyright Stephen Frink.)*

GIANT SQUID

The giant ("colossal") squid (possibly *Mesonychoteuthis hamiltoni*), a cephalopod (10 arms), grows to a length in excess of 17.4 m (57 feet) and weight of 909 kg (2000 lb), with long (10-m [32.8-feet]) menacing tentacles, eyes with a diameter of nearly 35 cm (13.7 inches, the size of a dinner plate), and a razor-sharp beak that it uses to eat prey. *Architeuthis dux,* the "giant squid," may have a mantle that does not exceed 2.25 m (7.4 feet). It has been filmed underwater by Japanese scientists at an overall estimated length of 8 m (25 feet). The tentacles are armed with chitinous serrated rings equipped with teeth on each of the suckers. The suckers are approximately 4 cm (1.5 inches) in diameter. The giant Humboldt squid (Figures 73-109 to 73-111) demonstrates typical giant squid features. Sperm whales have been examined with sucker wounds with a diameter of 46 cm (18 inches), which would extrapolate to a truly monstrous squid,

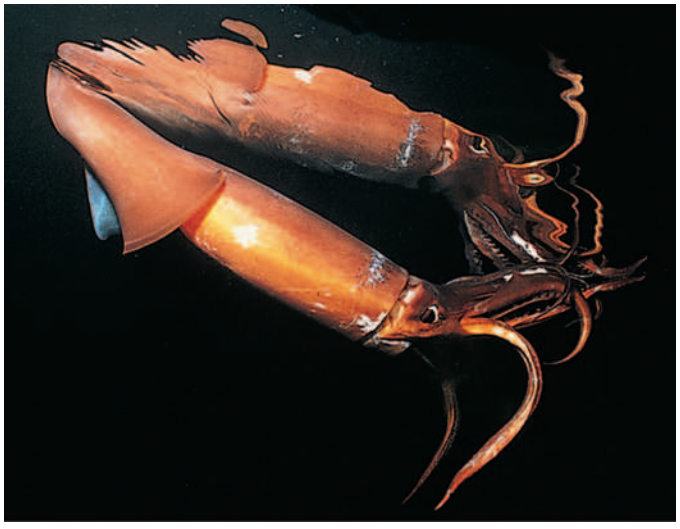

FIGURE 73-109 Giant Humboldt squid *(Dosidicus gigas)* attains a length of 15 feet and weight of 50 pounds. It is a voracious carnivore. *(Copyright 2000 Norbert Wu:* norbertwu.com.*)*

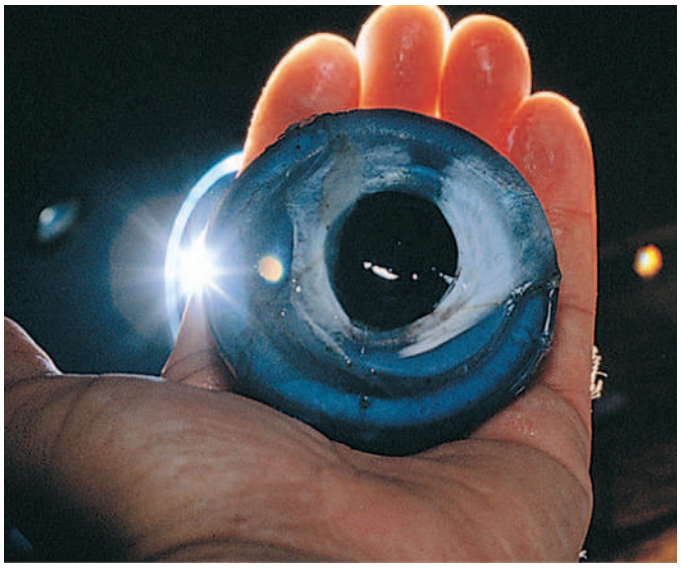

FIGURE 73-110 Eyeball of a giant Humboldt squid cut up by local fishermen. *(Copyright 2000 Norbert Wu:* norbertwu.com.*)*

estimated at 60 m (197 feet) in length. However, sucker scars expand in size as a whale grows, casting doubt on these projections. The battles between sperm whales and colossal squid are legendary, but humans are unlikely to encounter this awesome animal, which is found at depths far beyond the range of a sport scuba diver.[66] With increased deep-sea exploration by small submersibles, we may learn more about this fascinating creature. It is possible that a hungry colossal squid might ingest a human, but this has not yet been observed and is not likely to occur.

GIANT OCTOPUS

The Pacific giant octopus *Octopus dofleini* is a predator that has been captured at 272 kg (598 lb) with an arm span of more than 9.1 m (30 feet). It ranges off the western North American coast from northern California to Alaska and off Eastern Asia southward to Japan. This cephalopod is armed with suckers on eight arms and a parrot-like chitinous mouth located centrally underneath the head. Although it exhibits curiosity, it does not exhibit aggression directed against humans. However, it possesses the strength and agility to easily overwhelm a human. The animals have been reported to remove a dive mask or pull a regulator from divers. In open water, it is capable of squirting a large cloud of ink,

FIGURE 73-111 Suckers of the giant Humboldt squid are lined with razor-sharp teeth. *(Copyright 2000 Norbert Wu:* norbertwu.com.*)*

FIGURE 73-112 Diver strokes the belly of a manta ray. *(Copyright Carl Roessler.)*

which it sheds as evasive strategy. Folklore from the South Pacific tells of native breath-hold divers being subdued and drowned by angered captive octopuses.

GIANT MANTA RAY

The giant manta ray *Manta birostris* can have a wingspan of more than 6 m (19.7 feet) and a weight of 1600 kg (3520 lb) (Figure 73-112). The caudal appendage carries a vestigial stinger that poses no threat to humans. However, the coarse dermal denticles can create severe abrasions, which generally occur when intrusive divers attempt to ride these gentle and accommodating creatures. Similar abrasions can occur from attempts to ride whale sharks, *R. typus,* which also have large caudal fins that can readily shed an offending diver during regular swimming locomotion. In addition to potential injury, riding of large marine animals is behaviorally altering and illegal in many areas.

MANTIS SHRIMP

The mantis shrimp (Crustacea: Stomatopoda, "foot-mouth") (Figure 73-113) is not a true shrimp but resembles a large flattened shrimp or miniature lobster (≤ 36 cm [14.2 inches]) equipped with a pair of legs that serve as specialized jackknife claws (Figure 73-114). The tail carries numerous sharp spines that may project beyond the edge of the sturdy tail fin. Lacerations may be induced by either the front raptorial (prey-acquiring) claws or the tail, particularly when the mantis shrimp attacks an unwary victim. The strike from the paired claws may be

FIGURE 73-113 Mantis shrimp. *(Copyright Stephen Frink.)*

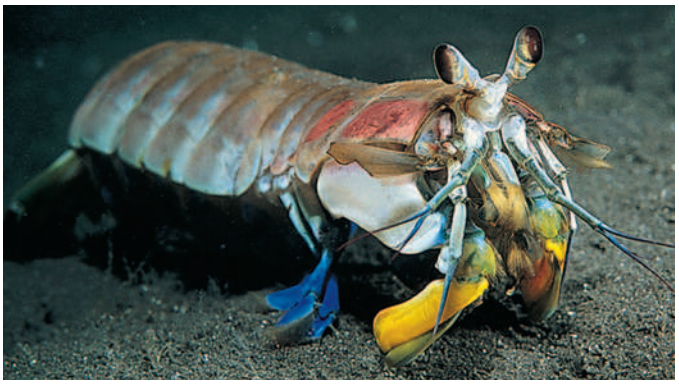

FIGURE 73-114 Mantis shrimp, ready to strike with its claws. *(Copyright 2000 Norbert Wu:* norbertwu.com.*)*

completed in a few milliseconds and is considered one of the fastest actions in the animal kingdom. It has been claimed that an attacking mantis shrimp struck with enough force to crack a diver's face mask and it is said that aquarium-held creatures have broken aquarium glass. Certain species use a spearing action, whereas others use a smashing technique. In the Caribbean, the mantis shrimp is known as "thumb splitter." The peacock mantis shrimp *Odontodactylus scyllarus* from the Indo-Pacific (Figure 73-115) can be afflicted with a disease that digests areas of its dorsal cuticle and eventually is lethal. This may explain one anecdotal report of a human finger wound (which led to amputation) characterized by cartilage destruction and from which no pathogenic organism could be cultured. The mantis shrimp is a superb predator, in part because it has the most highly developed eyes of any crustacean. One species, *Lysioquillina glabriuscula,* when faced with a rival male or a predator, adopts a position that accentuates fluorescent markings on its antennae and carapace, to make the creature more visible to an approaching enemy.

PIRANHA

South American freshwater characins include the piranha *Serrasalmus nattereri* (Figure 73-116), equipped with a formidable set of razor-sharp teeth (Figures 73-117 and 73-118). They are attracted by blood or commotion. Piranhas are widespread in rivers and lakes, and number approximately 30 species of the genera *Pygocentrus* and *Serrasalmus*.[81] These small fish may attack in schools of several hundred, although this reputation is largely borne of folklore rather than of documentation. Its reputation as an attacker of humans, like that of the barracuda, is greatly overstated. Natives living near piranha-inhabited waters express much more concern over freshwater stingrays (genus *Potamotrygon*) than about piranhas. Although an overwhelmed

FIGURE 73-115 Peacock mantis shrimp. *(Courtesy Marty Snyderman.)*

FIGURE 73-116 Piranha. *(Copyright 2000 Norbert Wu:* norbertwu.com.*)*

human could theoretically be reduced to a shiny skeleton in short order, most attacks on humans are caused by a single fish biting only once, resulting in a single, circular, crater-like wound (Figure 73-119). Bathers are injured most often in dammed waters because of fish proliferation, spawning, and parental-care

FIGURE 73-117 Teeth of the piranha. *(Courtesy V. Haddad, Jr.)*

FIGURE 73-118 Piranha teeth. *(Courtesy George Hertner, MD.)*

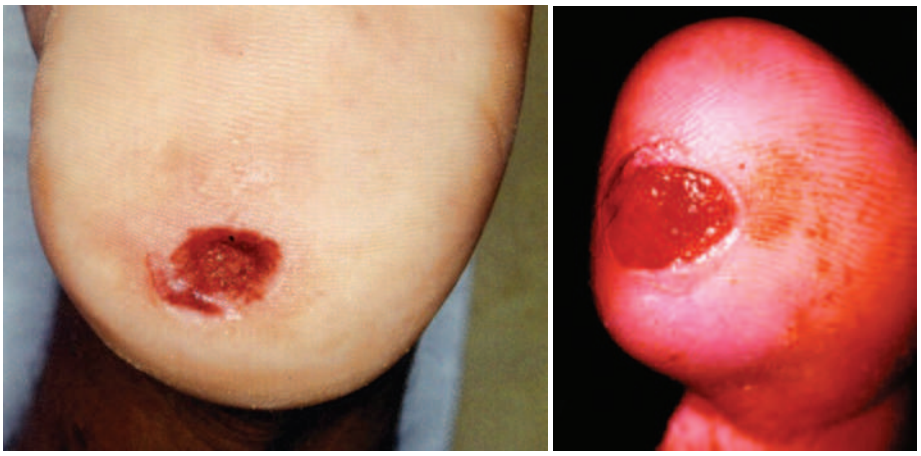

FIGURE 73-119 Crateriform bite wounds caused by piranhas. *(Courtesy Vidal Haddad, Jr.)*

behavior.[114,164,194] In one series of attacks by speckled piranhas *(Serrasalmus spilopleura),* it was noted that most bites occurred on the lower extremities, particularly on the heel. One bite was sufficient to amputate a toe.[81] Prevention measures might include clearance of waterweeds at bathing sites or placement of net enclosures around bathing areas. Other characid freshwater fish with fearsome teeth include the South American dogfish (Figure 73-120).

SNAPPING TURTLE

Snapping turtles (family Chelydridae) may bite humans when they are provoked on land; bites are not initiated while the animals are in the water. The biting speed is quite rapid and powerful, as evidenced by the aggression of the common snapper *Chelydra serpentina*. The larger alligator snapper *Macroclemys temminckii* is less aggressive.[36] The Florida snapping turtle *Chelydra osceola* is found only in Florida. Softshell turtles (Trionychidae) readily bite if harassed.

TRIGGERFISH

Triggerfish (named for its fin apparatus) (Figures 73-121 and 73-122) of the family Balistidae may be gregarious or unimposing, but during mating season the females of at least two species *(Pseudobalistes fuscus* and the larger titan triggerfish *Balistoides viridescens)* can become extremely territorial in guarding their nests and eggs during certain parts of the lunar cycle and thus aggressive, inflicting painful bites. The former can grow to 55 cm (22 inches) and the latter to 75 cm (30 inches). The strong jaws each carry eight long, protruding, and chisel-like teeth (Figure 73-123) in an outer row, backed by an inner row of six teeth.[156] Usually the fish "bites and runs," commonly on the legs (Figure 73-124), hands, or head of the human victim, but the orange-striped triggerfish *Balistoides undulatus* has been reported to bite and not release. It is common to have to strike the fish in some manner to get it to release. In the Gilbert Islands, a release technique is to bite the fish on the top of the head. If attacked by a triggerfish, one should retreat from the area of the nest by swimming laterally away, rather than straight up, to leave the cylinder of water above the nest. Care should be exercised when reaching into fishing nets in areas inhabited by triggerfishes; coauthor

FIGURE 73-120 South American freshwater characid dogfish. *(Courtesy Vidal Haddad, Jr.)*

FIGURE 73-121 Triggerfish. *(Copyright Lynn Funkhouser.)*

FIGURE 73-122 Titan triggerfish. *(Copyright Stephen Frink.)*

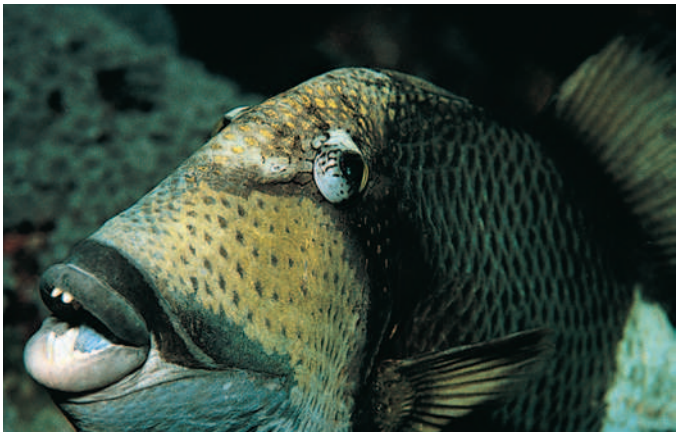

FIGURE 73-123 Triggerfish. *(Courtesy John Randall.)*

GHB received a painful bite to the first web space of the hand from a cryptic subadult grey triggerfish *(Balistes capriscus)* when sorting a trawl catch off the Florida Everglades.

SAWFISHES

Cartilaginous fishes that reach shark-like sizes (to 7 m), sawfishes are actually rays of the family Pristidae. Five species inhabit tropical waters worldwide. All species are highly endangered due to their habitat choices (shallow nearshore waters, including estuaries and lower stretches of rivers) and the presence of a peculiar elongated, toothed rostrum (the "saw"); humans frequent, modify, and fish in the waters in which sawfishes are found. Sawfish rostra are easily entangled in nets, and the animals readily take a baited hook.

There are no documented cases of sawfish-diver interactions, but fishery-caught sawfishes are very dangerous to handle when brought up to the boat, dock, or beach. They rapidly shake their heads from side to side defensively, and the combination of great size and power and sharp rostral teeth makes live release a difficult task. It is best to simply cut the fishing line, leaving the hook in the mouth (as is best done with live sharks). The hook will eventually rust and be dislodged, and these tough creatures hopefully do not suffer from the inconvenience. A net-caught sawfish is a bigger problem and must be cut out of the net.

Recommended medical treatment is the same as measures applied for shark attack. The complications can also be similar, including retained foreign bodies and wound infections.

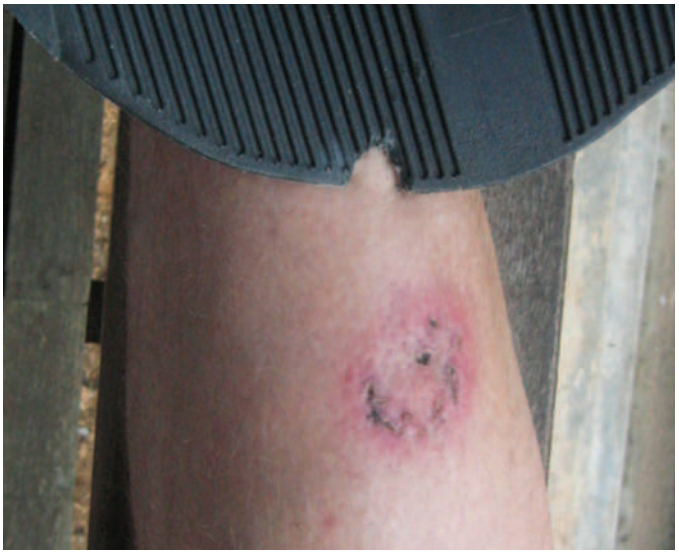

FIGURE 73-124 Leg and dive fin bitten by *Pseudobalistes flavimarginatus* triggerfish. *(Copyright Corinne Paollilo.)*

FIGURE 73-125 Coral garden. *(Courtesy Paul S. Auerbach, MD.)*

STONY CORALS

LIFE AND HABITS

The anthozoan Madreporaria, or true (stony) corals, exist in colonies that possess calcareous outer skeletons (the origin of calcium carbonate, or limestone) with pointed horns or razor-sharp edges, or both (Figure 73-125). There are nearly 1000 species of corals. Reef-forming corals live in waters at temperatures of 20° C (68° F) or higher, generally at depths of up to 20 fathoms (120 feet), although they are seen at depths of up to 83 fathoms (500 feet). A "coral head" is actually a colony of individual polyps. Certain coral species, such as *Plexaura homomalla,* have been investigated as sources of prostaglandins and other pharmaceutical precursors to treat conditions as diverse as asthma, leukemia, and infections. Pieces of coral have been evaluated for use as bone grafts.

Coral reefs are under pressure worldwide from climatic changes, human-induced sedimentation and salinity modification, chemical poisons (e.g., cyanide used for fishing, pollution), natural predators (e.g., crown-of-thorns sea star), and mechanical destruction (e.g., ship anchors, diver contact, and explosives).

CLINICAL ASPECTS

Snorkelers and divers, particularly photographers and spear fishermen, frequently handle or brush against these living reefs, resulting in superficial cuts and abrasions on the extremities (Figure 73-126) while simultaneously injuring the corals. Coral cuts are probably the most common injuries sustained underwater. The initial reaction to a coral cut is stinging pain, erythema, and pruritus, most commonly on the forearms, elbows, and

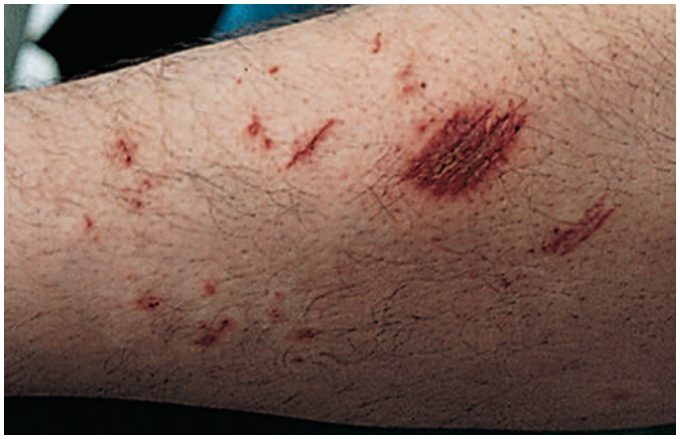

FIGURE 73-126 Abrasions of the leg from bumping against sharp coral. *(Courtesy Paul S. Auerbach, MD.)*

knees. Divers without gloves frequently receive cuts to the hands. A break in the skin may be surrounded within minutes by an erythematous wheal, which fades over 1 to 2 hours. The red, raised welts and local pruritus are called *coral poisoning*. Low-grade fever may be present and does not necessarily indicate an infection. Blistering may occur. With or without prompt treatment, the wound may progress to cellulitis with ulceration and tissue sloughing. These wounds heal slowly (3 to 6 weeks) and result in prolonged morbidity. There may be a stage of subacute fleshy granulomatous dermatitis, followed by chronic lichenoid dermatitis, in which the lesions harden, become smaller, and take on a shiny, lichenoid appearance.[62] In an extreme case, the victim develops cellulitis with lymphangitis, reactive bursitis, local ulceration, and wound necrosis. Chronic dermal granulomata following a coral scrape or cut should invoke suspicion for *Mycobacterium* infection, including species *marinum* or *haemophilum*.[172]

TREATMENT

Coral cuts should be promptly and vigorously scrubbed with soap and water and then irrigated copiously with a forceful stream of fresh water or normal saline to remove all foreign particles. Using medicinal hydrogen peroxide to bubble out "coral dust" is occasionally helpful. Any fragments that remain can become embedded and increase the risk for an indolent infection or foreign body granuloma. If stinging is a major symptom, there may be an element of envenomation by nematocysts (see Chapter 74). A brief rinse with diluted acetic acid (vinegar), lidocaine, or nonscalding hot water may diminish the discomfort (after the initial pain from contact with the open wound). Topical decontamination should be followed by a normal saline or tap water rinse. If a coral-induced laceration is severe, it should be closed with adhesive strips rather than sutures if possible; preferably it should be debrided for 3 to 4 consecutive days and closed in a delayed fashion.

A number of approaches can be taken with regard to subsequent wound care. One method is to apply twice-daily sterile wet-to-dry dressings, using saline or a dilute antiseptic (povidone-iodine 1% to 5%) solution. Alternatively, a nontoxic topical antiseptic or antibiotic ointment (mupirocin, bacitracin, or polymyxin B–bacitracin-neomycin) may be used sparingly and covered with a nonadherent dressing (e.g., Telfa). Secondary infections are dealt with as they arise. A final approach is to apply full-strength antiseptic solution, followed by a powdered topical antibiotic, such as tetracycline. No method has been supported by any prospective trial.

Despite the best efforts at primary irrigation and decontamination, the wound may heal slowly, with moderate-to-severe soft tissue inflammation and ulcer formation (Figure 73-127). All devitalized tissue should be debrided regularly using sharp dissection. This should be continued until a bed of healthy granulation tissue is formed. Wounds that appear infected should be cultured and treated with antibiotics as previously discussed. Lichenoid papules, which may be flat or dome shaped, may respond to treatment with betamethasone dipropionate 0.05% cream applied twice daily for 2 weeks under occlusive dressings.[45] Residual postinflammatory hyperpigmentation is possible.

The victim who demonstrates malaise, nausea, and low-grade fever may have a systemic form of coral poisoning or be manifesting early signs of a wound infection. It is prudent at this point to search for a localized infection, procure wound cultures or biopsy specimens as indicated, and initiate antibiotics pending confirmation of organisms. If the victim is started on an antibiotic and does not improve, a supplemental trial of a systemic glucocorticoid (prednisone 80 mg tapered over 2 weeks) is not unreasonable. In the absence of an overt infection, the natural course of the wound is to improve spontaneously over a 4- to 15-week period.

A hypertrophic scar may form following coral abrasion. First-line therapy is silicone sheets and gels applied to the scar. Intralesional corticosteroid injection is second-line therapy. One therapeutic regimen is triamcinolone acetonide in concentrations of 10 to 40 g/mL injected every 4 to 6 weeks. This is felt to alter collagen and glucosaminoglycan synthesis and reduce inflammation and fibroblast proliferation. Another approach is compression therapy to thin the skin by reducing the cohesiveness of collagen fibers in hypertrophic scars. Select newer therapies to treat hypertrophic scars include intralesional interferon, 5-fluorouracil, or bleomycin; application of topical retinoic acid, imiquimod, or tacrolimus; cryotherapy; excision; and laser therapy.[132]

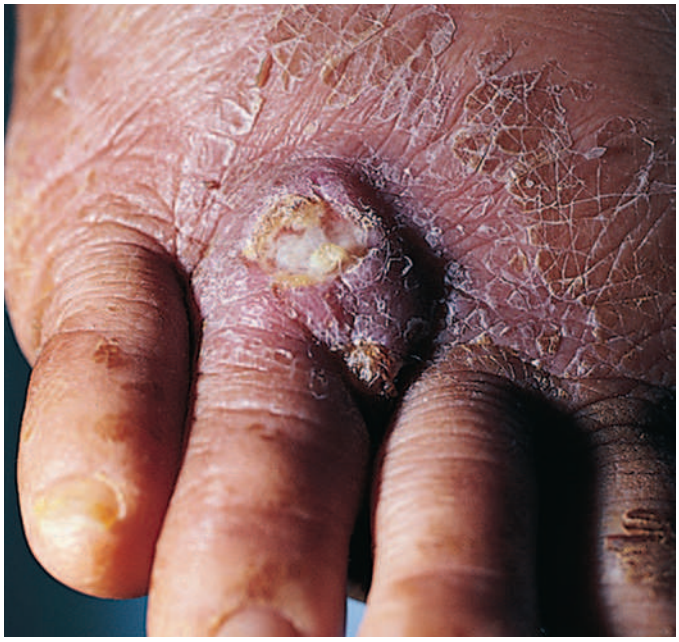

FIGURE 73-127 Poorly healing wound following coral cut. *(Courtesy Paul S. Auerbach, MD.)*

PREVENTION

Divers exploring near coral reefs must take every care to avoid coral cuts. Protective clothing and gloves should be impenetrable. Snorkelers and underwater photographers in shallow water should wear adequate hand, elbow, and knee protection.

ELECTRIC FISH AND RAYS

Only two groups of electric fish are marine; the remainder are freshwater animals. They rarely pose a health hazard but rather are curious creatures surrounded by superstition and folklore. The marine electric fish include stargazers *(Astroscopus)* (Figure 73-128), electric rays *(Torpedo* and *Narcine),* and skates (Rajidae). The electric eel (Figure 73-129) is a freshwater Amazonian animal (see below).

Electric rays are found in temperate and tropical oceans. Of the class Chondrichthyes, they are round-bodied, with short tails and thick bodies (compared with stingrays). In California, *Torpedo californica* (Figure 73-130) attains a length of 1.2 m (4 feet) and weight of 36 to 41 kg (80 to 90 lb). It swims slowly and sluggishly and is usually found partially buried in bottom mud and sand. Well camouflaged, its dorsal surface is multicolored and the ventral surface creamy white. The externally visible electric organs are located on each side of the anterior part of the disk between the anterior extension of the pectoral fin and the head, extending from above the level of the eye backward past the gill region onto the ventral surface. The electric organs are composed of a honeycomb network of modified muscles organized into columnar prism-like structures and connective tissue, which generate an electrical charge by neuromuscular activity. The muscle cells (electroplaques) are stacked 500 to 1000 deep, creating up to 500 cm^2 of surface area. The electroplaques depolarize in series and in parallel simultaneously, producing amperage sufficient to stun prey. Species in the tropical eastern Pacific include

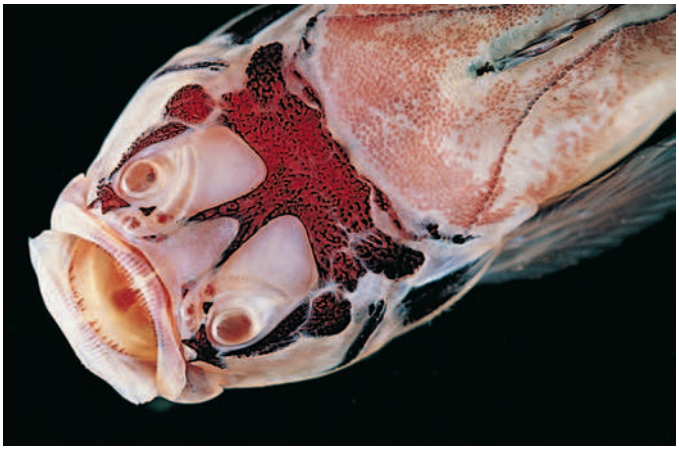

FIGURE 73-128 Stargazer *(Astroscopus zephyreus)* with electric plates above each eye. *(Copyright 2000 Norbert Wu:* norbertwu.com.*)*

the smaller-bodied lesser ray *Narcine entemedor* and the bullseye ray *Diplobatis ommata* (Figure 73-131).

Generally the ventral surface of the ray is negative and the dorsal side is positive. An electrical discharge is reflexively produced on contact, often in a series exhaustive for the fish. This necessitates a period of recharging. Electricity is delivered in doses of 8 to 220 volts. The Atlantic *Torpedo nobiliana* produces 180 to 220 volts. Although the shock is of low amperage, it is sufficient to stun a grown man and might induce drowning. Recovery from the shock has been reported anecdotally to usually be uneventful. An electric ray should not be handled. The energy generated by skates is considerably less, measured in millivolts to 1 to 2 volts.

The electric eel, *Electrophorus electricus,* is a freshwater fish (not related to true eels) that is a member of the knifefishes. Electric eels reside in the Amazon and Orinoco Rivers and other related bodies of water in South American basins. This species generates the potential to electrically shock victims by manipulating the sodium ion concentration in specialized cells called electrocytes. The current generated has been estimated to attain a maximum of 500 to 650 volts in the adult animal, with lesser amounts in juvenile animals. This is of a severity that may incapacitate a human. Because the creatures may deliver repeated

FIGURE 73-129 Electric eel, Steinhart Aquarium. *(Copyright 2000 Norbert Wu:* norbertwu.com.*)*

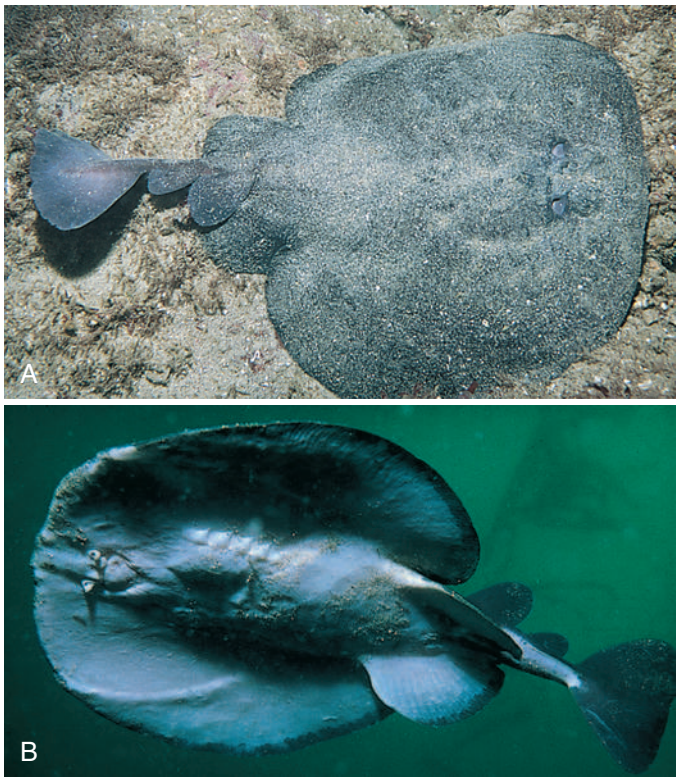

FIGURE 73-130 Electric ray *(Torpedo californica).* **A,** Dorsal view. **B,** Ventral view. *(Copyright 2000 Norbert Wu:* norbertwu.com.*)*

FIGURE 73-131 Bull's-eye electric ray. *(Courtesy Paul S. Auerbach, MD.)*

shocks, they should be given wide berth and not be handled. The mechanism of electricity generation is sufficiently unique to warrant study for application to development of a new type of battery.

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CHAPTER 74

Envenomation by Aquatic Invertebrates

PAUL S. AUERBACH AND ALEXANDRA E. DiTULLIO

Stinging aquatic animals pose a hazard for swimmers and divers. They constitute a large collection of marine organisms that include invertebrates and vertebrates, and that range from primitive to extremely sophisticated organisms. This chapter discusses envenomation by aquatic invertebrate life-forms. Chapter 75 discusses envenomation by aquatic vertebrate life-forms. Chapter 73 discusses infections associated with aquatic wounds and the relevant antimicrobial therapies. Standard wound care measures, such as antitetanus immunization, should be undertaken whenever there is penetration of the skin.

The science of poisons, biotoxicology, is divided into plant poisons, or phytotoxicology, and animal poisons, or zootoxicology. *Toxinology* connotes the science of toxic substances produced by or accumulated in living organisms, their properties, and their biologic significance for the organisms involved.[139] Animals in which a definite venom apparatus is present are sometimes called phanerotoxic, whereas animals whose body tissues are toxic are termed cryptotoxic.[173] Naturally occurring aquatic zootoxins may be designated as oral toxins (which are poisonous to eat and include bacterial poisons and products of decomposition), parenteral toxins (venom produced in specialized glands and injected mechanically [by spine, needle, fang, fin, or dart]), and crinotoxins (venom produced in specialized glands and administered as slime, mucus, or gastric secretion). Within these three subdivisions, further classifications are by phylogeny, chemical structure, and clinical syndrome.

Although all venoms are poisons, not all poisons are venoms. Venoms can be released in varying amounts and have evolved for conquest and defense. It is theorized that offensive (prey capture and digestion) venoms are generally perioral (mouth, fang, or tentacle) and that defensive venoms are aboral (tail and sting) or dermal (barb and secretion). In the evolutionary scheme, it appears that many venomous fish seek a specific form of self-defense, whereas poisonous fish are noxious in a nonspecific manner.[7] A brief comparison of the features of venoms and poisons shows that, generally, poisons produced in skin, muscle, blood, or organs are heat stable (46° to 49°C [115° to 120°F]) and gastric acid stable and carry seasonal toxicity. They are not "released," and may lack a well-defined biologic function. Venoms are more commonly heat labile, gastric acid labile, and nonseasonal in toxicity.

In snakes, the latency, toxicity, and duration of venom effects are related to the route of envenomation. Intravascular injection is significantly more lethal than intraperitoneal or transcutaneous injection, as determined by the dose that produces 50% lethality in a group (LD_{50}). This principle is not commonly applied to marine venoms because few encounters involve direct intravascular injection.

Most venoms are high-molecular-weight amalgams of vasoactive amines, proteolytic enzymes, and other biogenic compounds. These substances denature membranes, catabolize cyclic 3′,5′-adenosine monophosphate, degranulate mast cells, provoke histamine release, initiate arachidonate metabolism, accelerate coagulopathy, interfere with cellular transport mechanisms, disrupt metabolic pathways, impede neuronal transmission, and evoke anaphylaxis and shock. Toxin-containing venoms from marine and other creatures include components, such as incretin mimetics, sarafotoxins, antiarrhythmics, and bradykinin-potentiating and natriuretic peptides, that may be applicable to cardiovascular drug discovery.[90] Although many marine venoms are composed of protein and polypeptide subunits, they lack sufficient immunogenicity to allow development of antitoxins or antivenoms. Poisons represent metabolic by-products and are usually of lower molecular weights.

The taxonomy of marine animals can sometimes be confusing. The hierarchy, in descending order, is kingdom, phylum, class, order, family, genus, and species.

Treatment recommendations are constantly evolving in response to acquisition of data, clinical observations, and preferences of expert rescuers and physicians.

ALLERGIC REACTIONS

ANAPHYLAXIS

An envenomation or the administration of antivenom can elicit an allergic reaction. In the previously sensitized individual, the antigen (venom, aquatic protein, or animal serum) forms a complex with immunoglobulin E (IgE) and perhaps with IgG homocytotropic antibodies or activated complement cleavage products attached to the membranes of mast cells and basophils. This induces membrane permeability, which allows degranulation or membrane production of histamine, serotonin, kinins, prostaglandins, platelet-activating factor, eosinophil and neutrophil chemotactic factors, leukotrienes, and other bioactive chemical mediators.[9]

The signs and symptoms of anaphylaxis may occur within minutes of exposure. They include hypotension, bronchospasm, tongue and lip swelling, laryngeal edema, pulmonary edema, seizures, cardiac arrhythmia, pruritus, urticaria, angioedema, rhinitis, conjunctivitis, nausea, vomiting, diarrhea, abdominal pain, gastrointestinal bleeding, and syncope. Most severe allergic reactions occur within 15 to 30 minutes of envenomation, and nearly all occur within 6 hours. Fatalities are often related to airway obstruction or hypotension. Acute elevated pulmonary vascular resistance may contribute to hypotension that results from generalized arterial vasodilation.[10,12]

Treatment

Decisive treatment should be instituted at the first indication of hypersensitivity. Specific treatment recommendations for anaphylaxis are found in Box 67-7.

ANTIVENOM ADMINISTRATION

A number of marine envenomations, such as those by the box-jellyfish and certain sea snakes, may provoke administration of specific antivenom by the treating clinician. Marine antivenoms are raised in horses or sheep and therefore may be antigenic in humans, inducing both immediate and delayed hypersensitivity. Most authorities recommend that a skin test be performed for sensitivity to horse serum, if the clinical situation permits, after a sea snake envenomation. A skin test should be done only after deciding to administer antivenom; it is *not* done to determine whether antivenom is necessary. The purpose of sensitivity testing is to allow adequate prophylaxis against anaphylaxis. The skin test is performed with an intradermal injection into the upper extremity of 0.02 mL of a 1:10 dilution of horse serum test material in saline, with 0.02 mL saline in the opposite extremity as a control. Erythema and a wheal with pseudopodia appear in 15

to 30 minutes in a positive response. Because antivenom contains many times the protein content of horse serum used for skin testing, the use of antivenom for skin testing may increase the risk of anaphylactic reaction. If the skin test is positive, the antivenom intended for intravenous (IV) infusion should be diluted in sterile water to a 1:100 concentration for administration. Successive vials should be less dilute if the allergic reaction is minimal (controlled by antihistamines and epinephrine). A negative skin test does not preclude the possibility of an anaphylactic response to antivenom administration.

The rationale for administering antivenom is to provide early and adequate neutralization of the toxin at the tissue site of entry before it gains systemic dominance. Except for stonefish antivenom, the product is preferentially administered intravenously, taking care to provide adequate doses for children and older adults, who have a decreased volume of distribution and increased sensitivity to venom effects. The antivenom intended for IV administration should always be diluted with normal saline, Ringer's lactate, or dextrose 5% in water.

Marine antivenoms are produced and distributed in the Indo-Pacific regions. They include the following:

Chironex fleckeri (box-jellyfish) antivenom, from Commonwealth Serum Laboratories (CSL), Parkville, Victoria, Australia. This hyperimmune sheep globulin preparation may be used to neutralize the stings of *C. fleckeri* and *Chiropsalmus* species. It may not be as efficacious as commonly believed.

Enhydrina schistosa (beaked sea snake) antivenom, from CSL. This hyperimmune horse globulin preparation may be used to neutralize the bites of most sea snakes. It is prepared by immunizing horses with venom from *E. schistosa* and the Australian tiger snake *Notechis scutatus*.

Notechis scutatus (tiger snake) antivenom, from CSL, has traditionally been recommended as the antivenom of second choice against the bites of most sea snakes. However, it has been written that tiger snake antivenom is not effective against sea snake bites, and so it should not be relied upon for clinical efficacy in humans.[228]

Synanceja trachynis (stonefish) antivenom, from CSL. This hyperimmune horse globulin preparation may be used to neutralize the stings of stonefish and more virulent scorpionfish species, although it is rarely used for the latter.

A person who is known to be sensitive to horse or sheep serum, has a positive skin test, or develops signs of an allergic reaction or anaphylaxis during antivenom therapy requires aggressive medical management. A recipient of antivenom should be pretreated with 50 to 100 mg of IV diphenhydramine (1 mg/kg in children). After this, the initial dose of antivenom is administered at a rate no faster than one vial each 5 minutes. If no allergic manifestation ensues, the antivenom can be administered at a more rapid rate. If signs of anaphylaxis develop, usually heralded by an urticarial eruption or pruritus, 0.1- to 0.2-mL aliquots of antivenom should be alternated with 3- to 10-mL (0.03- to 0.1-mg) IV doses of aqueous epinephrine 1:100,000 (infused over 5 to 10 minutes). Alternatively, an epinephrine drip may be prepared as discussed in Chapter 67. The victim should be managed in an intensive care unit, with electrocardiographic and blood pressure monitoring. The dose of epinephrine should not elevate the pulse rate to greater than 150 beats/min. The administration of IV epinephrine may cause transient hypokalemia as potassium is driven intracellularly; cessation of the epinephrine infusion may create transient hyperkalemia as the potassium regains entry into the extracellular space. If a victim is highly allergic to antivenom, serious consideration should be given to supportive therapy (including hemodialysis) without antivenom administration.

In one series, stonefish antivenom was administered to 24 victims in a dose of one or two ampules by the intramuscular (IM) route, without any "immediate reactions" reported.[198] In this same report, six victims received box-jellyfish antivenom by the IV route without immediate or delayed reactions. Anecdotal reports indicate that box-jellyfish antivenom has been administered by the IM route in the field more than 90 times to date without any episode of anaphylaxis.

SERUM SICKNESS

The formation of IgG antibodies in response to antigens present in antivenom (prepared in heterologous serum) results in the deposition of immune complexes in many tissue sites, notably in the walls of blood vessels. These complexes induce vascular permeability, activate the complement cascade and chemotactic factors, degranulate mast cells, and trigger the release of proteolytic enzymes. Decreased levels of C_3 and C_4 are accompanied by increased C_{3a}/C_{3a} des-arginine, a split product C_3.[74,112] Although immune complexes can be measured by various tests (Raji cell IgG assay and C_{1q}-binding assay), levels of immune complexes may not correlate with the clinical presentation.[74,147] Cutaneous venulitis may precede vasculitis. Dermal biopsy of lesional skin may reveal leukocytoclastic vasculitis.

Symptoms are generally present within 8 to 24 days and include fever, arthralgias, malaise, urticaria, lymphadenopathy, urticarial and morbilliform skin rashes, peripheral neuritis, and swollen joints. It is not uncommon for the primary urticarial lesion to be noted at the injection site. Serum sickness is managed with administration of corticosteroids. An initial loading dose of prednisone (40 to 60 mg for adults, and 2 to 5 mg/kg, not to exceed 50 mg, for children) should be administered and maintained daily until symptoms markedly resolve. The corticosteroid should be tapered over a 2- to 3-week course to avoid induction of adrenal insufficiency. Aspirin or other nonsteroidal antiinflammatory agents are rarely helpful and may be contraindicated because of circulating immune complex–induced platelet dysfunction.

PHYLUM PORIFERA

SPONGES

Life and Habits

There are approximately 5000 species of sponges (phylum Porifera, predominantly of class Demospongiae), which are supported by horny, but elastic, internal collagenous skeletons of spongin, some forms of which we use as bath sponges. Sponges are without digestive, excretory, respiratory, endocrine, circulatory, and nervous systems. Embedded in the connective tissue matrices and skeletons are spicules of silicon dioxide (silica) or calcium carbonate (calcite), by which some sponges can be definitively identified. In general, sponges are stationary acellular animals that attach to the sea floor or coral beds and may be colonized by other sponges, hydrozoans, mollusks, cnidarians, annelids, crustaceans, echinoderms, fish, and algae. These secondary cnidarian inhabitants are responsible for the dermatitis and local necrotic skin reaction termed *sponge diver's disease (maladie des plongeurs)*.[192] In recognition of a medicinal property, the ancient Greeks burned sea sponges and inhaled the vapors for prophylaxis against goiter.[49] Sponges harbor various biodynamic substances, with possible antineoplastic, antibacterial, growth-stimulating, antihypertensive, neuropharmacologic, psychopharmacologic, and antifungal properties. A number of sponges produce crinotoxins that may be direct dermal irritants, such as subcritine, halitoxin (*Haliclona* species), *p*-hydroxybenzaldehyde, and okadaic acid. These may be present in surface or internal secretions. Murine monoclonal antibodies against okadaic acid intended for use in an assay system for the detection of diarrhetic shellfish poisoning have been prepared from the sponge *Halichondria okadai*.[209] The causative agent of Dogger Bank itch, (2-hydroxyethyl) dimethylsulfoxonium chloride, has been isolated from the marine sponge *Theonella aff. mirabilis*.[215]

Clinical Aspects

Two general syndromes, with variations, are induced by contact with sponges. The first is a pruritic dermatitis similar to plant-induced allergic dermatitis, although the dermatopathic agent has not been identified. Rarely, erythema multiforme or an anaphylactoid reaction may be present. A typical offender is the friable Hawaiian (Figure 74-1) or West Indian fire sponge *(Tedania ignis),* a brilliant yellow-vermilion-orange (Figure 74-2) or reddish-brown organism with a crumb-of-bread appearance

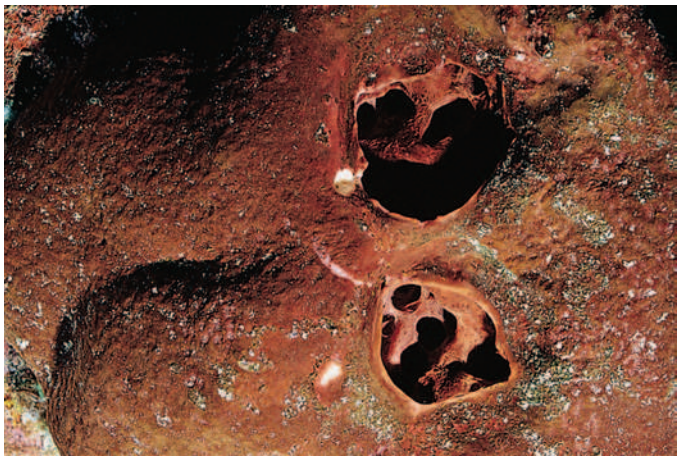


FIGURE 74-1 Pacific fire sponge. *(From Norbert Wu, with permission: norbertwu.com.)*

FIGURE 74-2 Atlantic fire sponge. *(Courtesy Dee Scarr.)*

found off the Hawaiian Islands and the Florida Keys.[180,189] Other "fire sponges" have a similar appearance (Figure 74-3). This sponge grows in thick branches, which extend from a larger base and are easily broken off. Other culprits include *Fibula* (or *Neofibularia*) *nolitangere,* the poison bun sponge (Figure 74-4) (and the related sponge *Neofibularia mordens*), and *Microciona*

FIGURE 74-3 Fire sponge. *(Courtesy Vidal Haddad, Jr.)*

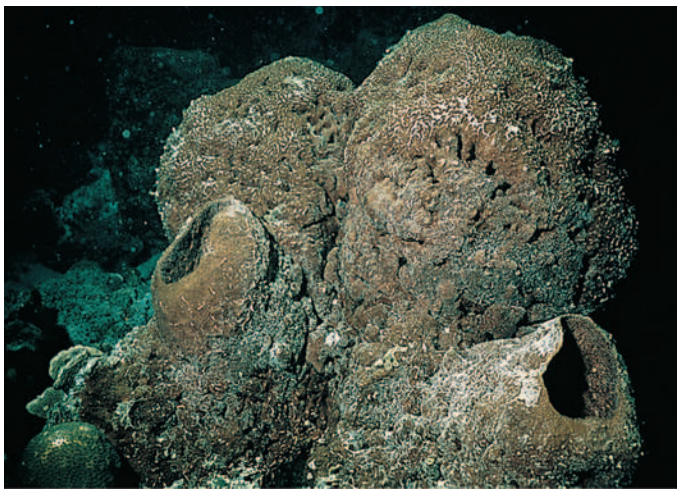


FIGURE 74-4 Poison bun sponge *Neofibularia nolitangere. (Courtesy Dee Scarr.)*

prolifera, the red moss sponge (found in the northeastern United States).[104] *F. nolitangere* is found in deeper water and grows in clusters, with holes (oscula) large enough to admit a diver's finger. It is brown (Figure 74-5) and bready in texture, so it may crumble in the hands.

Within a few hours after skin contact, but sometimes within 10 to 20 minutes, the reactions appear. They are characterized by itching and burning, which may progress to local joint swelling, soft tissue edema, vesiculation, and stiffness, particularly if small pieces of broken sponge are retained in the skin near the interphalangeal or metacarpophalangeal joint. Most victims of sponge-induced dermatitis have hand involvement, because they handled the sponges without proper gloves. In addition, abraded skin, such as that which has been scraped on stony coral, may allow more rapid or greater absorption of toxins.[173] When the sponge is penetrated, torn, or crumbled, the skin is exposed to the toxic substances. Untreated, mild reactions subside within 3 to 7 days. When large skin areas are involved, the victim may complain of fever, chills, malaise, dizziness, nausea, muscle cramps, and formication. Bullae induced by contact with *M. prolifera* may become purulent. Systemic erythema multiforme, dyshidrotic eczema, or an anaphylactoid reaction may develop 1 to 2 weeks after a severe exposure.[237] The skin may become mottled or purpuric, occasionally after a delay of up to 10 days.[189]

The second syndrome is irritant dermatitis and follows penetration of small spicules of silica or calcium carbonate into the skin. Most sponges have spicules; toxic sponges may possess crinotoxins that enter microtraumatic lesions caused by the spicules.

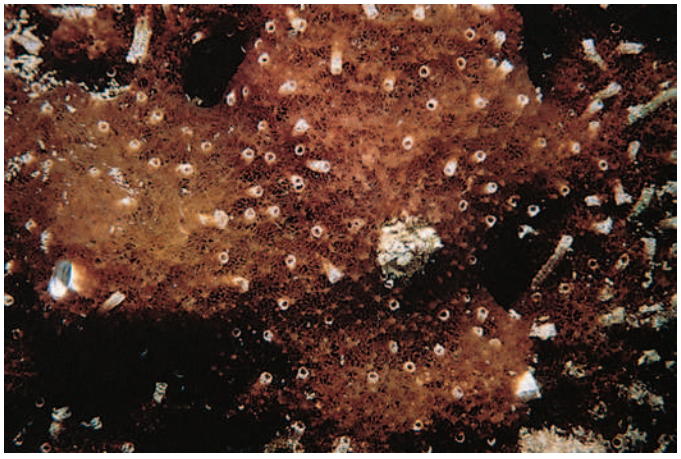


FIGURE 74-5 Crumb-of-bread appearance of poison bun sponge. *(Courtesy Dee Scarr.)*

In severe cases, surface desquamation of the skin may follow in 10 days to 2 months. No medical intervention can retard this process. Recurrent eczema and persistent arthralgias are rare complications.

Treatment

Because distinguishing clinically between the allergic and spicule-induced reactions is usually impossible, it is reasonable to treat for both. The skin should be gently dried. Spicules should be removed, if possible, using adhesive tape, a thin layer of rubber cement, or a facial peel. As soon as possible, dilute (5%) acetic acid (vinegar) soaks for 10 to 30 minutes 3 or 4 times a day should be applied to all affected areas.[189,193,236] Isopropyl alcohol (40% to 70%) is a reasonable second choice. Although topical steroid preparations may help relieve the secondary inflammation, they are of no value as an initial decontaminant. If they precede the vinegar soak, they may worsen the primary reaction. Delayed primary therapy or inadequate decontamination can result in the persistence of bullae, which may become purulent and require months to heal.

Erythema multiforme or dyshidrotic eczema may require administration of a systemic glucocorticoid, beginning with a moderately high dose (prednisone, 60 to 100 mg) tapered over 2 to 3 weeks. Anecdotal remedies for management of sponge envenomation that have been suggested without demonstration of efficacy include antiseptic dressings, broad-spectrum antibiotics, methdilazine, tripelennamine, phenobarbital, diphenhydramine, promethazine, and topical carbolic oil or zinc oxide cream.[189]

After the initial decontamination, a mild emollient cream or steroid preparation may be applied to the skin. If the allergic component is severe, particularly if there is weeping, crusting, and vesiculation, a systemic glucocorticoid (prednisone, 60 to 100 mg, tapered over 2 weeks) may be beneficial, as might a potent topical steroid preparation. Severe itching may be controlled with an antihistamine.

Clostridium tetani has been cultured from sea sponges, so proper antitetanus immunization should be part of sponge dermatitis therapy. Frequent follow-up wound checks are important because significant infections sometimes develop.[105] Infected wounds should be cultured and managed with antibiotics (see Chapter 73). Because of infection risk, sponges should not be used to pack wounds. If sponge poisoning induces an anaphylactoid reaction, standard resuscitation using epinephrine, bronchodilators, corticosteroids, and antihistamines should be undertaken.[237]

As mentioned previously, sponge diver's disease is not caused by any toxin produced by the sponge, but rather, is a stinging syndrome related to contact with the tentacles of the small anemone *Sagartia rosea* (family Sagartiidae) or anemones from the genus *Actinia* (family Actiniidae) that attach to the base of the sponge. Treatment should include that for cnidarian envenomation (see below).

Prevention

All divers and net handlers should wear proper gloves. Sponges should not be broken, crumbled, or crushed with bare hands. If the victim brings a specimen, the physician should take care to document its appearance. Dried sponges may remain toxic.

PHYLUM CNIDARIA

The phylum Cnidaria (previously called coelenterates [hollow gut]) contains an enormous group of approximately 10,000 species, at least 100 of which are dangerous to humans. Only members of the phylum Cnidaria (sometimes referred to as cnidarians) produce the capsule commonly called a cnida (also called cnidocyst).[55] The word *cnida* is derived from the Greek word κνίδη, which means "nettle." For practical purposes the cnidarians can be divided into four main groups: (1) hydrozoans, including hydroids, fire corals, and creatures such as the Portuguese man-of-war; (2) scyphozoans, such as true jellyfish; (3) anthozoans, such as soft corals (alcyonarians), stony corals, sea pens, and anemones; and (4) cubozoans, such as box-jellies. Gorgonians (order Gorgonacea, class Anthozoa, subclass Alcyonaria) secrete mucinous exudates having toxic effects in experimental animals that can be characterized as hemolytic, proteolytic, cholinergic, histaminergic, serotonergic, and adrenergic.[71] Fenner divides jellyfish into three main classes: scyphozoans (true jellyfish), with tentacles arising at regular intervals around the bell; cubozoans (e.g., box-jellyfish), with tentacles arising only from the corners (and these may be further divided into carybdeids [e.g., Irukandji jellyfish], with only one tentacle [except in rare cases] arising from each lower corner of the bell, and chirodropids, which have more than one tentacle in each corner of the bell); and other jellyfish, such as members of the hydrozoans (e.g., *Physalia* species).

MORPHOLOGY, VENOM, AND VENOM APPARATUS

Cnidarians are carnivorous predators that feed on other fish, crustaceans, and mollusks. They are radially symmetric animals of simple structure (95% water) and exist in two predominant life forms—either sedentary, asexual polyps (hydroids) or free-swimming and sexual medusae. They are the lowest form of life organized into different layers.[173] Generally, the polyps are sac-like creatures attached to the substrate at the caudal (aboral) end, with a single orifice or mouth at the upper end surrounded by stinging tentacles (dactylozooids). This form predominates in the hydrozoans and anthozoans. The medusa is a bell-shaped creature, with a floating gelatinous umbrella from which hang an elongated tubular mouth and marginal nematocyst-bearing tentacles. This form predominates in the scyphozoans and is also found in the hydrozoans.

Cnidocytes (include nematocytes, spirocytes, and ptychocytes) are mature living cells that encapsulate the nonliving intracytoplasmic capsules called cnidae (or cnidocysts: include nematocysts, spirocysts, and ptychocysts), within which are found the stinging apparatus. Cnidae are secreted by the Golgi apparatus of cells (cnidoblasts: include nematoblasts, spiroblasts, and pychoblasts) specialized for this function. Nematocysts are initially found in differentiating clusters. After differentiation into the different types of capsules, the clusters break up to allow single nematocytes to migrate to tentacles, where they become mounted in specialized tentacle epithelial cells, called battery cells.[200] The nematocytes are located on the outer epithelial surfaces of the tentacles (Figure 74-6) or near the mouth and are triggered by contact with the victim's body surface. The nematocyst is contained within the cnidoblast, to which is attached a single pointed "trigger," or cnidocil. The undischarged nematocyst (3 to 100 μm in diameter) varies in shape and is under high osmotic pressure created during capsule morphogenesis by synthesis of poly-γ-glutamate in the capsule matrix. Minicollagen networks determine the structure of the nematocyst wall.[46] The nematocyst contains a hollow, sharply pointed, coiled, or folded "thread" tubule (nema) (Figure 74-7). This tubule may attain

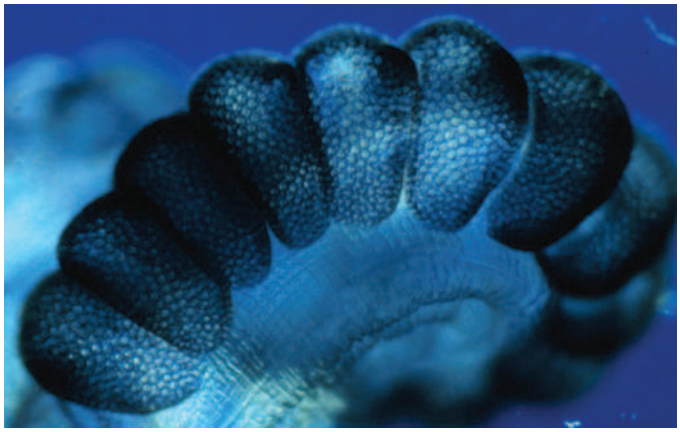


FIGURE 74-6 Unfired nematocysts on a *Physalia* tentacle. *(Courtesy Peter Parks.)*

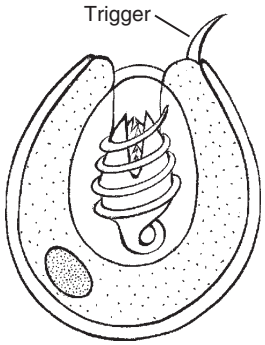


FIGURE 74-7 Nematocyst before discharge.

lengths of 200 to 850 μm and is sufficiently hardy to penetrate a surgical glove. The tubule is initially formed outside the capsule and then invaginates within the wall, so that in the undischarged state, the toxin is located in the folds and invaginations of the tubule's membrane. This membrane hardens via disulfide bond isomerization to form bridges between minicollagen peptides as the capsule attains its final size.[200]

The tubule is lined with hollow barbs, which help it penetrate and anchor into the victim. In the undischarged state, the barbs occupy the lumen of the twisted and folded tubule. When the cnidocil is stimulated, either by physical contact or by a chemoreceptor mechanism, it causes the opening of a trapdoor (operculum) in the cnidoblast, and the venom-bearing tubule is everted (Figure 74-8) within 3 μsec. This exocytosis has been hypothesized to occur because of osmotic swelling of the capsular matrix caused by high concentration of poly-γ-glutamate, influx of water (leading to a hydrostatic pressure of up to 150 atm), release of intrinsic tensile forces (up to 375 MPa on the inner capsule wall), or deformation of the wall-induced internal pressure.[91,92,200] The sharp tip of the thread tube enters the victim's skin (Figures 74-9 and 74-10), and envenomation occurs as toxin is translocated by hydrostatic forces from the surface of the everted and extended tubule through the now helically arranged (Figure 74-11) and extended hollow barbs.[121,122] It has been estimated that the velocity of ejection attains 2 m/sec, which corresponds to an acceleration of 40,000 g, with an estimated skin striking force of 2 to 5 psi.[53] This is one of the most rapid mechanical events found in nature. A human encounter with a large Portuguese man-of-war could conceivably trigger the release of several million stinging cells (Figure 74-12). It has been estimated that more than

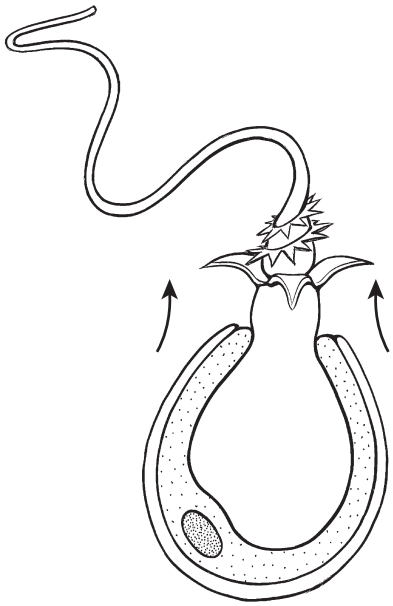


FIGURE 74-8 Nematocyst after discharge.

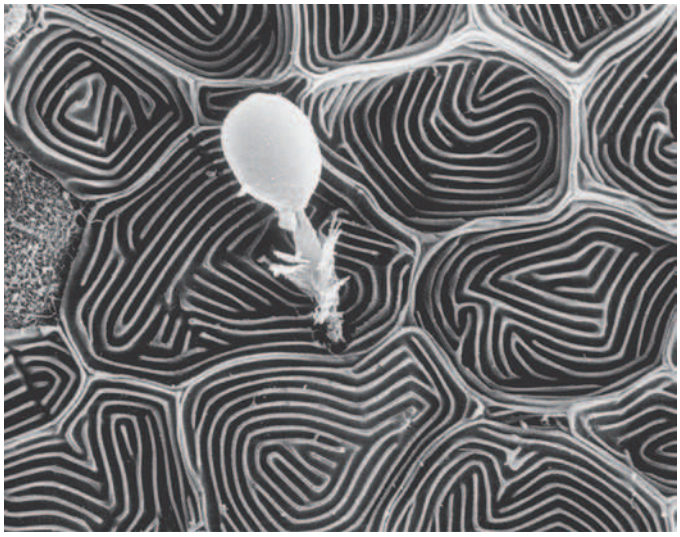


FIGURE 74-9 Discharged nematocyst that penetrated human skin. *(Scanning electron micrograph by Thomas Heeger, MD.)*

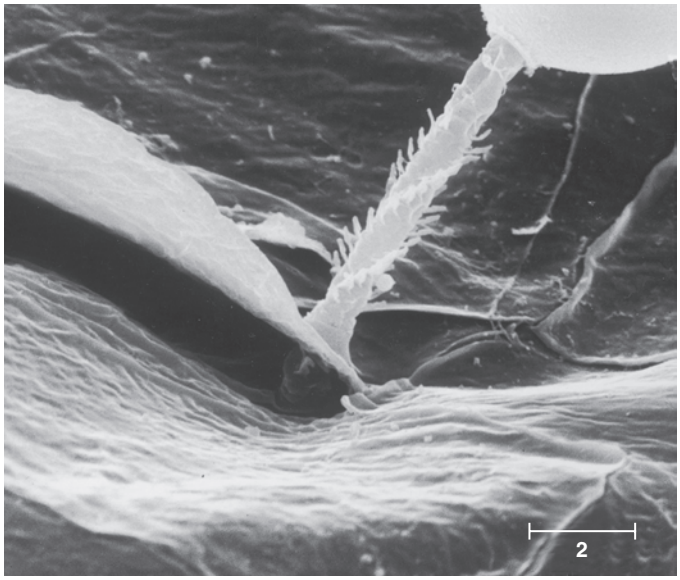


FIGURE 74-10 An everted tubule of a nematocyst from a lion's mane jellyfish *(Cyanea capillata)* has entered the skin and has lifted an epithelial cell. *(Scanning electron micrograph by Thomas Heeger, MD.)*

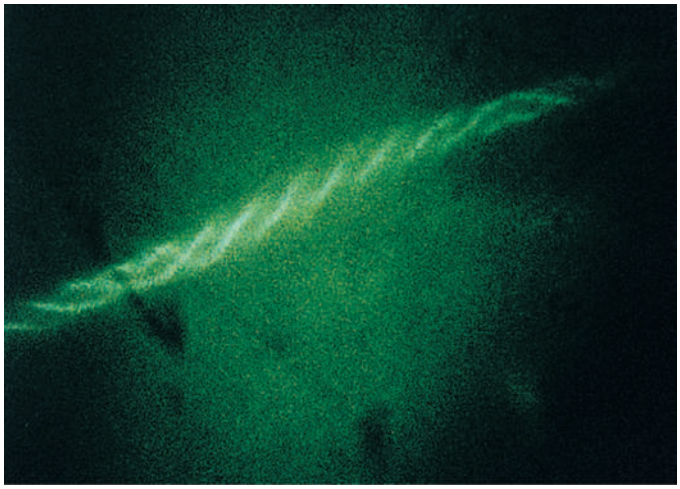


FIGURE 74-11 Helical arrangement of barbs on the tubule of a nematocyst. *(Courtesy Amit Lotan.)*

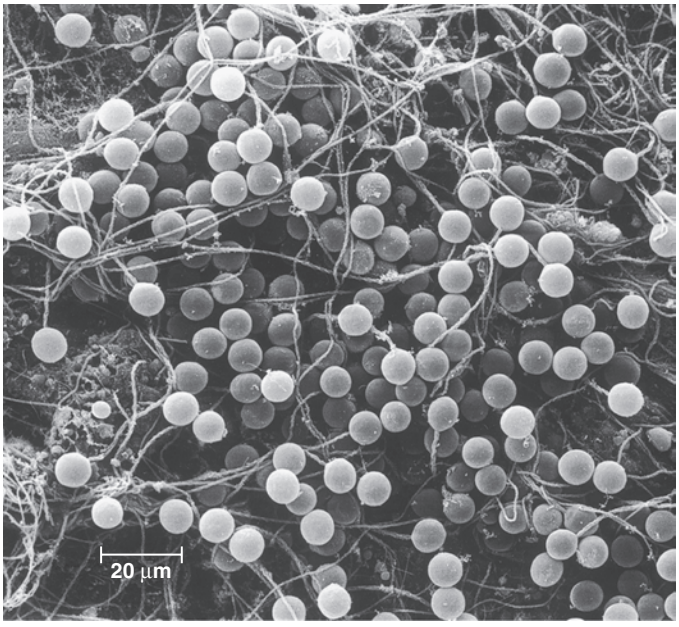


FIGURE 74-12 Nematocysts of a jellyfish (*Versuriga anadyomene*, Philippines), mostly discharged as seen by everted tubules. *(Scanning electron micrograph by Thomas Heeger, MD.)*

2000 sting penetrations can occur within a single square millimeter of skin. The threads penetrate the epidermis and upper dermis, where the venom diffuses into the general circulation. The agitated victim moves about and assists the venom's distribution by the muscle-pump mechanism. On the basis of mouse studies, it appears that the rapid death of a victim is related to the venom that is discharged directly into capillaries, as opposed to that which must diffuse from the dermis into the bloodstream.

In the case of the Indo-Pacific box-jellyfish *C. fleckeri,* which may carry up to 59 tentacles bearing millions of nematocysts, it is the cigar-shaped microbasic p-mastigophores that are most important in human envenomation (Figure 74-13). The capsule of the structure holds a hollow coiled tube and granular matrix. The thread tube has a thick butt end that is attached to the operculum. The tube contains three rows of helically arranged spines. When the nematocyst fires into the human victim, the tube everts through the opercular end of the nematocyst, with the butt anchoring first to keep the nematocyst adherent to the victim. The thread then everts through the hollow butt and uncoils, presenting the spines and accompanying toxins to the living tissue. Although the major toxic fractions appear to be present in the nematocysts, there appears to be toxic material present in tentacles denuded of such organelles.[23] The largest nematocysts of *C. fleckeri* can penetrate human skin to a depth of 0.9 mm.[139]

Cnidarian venoms are viscous mixtures of proteins, carbohydrates, and other nonproteinaceous components. Although they are heat labile in vitro, this does not seem to apply in the clinical setting. To date, they have been difficult to fractionate. The primary difficulties encountered in jellyfish venom purification have been lack of stability and tendency of active toxins to adhere to each other and to support matrices.[156] Lyophilized crude venom can be prepared in water by homogenization, sonication, and rapid freeze-thawing. A second technique consists of grinding samples with a glass mortar and pestle and using phosphate-buffered saline. This has been done to prepare crude venom from isolated nematocysts of the box-jellyfish, the bells of Irukandji jellyfish, and the oral lobes of blubber jellyfish.[227] Analyses of Western blot tests showed that box-jellyfish antivenom reacted specifically with the venom of each jellyfish, but there is not yet any clinical significance to this observation. Because toxicity was found in the Irukandji jellyfish venom derived by the mortar-and-pestle method, but not by the lyophilization method, the former was deemed the more efficacious method. Within box-jellyfish venom are protein components ranging from 18 to more than 106 kDa.

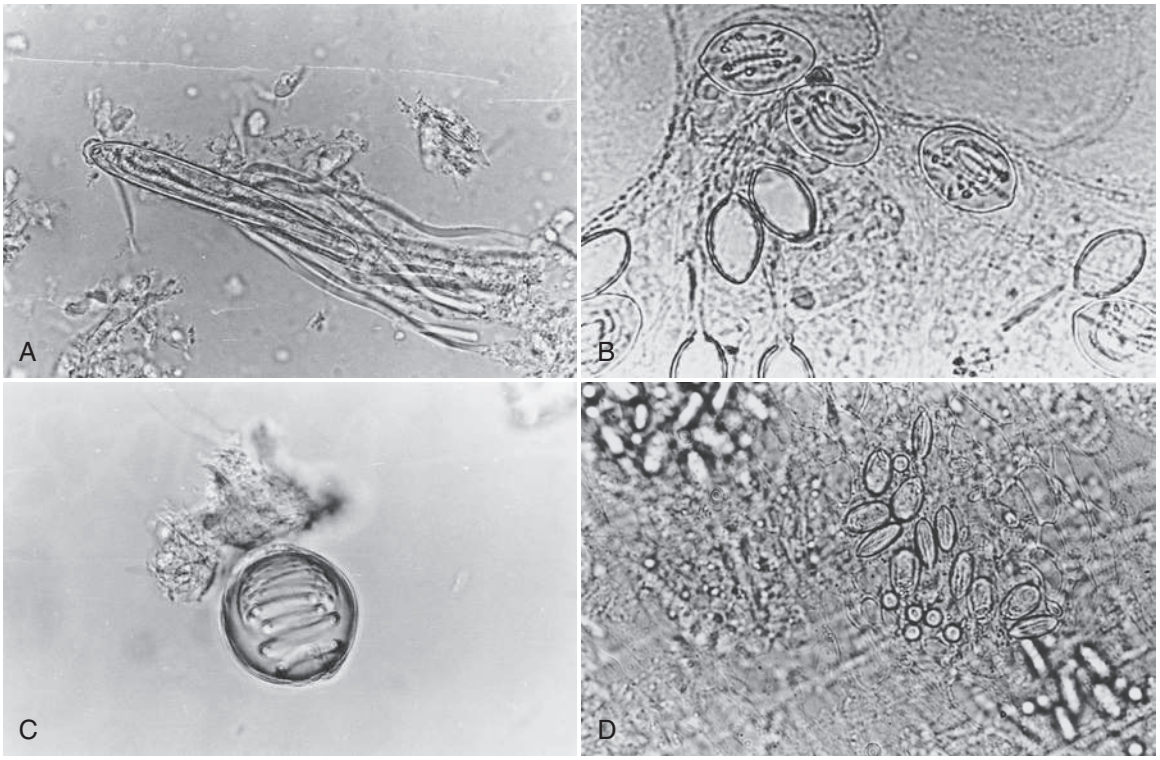


FIGURE 74-13 Nematocyst identification guide. **A,** Microbasic p-mastigophore (undischarged) of *Chironex fleckeri.* Capsule length, 75 µm. **B,** Same (discharged and undischarged) of Irukandji. **C,** Isorhiza (undischarged) of bluebottle *(Physalia physalis).* **D,** Clustered isorhizas and euryteles on tentacle of "hair jelly" *(Cyanea). (Courtesy Bob Hartwick.)*

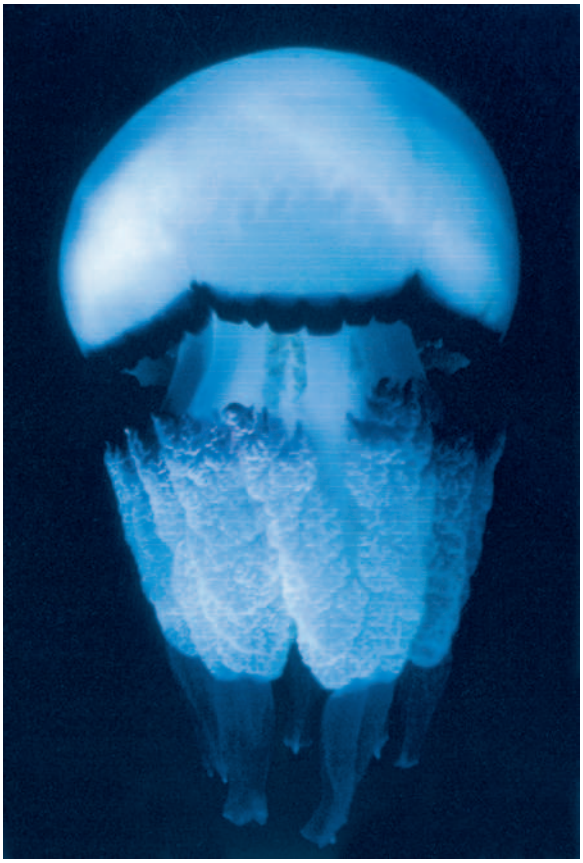


FIGURE 74-14 Rhizostome medusa, *Rhizostoma pulmo* (Mediterranean Sea). *(Courtesy Thomas Heeger, MD.)*

Cytolytic toxins have been characterized from *Physalia physalis, Rhizostoma pulmo* (Figure 74-14), *C. fleckeri,* and *Carybdea marsupialis*. Hemolytic activity, phospholipase A_2, and α-chymotrypsin–like serine protease activity have been noted in the venom of *Rhopilema nomadica*.[80] Many jellyfish and marine animal venoms generate autonomic neurotoxicity.[36] This may be a result of their ability to affect ion transport (sodium and calcium in particular), induce channels or pores in nerve and muscle cell membranes, alter membrane configurations, and release mediators of inflammation. Cnidarian venoms can target the myocardium, Purkinje fibers, atrioventricular node, and aortic ring, as well as injure the hepatic P-450 enzyme family.

Freshwater jellyfish, such as the Appalachian mountain jellyfish *Craspedacusta sowerbyi,* do not appear to pose a hazard to humans.

CNIDARIAN SYNDROME

Clinical Aspects

For clinical purposes, a considerable phylogenetic relationship exists among all stinging species, so that the clinical features of the cnidarian syndrome are fairly constant, with a spectrum of severity. The severity is related to the season and species (venom potency and configuration of the nematocyst), number of nematocysts triggered and size of the animal (venom inoculum), size and age of the victim (the very young and old and the smaller person tend to be more severely affected), location and surface area of the sting, and health of the victim. The wise clinician suspects a cnidarian envenomation in all unexplained cases of collapse in the surf, diving accidents, and near-drownings. Any victim in distress pulled from marine waters should be carefully examined for one or more cutaneous lesions that may provide the clue to a cnidarian envenomation.

Mild envenomation may result in only an annoying dermatitis, whereas severe envenomation can progress rapidly to involve virtually every organ system, resulting in significant rates of morbidity and mortality. Clinical envenomation is described here by severity, with the understanding that there is a fair amount of overlap. In the following paragraphs, syndromes associated with specific classes of creatures are discussed in greater detail.

Mild Envenomation. The stings caused by the hydroids and hydroid corals, along with lesser envenomations by *Physalia, Velella velella* (Figure 74-15), *Drymonema dalmatinum* (stinging cauliflower), *Olindias sambaquiensis* (Figure 74-16) (known as *relojinho* in Portuguese; endemic to the Blanca Bay area south of Buenos Aires province and found on the southeastern Brazilian coast) (Figure 74-17), scyphozoans, and anemones, result predominantly in skin irritation.[82,106] *Nemopilema nomurai (echizen kurage)* is a large stinging jellyfish, with a maximum bell size of 2 m and weight of 200 kg, that blooms in the orient.[98] There is usually an immediate pricking or stinging sensation, accompanied by pruritus, paresthesias, burning, throbbing, and radiation of the pain centrally from the extremities to the groin, abdomen, and axillae. The area involved by the nematocysts becomes red-brown-purple, often in a linear whiplike fashion, corresponding to tentacle prints (Figures 74-18 and 74-19). Other features are blistering, local edema, angioedema, and wheal formation (Figures 74-20 to 74-23), as well as violaceous petechial hemorrhages. Dyspnea due to upper airway obstruction associated with severe facial swelling is possible.[5] The papular inflammatory skin rash is strictly confined to areas of contact and may persist for up to 10 days. Areas of body hair appear to be somewhat more protected from contact than hairless areas. If envenomation is slightly more severe, the aforementioned symptoms, which are evident in the first few hours, can progress over a course of days to local necrosis, skin ulceration, and secondary infection. This is particularly true of stings from certain anemone *(Sagartia, Actinia, Anemonia, Actinodendron,* and *Triactis).* A painless "jellyfish sting," in which there is a pattern of hyperpigmented linear streaks, might represent phytophotodermatitis (e.g., from citrus juice spilled on skin and later exposed to light).[21]

Untreated, the minor to moderate skin disorder resolves over 1 to 2 weeks, with occasional residual hyperpigmentation for 1 to 2 months. Rubbing can cause lichenification. Local hyperhidrosis, fat atrophy, and contracture may occur.[27] Mondor's disease of the breast has been reported following jellyfish stings.[94] Facial swelling with sterile abscess formation has been reported.[201] Permanent scarring or keloids may result. Persistent papules or plaques at the sites of contact may demonstrate a predominantly mononuclear cell inflammatory infiltrate, which may represent a delayed hypersensitivity response to an antigenic component of the cnidarian nematocyst or venom. This may be accompanied by localized arthritis and joint effusion. It has been suggested that sensitization may occur without a definite history of a previous sting, because cnidarians may release antigenic and allergenic venom components into the water. Granuloma annulare, which is usually both a sporadic and familial inflammatory

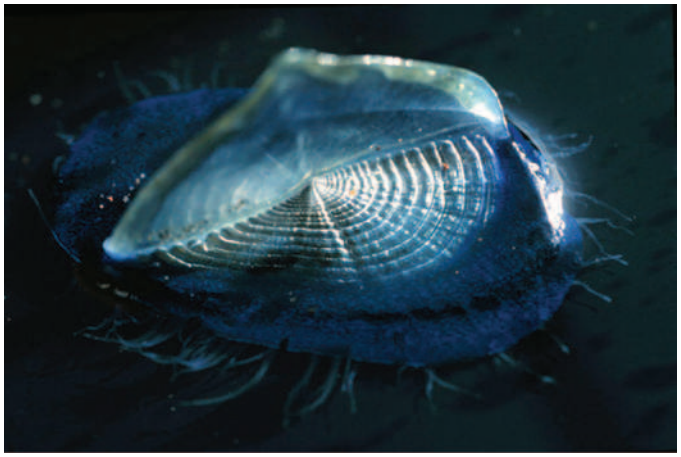


FIGURE 74-15 By-the-wind sailor, *Velella velella. (From Norbert Wu, with permission:* norbertwu.com.*)*

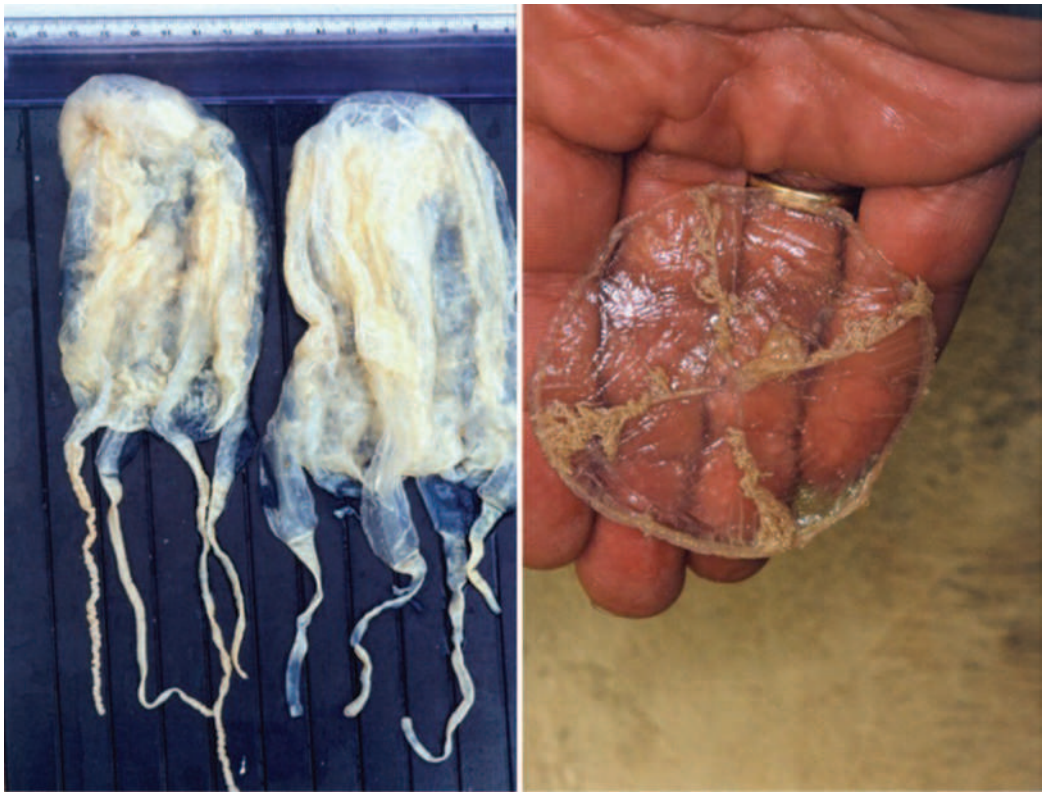


FIGURE 74-16 *Tamoya* and *Olindias* species jellyfishes. *(Courtesy Vidal Haddad, Jr.)*

dermatosis, has been associated with *Physalia utriculus* envenomation.[128] Gangrene has been observed.

Moderate and Severe Envenomation. The prime offenders in this group are the anemones, *Physalia* species, and scyphozoans. The skin manifestations are similar or intensified (as with *Chironex*) and compounded by the onset of systemic symptoms, which may appear immediately or be delayed by several hours:

Neurologic: Malaise, headache, aphonia, diminished touch and temperature sensation, vertigo, ataxia, spastic or flaccid paralysis, mononeuritis multiplex, Guillain-Barré syndrome, parasympathetic dysautonomia, plexopathy, radial-ulnar-median nerve palsies, brainstem infarction (not a confirmed relationship), delirium, loss of consciousness, convulsions, coma, and death[28,39,65,140,160]

Cardiovascular: Anaphylaxis, hemolysis, hypotension, small artery spasm, bradyarrhythmias (including electromechanical dissociation and asystole), tachyarrhythmias, elevated serum troponin I level in the absence of myocardial injury, vascular spasm, deep venous thrombosis, thrombophlebitis, acute myocardial infarction, congestive heart failure, and ventricular fibrillation[87,133,176]

Respiratory: Rhinitis, bronchospasm, laryngeal edema, dyspnea, cyanosis, pulmonary edema, and respiratory failure

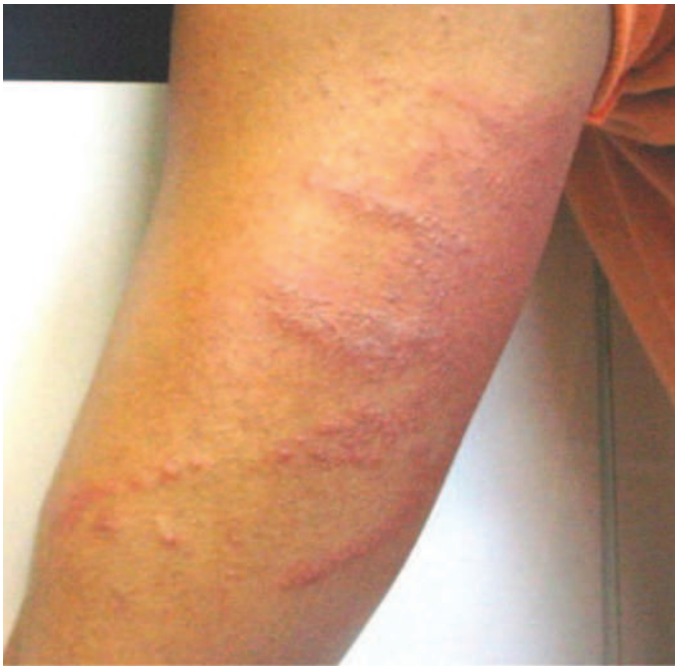


FIGURE 74-17 Skin irritation from sting of *Olindias* species. *(Courtesy Vidal Haddad, Jr.)*

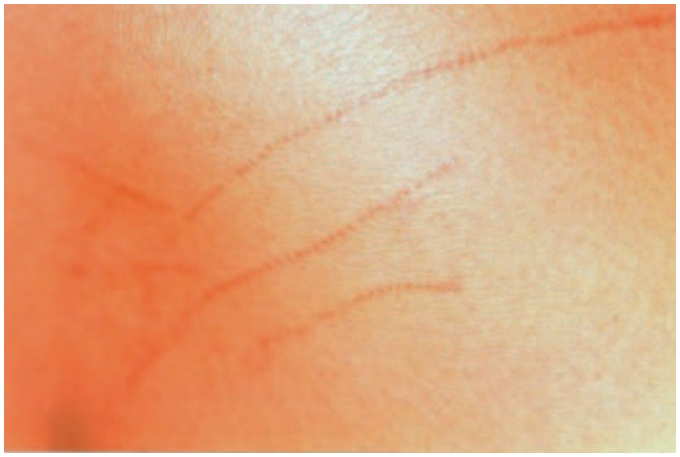


FIGURE 74-18 Telltale *Physalia* species sting pattern. *(Courtesy Vidal Haddad, Jr.)*

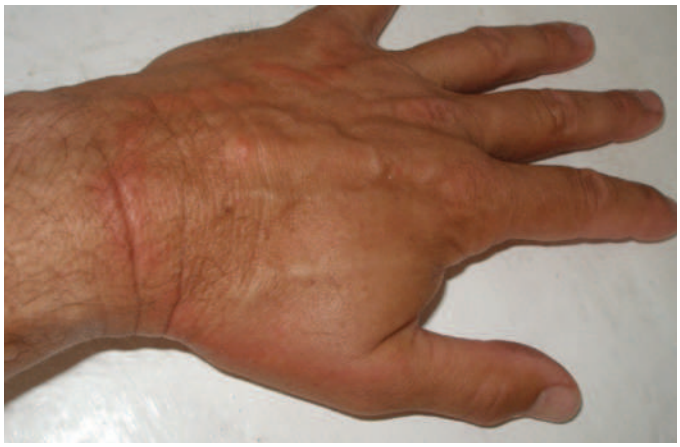


FIGURE 74-19 Man-of-war sting. *(Courtesy Paul S. Auerbach, MD.)*

Musculoskeletal or rheumatologic: Abdominal rigidity, diffuse myalgia and muscle cramps, muscle spasm, fat atrophy, arthralgias, reactive arthritis (seronegative symmetric synovitis with pitting edema),[217] and thoracolumbar pain

Gastrointestinal: Nausea, vomiting, diarrhea, paralytic ileus,[163] dysphagia, hypersalivation, and thirst

Ocular: Conjunctivitis, chemosis, corneal ulcers, corneal epithelial edema, keratitis, iridocyclitis, elevated intraocular pressure, synechiae, iris depigmentation, chronic unilateral glaucoma, and lacrimation[75,76,229]

Other: Acute renal failure, lymphadenopathy, chills, fever, and nightmares

The extreme example of envenomation occurs with *C. fleckeri,* the dreaded box-jellyfish. *Physalia* and anemone stings, although extremely painful, are rarely fatal. Death after *Physalia* stings has been attributed to primary respiratory failure or cardiac arrhythmia, which may have reflected an element of anaphylaxis.[32,194] Confirmed deaths after cnidaria envenomation have been attributed to *C. fleckeri, Chiropsalmus quadrigatus,* and *Chiropsalmus quadrumanus* (Figure 74-24).[139] *Stomolophus nomurai* (the sand jellyfish) has caused at least eight deaths in the South China Sea.[56] Although there have been other deaths, the animals have not been definitively identified.

Clinical reports and studies on the serologic response to jellyfish envenomation suggest that allergic reactions may play a significant pathophysiologic role in humans. When crude or partially purified nematocyst venom and an antigen are used in an enzyme-linked immunosorbent assay (ELISA), both IgG and IgE can be detected.[74,174] Elevated specific anti–jellyfish IgG and IgE may persist for several years, recurrence of the clinical cutaneous reaction to jellyfish stings may occur within a few weeks

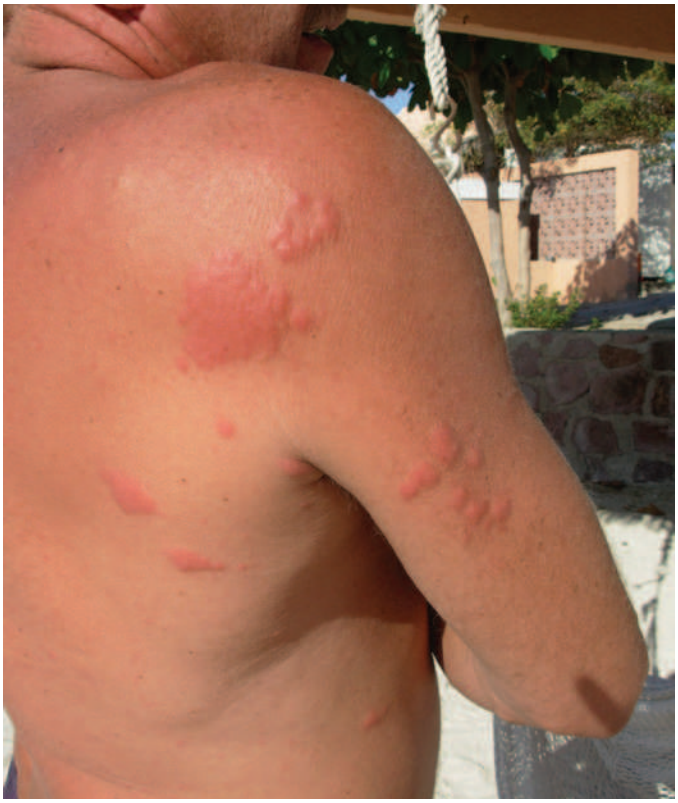


FIGURE 74-21 Jellyfish sting. *(Courtesy Paul S. Auerbach, MD.)*

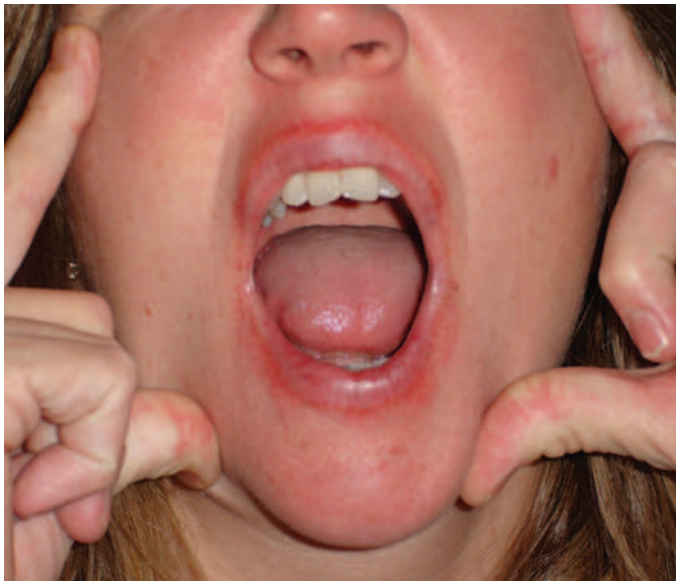


FIGURE 74-20 Jellyfish sting around the lips.

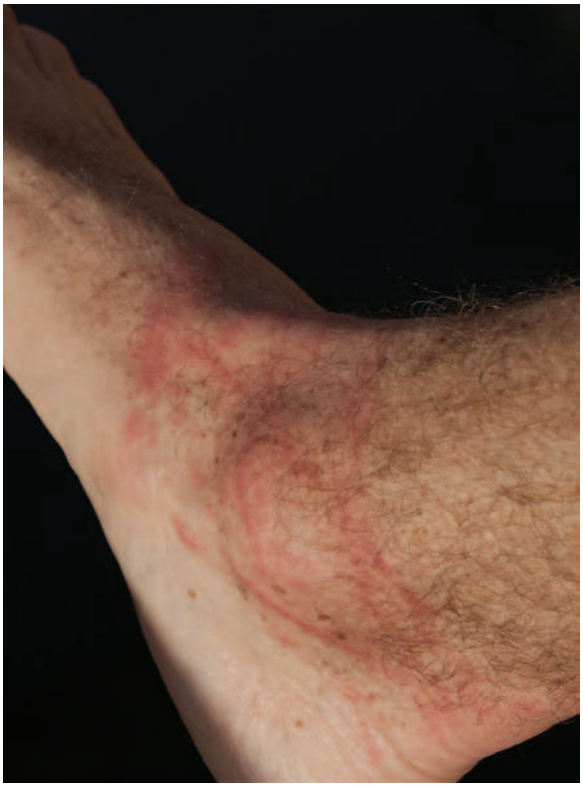


FIGURE 74-22 Jellyfish sting of the ankle. *(Copyright Stephen Frink.)*

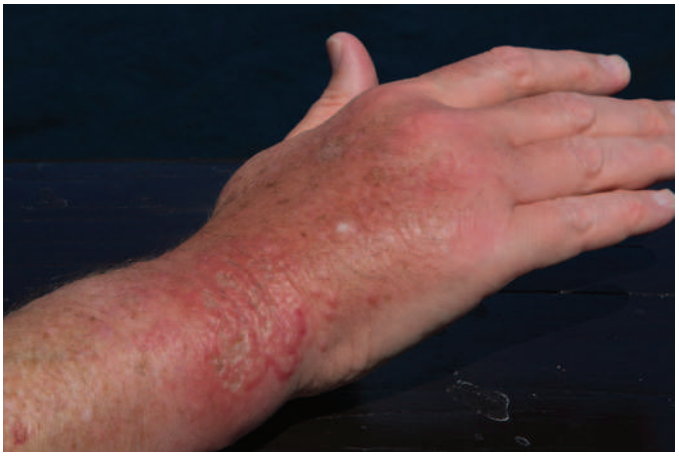


FIGURE 74-23 Severe jellyfish sting of the wrist. *(Copyright Stephen Frink.)*

without additional contact with the tentacles, and serologic cross-reactivity occurs between the sea nettle *(Chrysaora quinquecirrha)* and *P. physalis*. In a case of significant envenomation by the moon jellyfish *Aurelia aurita* (Figure 74-25), the victim developed significant cross-reacting antibodies to *C. quinquecirrha* antigens.[31]

Persons with extracutaneous or anaphylactoid responses to a cnidarian sting have been noted to have higher specific IgG and IgE antibody levels.[174] However, elevated persistent specific anti–jellyfish serum IgG concentrations are not protective against the cutaneous pain resulting from a natural sting.[30] A false-positive ELISA serologic test to venom may occur, as demonstrated by negative skin testing.

A person stung by *P. physalis* may have recurrent cutaneous eruptions for 2 to 3 weeks after the initial episode, without repeated exposure to the animal. This may take the forms of lichenification, hyperhidrosis, angioedema, vesicles, large bullae, nodules that resemble erythema nodosum, granuloma annulare, or a more classic linear urticarial eruption.[8,29,129] Recurrent eruptions have also followed a solitary envenomation by the cnidarian *Stomolophus meleagris*.[26] In a histologic study of delayed reaction to a Mediterranean Sea cnidarian, skin biopsy demonstrated grouping of human leukocyte antigen–DR-positive cells with Langerhans cells and helper/inducer T lymphocytes, which indicates the possibility of a type IV immunoreaction.[162]

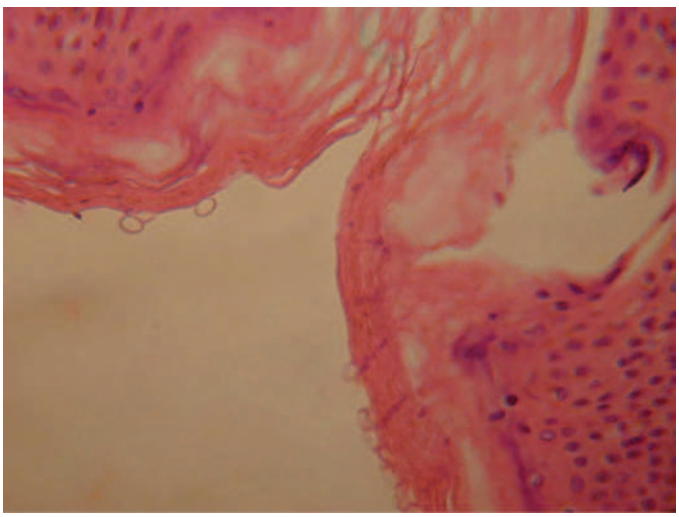


FIGURE 74-24 Skin biopsy from a child after fatal sting from *Chironex fleckeri*. Nematocysts are seen on the skin. *(Courtesy Jamie Seymour, MD.)*

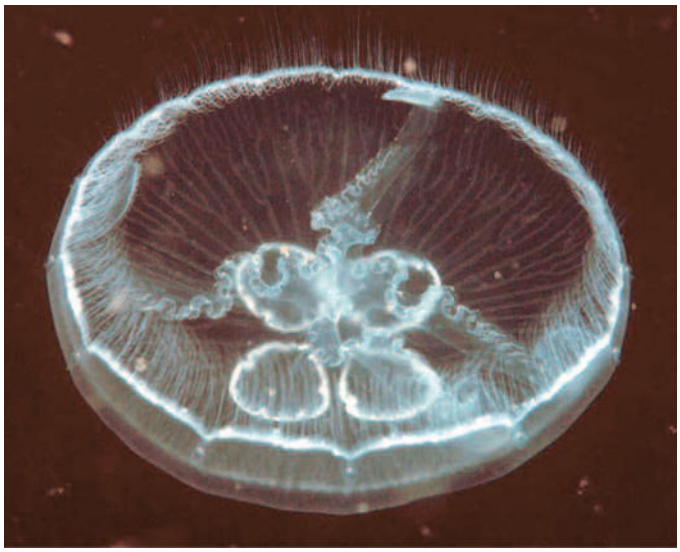


FIGURE 74-25 Moon jellyfish, *Aurelia aurita*. *(From Norbert Wu, with permission:* norbertwu.com.*)*

Venom-specific IgG antibodies appear to persist for longer periods than IgM antibodies. The binding of brown recluse spider venom and purified cholera toxin to anti-*Chrysaora* and anti-*Physalia* monoclonal antibodies indicates that there may be a common or cross-reacting antigenic site or sites between these toxic substances and certain cnidarian venoms.[154]

Acute regional vascular insufficiency of the upper extremity has been reported after jellyfish envenomation. It can be manifested by acral ischemia, signs and symptoms of compartment syndrome, and massive edema.[222]

Treatment

Therapy is directed at stabilizing major systemic decompensation, opposing the venom's multiple effects, and alleviating pain. The following is a generalized overview; treatment related to the specific class of organism is discussed in detail in later paragraphs.

Systemic Envenomation. Generally, only severe *Physalia* or Cubomedusae stings result in rapid decompensation. In both cases, supportive care is based on the signs and symptoms. Hypotension should be managed with prompt IV administration of crystalloid, such as lactated Ringer's solution or normal saline. This must be done in concert with detoxification of any nematocysts (particularly those of *Chironex* or *Chiropsalmus*) that are still attached to the victim, to limit perpetuation of envenomation. Hypotension is usually limited to very young or older adult victims who suffer severe and multiple stings, the effects of which are worsened by fluid depletion that accompanies protracted vomiting. Hypertension is an occasional side effect of a cubomedusan envenomation, such as that of the Irukandji *Carukia barnesi*. Excessive catecholamine stimulation is one putative cause, which has prompted clinical intervention with benzodiazepines, magnesium, and phentolamine, an α-adrenergic blocking agent (5 mg intravenously as an initial dose, followed by an infusion of up to 10 mg/hr). Bronchospasm may be managed as an allergic component. If the victim is in respiratory distress with wheezing, shortness of breath, or heart failure, supplemental oxygen administration will be necessary by face mask or a continuous positive airway pressure/bilevel positive airway pressure (CPAP/BiPAP) circuit. Arterial blood gas measurement may be used to guide oxygen therapy. Seizures are generally self-limited but should be managed with IV diazepam for 24 to 48 hours, after which time they rarely recur.

Any victim with a systemic component should be observed for a period of at least 6 to 8 hours, because rebound phenomena after successful treatment are not uncommon. All older adult victims should undergo electrocardiography and be observed on

a cardiac monitor, with frequent checks for arrhythmias. Urinalysis demonstrates the presence or absence of hemoglobinuria, indicating hemolysis after the putative attachment of *Physalia* venom to red blood cell membrane glycoprotein sites.[79] If this is the case, the victim's urine should be alkalinized with bicarbonate to prevent precipitation of pigment in the renal tubules, while moderate diuresis (30 to 50 mL/hr) is maintained with a loop diuretic (such as furosemide or bumetanide) or mannitol (0.25 g/kg intravenously every 8 to 12 hours). In rare instances of acute progressive renal failure, peritoneal dialysis or hemodialysis may be necessary.

If there are signs of distal ischemia or an impending compartment syndrome, standard diagnostic and therapeutic measures apply. These include Doppler ultrasound or angiography, or both, for diagnosis; regional thrombolysis for acutely occluded blood vessels; measurement of intracompartmental tissue pressures to guide fasciotomy; and so forth. Reversible regional sympathetic blockade may be efficacious if vasospasm is a dominant clinical feature. However, vasospasm associated with a jellyfish envenomation may be severe, prolonged, and refractory to regional sympathectomy and intraarterial reserpine or pentoxifylline.[1]

A small child may pick up tentacle fragments on the beach and place them into his or her mouth, resulting in rapid intraoral swelling and potential airway obstruction, particularly in the presence of exceptional hypersensitivity. In such cases, an endotracheal tube should be placed before edema precludes visualization of the vocal cords. In no case should any liquid be placed in the mouth if the airway is not protected. In 1999, a lifeguard in Cairns, Australia, drank from a container containing 4-day-old *C. fleckeri* tentacles. He fortunately suffered only a sore throat and transient shortness of breath.

C. fleckeri, the box-jellyfish, produces the only cnidarian venom for which a specific antidote exists (see below). To date, the venoms of *Physalia* and *Chrysaora* species have not been sufficiently purified as antigens to permit the production of an antitoxin. Antivenom administration should accompany the first-aid protocol previously described.

Pain Control. Often, mild pain can be controlled by treating the dermatitis. However, if pain is severe and there is no contraindication (such as head injury, altered mental status, respiratory depression, allergy, or profound hypotension), administration of a narcotic (fentanyl 50 to 100 mcg intravenously; morphine sulfate 2 to 10 mg intravenously; hydromorphone 1 to 2 mg intravenously) will be appreciated by the victim. Severe muscle spasm has been empirically noted to respond to 10% calcium gluconate (5 to 10 mL intravenously by slow push), diazepam (5 to 10 mg intravenously), or methocarbamol (1 g, no faster than 100 mg/min through a widely patent IV line).

Treatment of Dermatitis. If a person is stung by a cnidarian, the following steps should be taken:

Immediately rinse the wound with seawater, not with freshwater. Do not rub the wound with a towel or with clothing to remove adherent tentacles. Nonforceful rinsing with fresh water or a rubbing variety of abrasion (the latter in the absence of simultaneous application of a decontaminant such as papain or vinegar) is felt to stimulate any nematocysts that have not already fired. Surf lifesavers (lifeguards) in the United States and Hawaii have reported that a hot shower applied with a forceful stream may decrease the pain of an envenomation. If this is successful, theoretical explanations are that the mechanical effect of the water stream (which dislodges tentacle fragments and stinging cells) supersedes the deleterious (sting-stimulating) effect of the hypotonic water, or that the heat has a beneficial effect. Remove any gross tentacles with a forceps or a well-gloved hand. In an emergency, the keratinized palm of the hand can be used because it is relatively protected, but care must be taken to avoid becoming envenomed.

Acetic acid 5% (vinegar) is the treatment of choice to inactivate *C. fleckeri* toxin. Vinegar does not always alleviate the pain from a *Chironex* sting, but it interrupts the envenomation. It may not be extremely effective against *Chrysaora* or *Cyanea*. The detoxicant should be applied continuously for at least 30 minutes or until the pain is relieved. Then the tentacles should be removed. A sting from the Australian *P. physalis,* a relatively recently differentiated species, should not be doused with vinegar, because this may cause discharge of up to 30% of nematocysts.[63]

For stings from other species, there are substances that may be more specific and therefore more effective (see below). Alternatively, nonspecific substances may be effective. Depending on the species, the most popular remedies include lidocaine (4% to 15%), isopropyl alcohol (40% to 70%), dilute ammonium hydroxide (which may prove to be caustic), sodium bicarbonate (particularly for stings of the sea nettle *C. quinquecirrha*), olive oil, sugar, urine, and papain (papaya latex [juice] or unseasoned meat tenderizer [powdered or in solution]). The last is supposed to work by cleaving active polypeptides into nontoxic amino acids. Lime or lemon juice has been observed on occasion to be effective. Ammonia has been noted to be relatively ineffective for stings of *Carybdea marsupialis* in the Adriatic Sea.[159] There is some evidence that alcohol may stimulate the discharge of nematocysts in vitro; the clinical significance is as yet undetermined. The rescuer must remember that pain relief may not equate with nematocyst inhibition.[139] A commercial aqueous solution of aluminum sulfate (20%) and 1.1% anionic surfactant in aqueous solution (Stingose) has been mentioned in the past as effective on the basis that the aluminum ion interacts with proteins and long-chain polysaccharide components to denature and inactivate venom. Prior treatment with topical alcohol or methylated spirits reduces effectiveness of the aluminum sulfate solution. This product has essentially fallen out of favor with clinician jellyfish experts in Australia.

Perfume, aftershave lotion, and high-proof liquor are not particularly efficacious and may be detrimental. Other substances mentioned to be effective at one time or another, but that are to be condemned on the basis of inefficacy and toxicity, are organic solvents such as formalin, ether, and gasoline. Household ammonia has been recommended, but may be caustic.

Immersing the area in hot water is increasingly recommended, despite the premise that a hypotonic solution is felt to cause nematocysts to discharge. One study compared hot (40° to 41°C [104° to 105.8°F]) water immersion to papain meat tenderizer or vinegar for treatment of a single-tentacle *Carybdea alata* (Hawaiian box-jellyfish; also known as *Alatina alata*) sting to the forearm, and the hot water immersion was found to be the most efficacious.[150] In a crayfish model of envenomation, exposure to heat reduced the lethality of extracted *C. fleckeri* venom.[38] At temperatures of 43°C (109.4°F) and greater, venom lost its lethality more rapidly the longer the exposure time. Because of the speed of onset of symptoms after *C. fleckeri* envenomation, this approach may be of limited clinical usefulness, and until human clinical confirmation against other species is obtained, hot water application should not automatically be extrapolated to other species.

Once the wound has been soaked with a decontaminant (e.g., vinegar), remaining (and often essentially invisible) nematocysts must be removed. The easiest way to do this is to apply shaving cream or a paste of baking soda, flour, or talc and to shave the area with a razor or similar tool. If sophisticated facilities are not available, the nematocysts should be removed by making a sand or mud paste with seawater and using this to help scrape the victim's skin with a sharp-edged shell or piece of wood. The rescuer must take care not to become envenomed; bare hands must be rinsed frequently. If a scrub brush or pad has been used to treat the envenomation, this step may not result in much, if any, clinical improvement.

No systemic drugs (other than antivenom for a *Chironex* envenomation) are of verifiable use. Ephedrine, atropine, calcium, methysergide, and hydrocortisone have all been touted at one time or another, but no proof exists that they help. Antihistamines may be useful if there is a significant allergic component. Administration of epinephrine is appropriate only in the setting of anaphylaxis.

It is not recommended to use the pressure-immobilization technique for venom containment because this may discharge more nematocysts. A venolymphatic proximal (to the injury) occlusive tourniquet should be considered only if a topical detoxicant is unavailable, the victim suffers from a severe systemic reaction, and transport to definitive care is delayed.

A topical anesthetic ointment (lidocaine 2.5%) or spray (benzocaine 14%), antihistaminic cream (diphenhydramine or tripelennamine), or mild steroid lotion (hydrocortisone 1%) may be soothing. These are used after the toxin is inactivated. Paradoxic reactions to benzocaine are rarely noted.

Victims should receive standard antitetanus prophylaxis.

Prophylactic antibiotics are not automatically indicated. Each wound should be checked at 3 and 7 days after injury for infection. Any ulcerating lesion should be cleaned three times a day and covered with a thin layer of nonsensitizing antiseptic ointment, such as mupirocin. A jellyfish sting to the cornea may cause a foreign body sensation, photophobia, and decreased or hazy vision. Ophthalmologic examination reveals hyperemic sclera, chemosis, and irregularity of the corneal epithelium with stromal edema. Depending on the extent of the wound, the anterior chamber may demonstrate the inflammatory response of iridocyclitis (flare with or without cells).[233] The victim should be referred to an ophthalmologist, who may prescribe steroid-containing eye medications, such as prednisolone acetate 1% with hyoscine 0.25%. Applying a traditional skin detoxicant directly to the cornea is not recommended, because it is likely to worsen the tissue injury. Cycloplegia achieved with topical cyclopentolate (0.5% to 1%) may prove useful to achieve pain relief.[229]

It is worth commenting on the perpetual discussions about the efficacy of topical decontaminants. It has been observed that certain substances that have been used to diminish the pain of a jellyfish sting, such as isopropyl alcohol, when tested in vitro (e.g., with tentacle preparations) may cause the nematocysts that reside on the tentacles of a jellyfish to discharge their contents. These observations have provoked some persons to advise against the use of the substances as remedies for jellyfish stings, sometimes stating that it would be dangerous to use them. However, what is observed under the microscope does not always match up with the observed beneficial clinical effect. Clearly, more research needs to be done to determine which decontaminants are clinically beneficial and which are detrimental, and the meaning of the various forms and activities of nematocysts under different conditions, including exposure to topical first-aid remedies.

Delayed Reaction. A delayed reaction, similar in appearance to erythema nodosum, may be noted in areas of skin contact and may be accompanied by fever, weakness, arthralgias, painful joint swelling, and effusions. This may recur multiple times over the course of 1 to 2 months. The treatment is a 10- to 14-day tapered course of prednisone, starting with 50 to 100 mg. Prednisone administration may need to be prolonged or repeated with each flare of the reaction.

Persistent Hyperpigmentation. Postinflammatory hyperpigmentation is common after the stings of many jellyfish and other lesser cnidarians. A solution of 1.8% hydroquinone in a glycol and alcohol base (70% ethyl alcohol and propylene glycol mixed at a 3:2 ratio), twice a day as a topical agent for 3 to 5 weeks, has been used successfully to treat hyperpigmentation after a *Pelagia noctiluca* sting.

Persistent Cutaneous Hypersensitivity. Persistent local dermal hypersensitivity may occur after a jellyfish sting, such as that from the Hawaiian box-jellyfish *C. alata*.[203] This is characterized by erythematous papulonodular lesions in the pattern of the original sting, which may persist for months. Treatment, which may be unsatisfactory, consists of topical and intralesional steroids.

Prevention

A topical jellyfish sting inhibitor has been commercialized. Safe Sea ("jellyfish-safe sunblock") by Nidaria Technology, Ltd, Zemah, Jordan Valley, Israel (nidaria.com) was compared in a blinded fashion with conventional sunscreen for protection against *Chrysaora fuscescens* (sea nettle) and *Chiropsalmus quadrumanus* jellyfish. Subjects were stung with jellyfish tentacles on each forearm for up to 60 seconds, and erythema and pain were assessed at 15-minute intervals over a 2-hour period. The jellyfish sting inhibitor prevented sting symptoms of *C. fuscescens* in 10 of 12 subjects and diminished the pain of the jellyfish sting in the remaining two subjects.[103] It was equally impressive with *C. quadrumanus*. Another author performed a double-blind, randomized, placebo-controlled field trial using Safe Sea in an ocean setting, with participants snorkeling in the Gulf of Mexico and Caribbean. This study showed a relative risk reduction of 82% when Safe Sea was used to prevent jellyfish stings as compared with placebo (sunscreen), where notable common species encountered were *C. quinquecirrha* (sea nettle), *C. quadrumanus*, and *Linuche unguiculata* (thimble jellyfish).[19] The inhibitor is formulated to inactivate jellyfish stinging in several ways: (1) it is hydrophobic and thus prevents tentacles from making sufficient skin contact to induce a sting; (2) glycosaminoglycans in the inhibitor mimic the same compounds found in the jellyfish bell, thus causing self-recognition; (3) the inhibitor contains a competitive antagonist to nonselective receptors on the jellyfish that bind to amino acids and sugar secretions from prey; and (4) calcium and magnesium within the inhibitor block transmembrane signaling channels of the jellyfish, thereby altering the osmotic forces required to generate the firing pressure within the nematocyst capsule[103] The product has not yet been tested prospectively against *Physalia, Carukia,* or *Chironex* species.

Derma Shield is a topical formulation that contains lanolin, aloe vera, and vitamin E. According to the manufacturer, this chemically inert (1-vinyl-2-pyrrolidione) barrier protectant is hydrophobic (dimethicone and stearic acid) and does not wash off but is shed as the epithelium sloughs naturally. It has been reported anecdotally by ocean bathers to protect against the agents of seabather's eruption.

Smerbeck and coworkers were assigned a U.S. patent in 1999 for a method and composition of polymeric quaternary ammonium salts for protecting the skin from jellyfish stings.

A protocol has been developed to establish the effectiveness of topical agents to block the firing of nematocysts.[35] Unreliable topical barriers include petrolatum, mineral oil, silicone ointment, cocoa butter, and mechanic's grease.

If jellyfish are sighted, they should be given a wide berth because the tentacles may trail great distances from the body. All swimmers and divers in hazardous areas should be on constant alert. Persons should not dive headfirst into jellyfish-infested waters; it is far safer to walk in. Bathers should wear protective clothing in infested areas. This includes Lycra stinger suits or a double thickness of pantyhose. In hot weather, it is possible to cause human heat storage while stinger suits are being worn during beach activities, so one should be cognizant of the potential for heat-related illness when out of the water.[190] If stinger enclosures are present, bathers should stay within the netted barriers, although it should be noted that the small (2-cm) Irukandji jellyfish will pass with ease through the mesh of a stinger net. Many bathers suffering from Irukandji envenomations in northern Queensland, Australia, were swimming in a stinger enclosure at the time of their envenomation.

Divers concerned about jellyfish tentacles dangling from the surface or congregations of creatures at the surface should remain deeper than 20 feet and should always check snorkel and regulator mouthpieces for tentacle fragments before entering the water in endemic areas. In areas inhabited by anemones and hydroid corals, protective gloves should be worn when handling specimens. Beached dead jellyfish or tentacle fragments washed up after a storm can still inflict serious stings. Any person stung by a jellyfish should leave or be assisted from the water because of the risk of drowning.

CLASS HYDROZOA

The hydrozoans range in configuration from the feather hydroids and sedentary *Millepora* hydroid coral to the free-floating siphonophore *Physalia* (Portuguese man-of-war).

Hydroids

Hydroids are the most numerous of the hydrozoans. The feather hydroids of the order Leptomedusae, typified by *Lytocarpus philippinus* (fire weed or fire fern), are feather-like or plumelike (Figure 74-26) animals that sting the victim who brushes against or handles them.[169] After a storm, the branches may be fragmented and dispersed through the water, so that merely diving

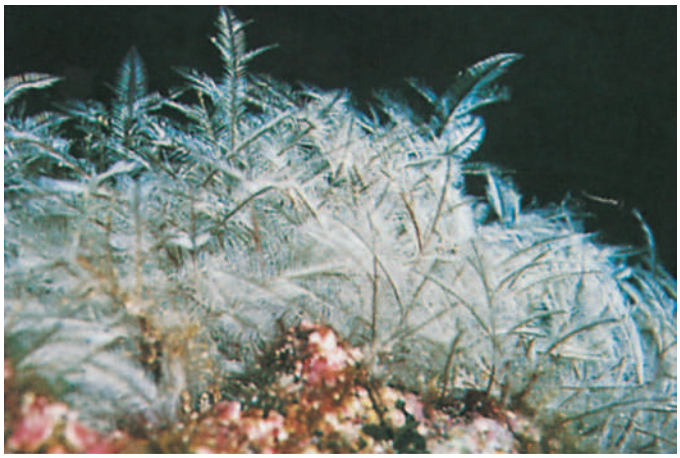


FIGURE 74-26 Cnidarian hydroid. *(Courtesy Paul S. Auerbach, MD.)*

or swimming in the vicinity causes itching and may induce visible skin irritation.

Clinical Aspects. Contact with the nematocysts of a feather hydroid induces a mild reaction, which consists of instantaneous burning, itching, and urticaria. If the exposure is brief, the skin rash may not be noticeable or may consist of a faint erythematous and miliary irritation (Figure 74-27). A second variety of envenomation consists of a delayed papular, hemorrhagic, or zosteriform reaction (Figure 74-28) with onset 4 to 12 hours after contact. Rarely, erythema multiforme or a desquamative eruption may develop. In turbulent waters or in a strong current, fragments may be washed into a diver's mask or regulator mouthpiece; this will be evident as a burning sensation in the conjunctivae or oral mucous membranes. Systemic manifestations (such as abdominal pain, nausea, vomiting, diarrhea, muscle cramps, and fever) are rarely reported and are associated with large areas of surface involvement. Allergic sensitization and subsequent anaphylaxis have been proposed.

Treatment. The skin should be rinsed with seawater and gently dried without abrasive activity. Application of freshwater and brisk rubbing are strictly prohibited because they encourage any nematocysts remaining on the skin to discharge and thus worsen envenomation. An application of 5% acetic acid (vinegar) or isopropyl alcohol (40% to 70%) to the skin for 15 to 30 minutes has traditionally been recommended to relieve the cutaneous reaction. In an in vitro evaluation, vinegar and urine caused discharge of a few nematocysts in 10% to 15% of defensive tentacle polyps; methylated spirits were found to cause gross discharge of microbasic mastigophores in all defensive polyps.[169] Fresh water did not cause discharge. On the basis of this study, the authors recommended that irrigation with fresh water and

FIGURE 74-27 Hydroid sting on the arm of a diver. *(Courtesy Neville Coleman.)*

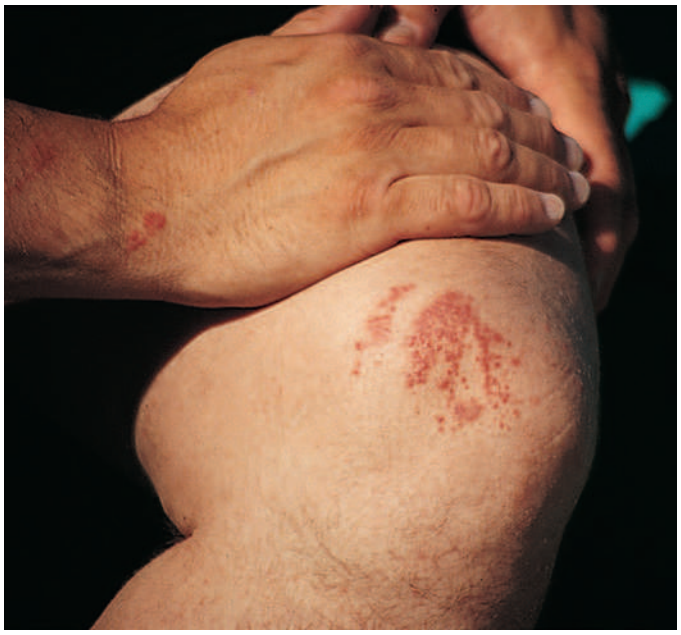


FIGURE 74-28 Fernlike hydroid print on the knee of a diver. *(Courtesy Paul S. Auerbach, MD.)*

the application of ice be used to treat acute stings. However, the clinical correlation remains to be described.

Alternative topical agents are addressed in the larger discussion on therapy for cnidarian stings. After pain relief is achieved, a mild steroid cream (hydrocortisone 1%) or moisturizing lotion may be applied.

Fire Coral

The stony, hydroid, and coral-like *Millepora* species (e.g., *Millepora alcicornis*), or fire corals, are not true corals. They are widely distributed in shallow tropical waters. Sessile creatures, they are found attached to the bottom in depths of up to 1000 m (3281 feet). They are often mistaken for seaweed because they attach to pilings, rocks, shells, or coral. Although smaller segments resemble Christmas trees or bushes 7.6 to 10.2 cm (3 to 4 inches) in height, they may attain heights of 2 m (6.6 feet). The color ranges from white to yellow-green, with pale yellow (Figure 74-29) most common. Rare purple fire corals exist. Fire coral is structured on a razor-sharp calcium carbonate (calcic limestone) exoskeleton, which is an important component in the development of coral reefs. The outcroppings assume upright, clavate, blade-like, honeycomb, or branching calcareous growth

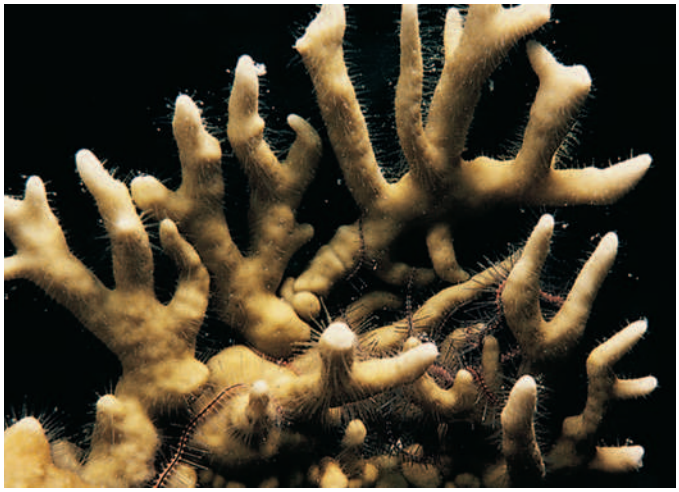


FIGURE 74-29 Fire coral. *(Courtesy Paul S. Auerbach, MD.)*

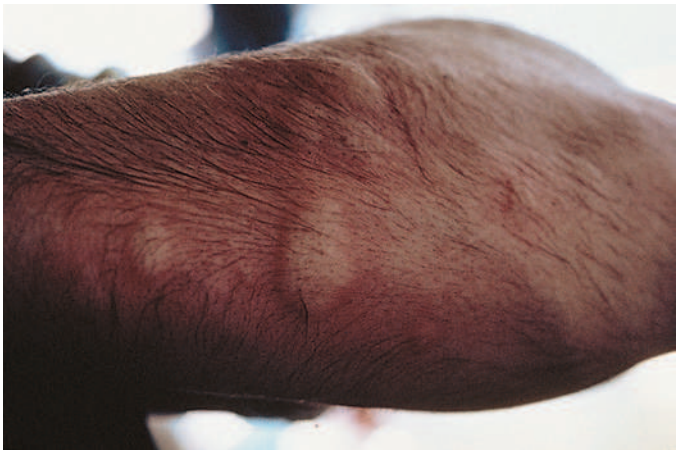


FIGURE 74-30 Fire coral sting of the author. *(Courtesy Kenneth Kizer, MD.)*

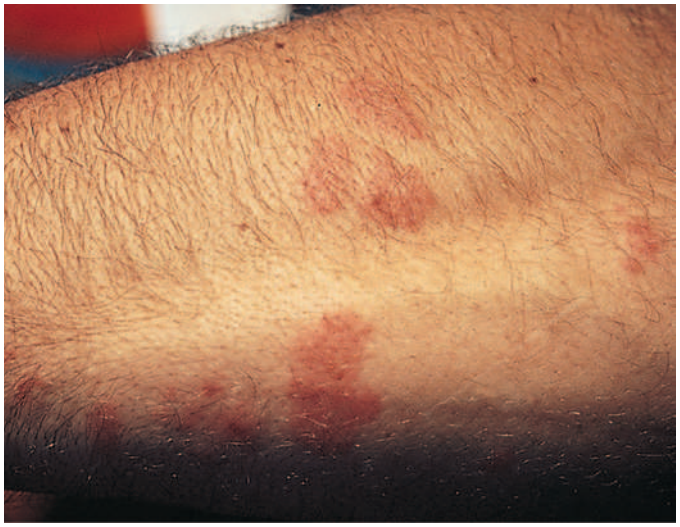


FIGURE 74-31 Hyperpigmentation of forearm depicted in Figure 74-24 after a fire coral sting. *(Courtesy Kenneth Kizer, MD.)*

structures that form encrustations over coral and objects such as sunken vessels. From numerous minute surface gastropores protrude tiny nematocyst-bearing tentacles, wherein lies the stinging apparatus. *M. alcicornis* probably accounts for more cnidarian envenomations than any other species. Unprotected and unwary recreational scuba enthusiasts handle, kneel on, or lean on this marine stinger.

Clinical Aspects. Immediately after contact with fire coral, the victim suffers burning or stinging pain, rarely with central radiation. Intense and painful pruritus follows within seconds, which frequently induces the victim to rub the affected area vigorously, worsening the envenomation. Over the course of 5 to 30 minutes, urticarial wheals develop, marked by redness, warmth, and pruritus (Figure 74-30). The wheals become moderately edematous and reach a maximal size in 30 to 60 minutes. Untreated, they flatten over 14 to 24 hours and resolve entirely over 3 to 7 days, occasionally leaving an area of hyperpigmentation (Figure 74-31) that may require 4 to 8 weeks to disappear. The pain generally resolves without treatment in 30 to 90 minutes.

A hemorrhagic or ulcerative lesion(s) may occur acutely. In the case of multiple stings, regional lymph nodes may become inflamed and painful. This does not necessarily indicate a secondary infection. The skin may take on the appearance of leukocytoclastic vasculitis.[157] Long thoracic mononeuritis with serratus anterior muscle paralysis has been described after *Millepora* sting, confirmed by demonstrated presence of immune-specific IgG.[142] Delayed skin reaction after Red Sea fire coral injury was characterized by superficial granulomas and atypical CD30+ lymphocytes (Figure 74-32).[141] In another series, contact with fire coral resulted in a typical pruritic urticarial lesion and blister formation, followed by a lichenoid stage that developed 3 weeks after the initial injury; resolution, with residual hyperpigmented macules, required 15 weeks.[2] A persistent cutaneous reaction characterized by eczematous dermatitis lasting more than 18 months is possible.[157] Grouped or linear papulonodular lesions, round or oval

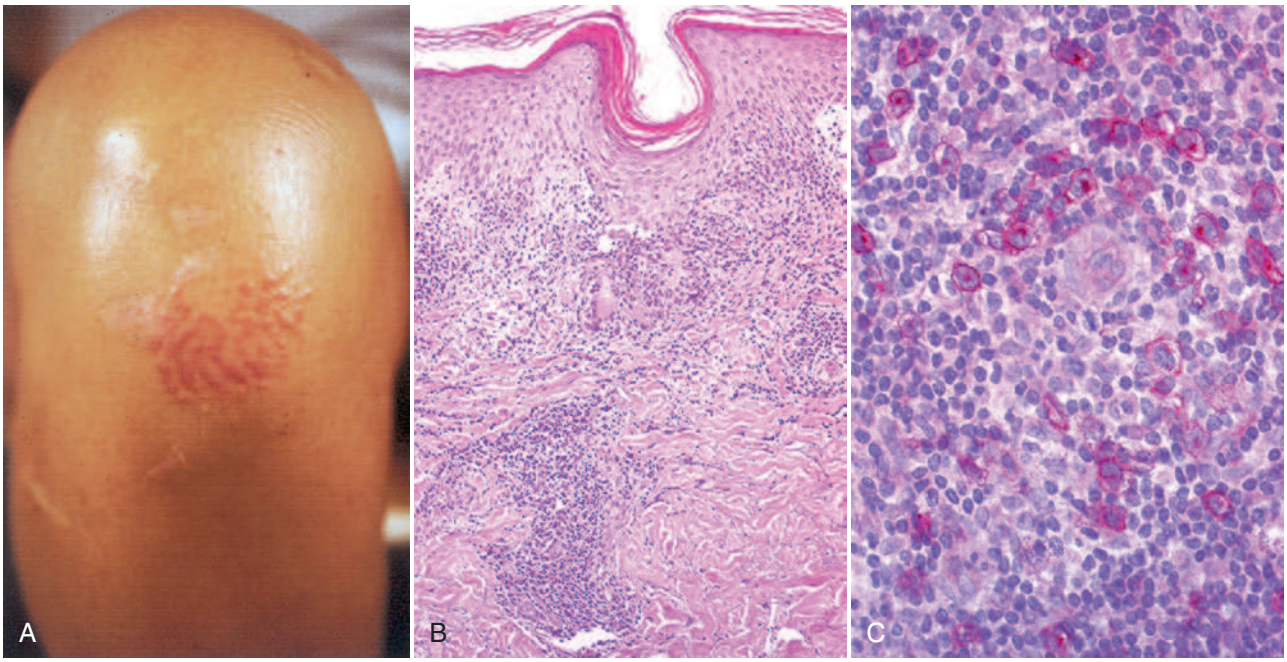


FIGURE 74-32 **A,** Streaks of red papules on the knee of a victim stung by a Red Sea fire coral. **B,** Wedge-shaped inflammatory infiltrate with edema of the papillary dermis and an epithelioid granuloma (hematoxylin and eosin, ×100). **C,** CD30+ atypical lymphoid cells (alkaline phosphatase–antialkaline phosphatase, ×400). *(Courtesy Dr. Clelia Miracco.)*

in shape, may follow as a delayed reaction to a jellyfish sting.[211] In a rare case, a full-thickness skin burn may occur.[175]

Renal minimal change disease (nephrotic syndrome, renal failure) responsive to corticosteroid therapy has been associated with fire coral exposure.[164]

Treatment. The skin should be rinsed liberally with seawater and then immediately soaked with acetic acid 5% (vinegar) or isopropyl alcohol (40% to 70%) until pain is relieved. Alternative topical agents are discussed in the larger cnidarian treatment section, earlier. Residual dermatitis is generally not very severe and can be managed in a fashion similar to that used after a feather hydroid sting. If the rash becomes eczematous and indolent, it may respond to a course of systemic corticosteroids (prednisone, 60 to 100 mg, tapered over 2 weeks). Divers should avoid touching with bare skin anything resembling coral. For example, the underwater statue of Jesus at John Pennycamp Park in Key Largo, Florida, is encrusted with fire coral, so posing divers have been envenomed.

Physalia (Man-of-War)

The Atlantic Portuguese man-of-war *(Physalia physalis)* of the phylum Cnidaria, order Siphonophorae, is a pelagic (open sea) polymorphic colonial siphonophore that inhabits the surface of the ocean. It is constructed of a blue or pink-violet and iridescent floating sail (pneumatophore) that is filled with nitrogen and carbon monoxide and up to 30 cm (11.8 inches) in length, from which are suspended multiple nematocyst-bearing tentacles, which may measure up to 30 m (98 feet) in length (Figures 74-33 and 74-34). It has been reported that an Australian version of *P. physalis* is present in northern Australian waters.[64] This jellyfish is characterized by float lengths of up to 15 cm (5.9 inches), up to five thick, dark blue "main" tentacles, and up to 10 other long, thin, and pale-colored tentacles. The smaller Pacific bluebottle *(Physalia utriculus)* usually has a single fishing tentacle, which attains lengths of up to 15 m (49.2 feet) (Figure 74-35). In some species, the sail can be deflated to allow the animal to submerge in rough weather.

FIGURE 74-33 Atlantic Portuguese man-of-war. *(From Norbert Wu, with permission:* norbertwu.com.*)*

FIGURE 74-34 Portuguese man-of-war. *(Copyright Stephen Frink.)*

The physaliae depend on the winds, currents, and tides for movement, traveling as individuals or in floating colonies that resemble flotillas. They are widely distributed but seem to abound in tropical waters and in the semitropical Atlantic Ocean, particularly off the coast of Florida and in the Gulf of Mexico. Envenoming has been reported as far south as the coast of Brazil.[47] Their arrival at surf's edge can transform a halcyon vacation into a stinging nightmare. Unfortunately, the peak appearance time for both the man-of-war and sea nettle is July through September, which is prime beach season.

As is the case for icebergs, much of the story is below the water surface. Because the tentacles are nearly transparent, they pose a hazard to the unwary (Figure 74-36). As the animal moves in the ocean, the tentacles rhythmically contract, sampling the water for potential prey. If the tentacle strikes a foreign object, the nematocysts are stimulated and discharge their contents into the victim. Each tentacle in a larger specimen may carry more than 750,000 nematocysts. To increase the intensity of the "attack," the remainder of the tentacle shortens in such a way as to create loops and folds, presenting a greater surface area and greater number of nematocysts for offensive action in "stinging batteries" (Figure 74-37).

Detached moistened tentacles, often found by the thousands fragmented on the beach, carry live nematocysts capable of discharging for months. Air-dried nematocysts may retain considerable potency, even after weeks (Figure 74-38). The loggerhead turtle *(Caretta caretta)* (Figure 74-39) feeds on *Physalia*. Like the clownfish with the sea anemone, the brightly colored fish *Nomeus*

FIGURE 74-35 Tiny stinging jellyfish on the beach in Hawaii. *(Courtesy Paul S. Auerbach, MD.)*

gronovii has a unique symbiotic relationship with the man-of-war, living freely among the tentacles. A species of nudibranch (sea slug), *Glaucus atlanticus*, eats the tentacles and nematocysts of *P. physalis*. The nematocysts are not digested and ultimately reside in the dorsal papillae of the nudibranchs, where they may sting on contact. Other nudibranchs are also able to ingest hydroids and store their stinging cells in the cerata, or flesh appendages. Dermatitis can also result from contact with water containing venom that has already been released from stimulated nematocysts. The Mediterranean octopus *Tremoctopus violaceous* stores intact dactylozooid segments in its suckers for later use.[29]

Clinical Aspects. *Physalia* envenomations can be quite painful. *P. utriculus* usually causes only local pain and dermatitis, or rarely, minor systemic symptoms, but *P. physalis* can potentially cause major systemic symptoms, as discussed previously. The most common presentation is immediate local stinging/searing/sharp pain from the sting followed by an erythematous maculopapular linear rash that can later show vesicles or even skin necrosis. Pain usually improves in the first few hours, and local symptoms resolve in 72 hours.[206] More severe systemic symptoms, which generally only occur with stings from *P.*

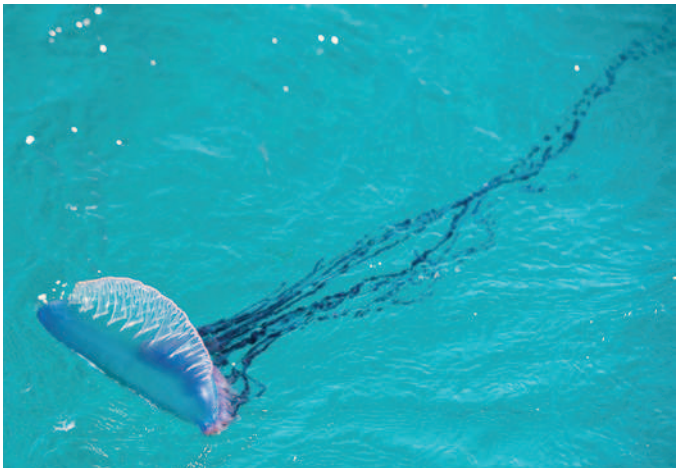


FIGURE 74-36 Stinging tentacles of Portuguese man-of-war trail in the water. *(Copyright Stephen Frink.)*

FIGURE 74-37 Tentacles of the Atlantic Portuguese man-of-war. Nematocysts may number in the hundreds of thousands on tentacles coiled into "stinging batteries." *(Courtesy Larry Madin, Woods Hole Oceanographic Institution.)*

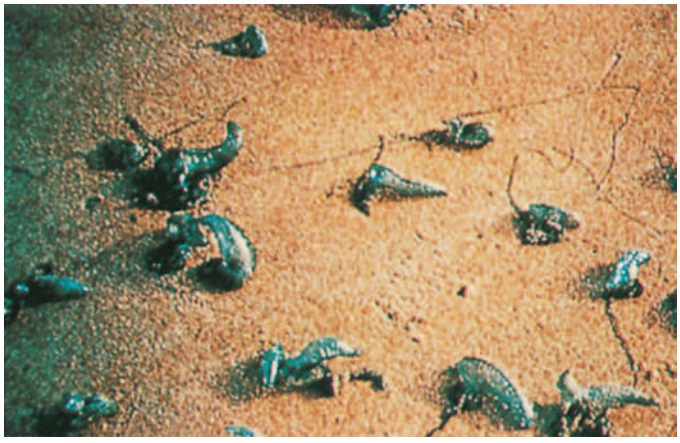


FIGURE 74-38 Pacific man-of-war washed ashore may retain stinging potency for weeks. *(Courtesy John Williamson, MD.)*

FIGURE 74-39 The loggerhead turtle sometimes dines on jellyfish tentacles. *(Courtesy Howard Hall.)*

physalis, include nausea, vomiting, muscle cramps, dyspnea, anxiety, abdominal pain, and headache; rarely, death occurs.[109]

Treatment. Treatment of *Physalia* envenomations is still controversial. As discussed earlier, if a specific decontaminant is not immediately available, washing with seawater and removal of any adherent tentacles is primary field treatment. Commercial (chemical) cold or ice packs applied over a thin dry cloth or plastic membrane have been shown to be effective when applied to mild or moderate *P. utriculus* (or bluebottle) stings.[53] Whether the melted water from ice applied directly to the skin can stimulate the discharge of nematocysts has not been determined. However, a recent randomized controlled trial of hot water (45°C [113°F]) immersion versus ice packs for pain relief for bluebottle stings showed hot water to be the favored treatment, with statistically significant reduction in reported pain.[123] To support this approach, it has been observed by physicians in Australia that hot packs and hot showers (45°C [113°F]) are efficacious for relieving pain of bluebottle stings. As stated previously, application of vinegar may increase nematocyst discharge in vitro and is not yet a universally accepted treatment. Other treatments that may be effective for pain relief include lidocaine, Stingose (20% $MgSO_4$), baking soda, and papain.

Seabather's Eruption

Seabather's eruption, commonly termed sea lice (pika-pika around the Belize barrier reef; sea poisoning, sea critters, and ocean itch are other names), refers to a dermatitis that results from contact with ocean water.[95] It has become a seasonal problem afflicting oceangoers in southern Florida and across the Caribbean; it has been reported in Brazil and Papua New Guinea.[81,210] It predominantly involves covered areas of the body and is commonly caused by pinhead-sized (0.5 mm) greenish brown to black larvae of the thimble jellyfish *Linuche unguiculata* (Figure 74-40), which breeds in Caribbean waters throughout the summer, with a peak in May.[208] *L. unguiculata* exists in three swimming stages during its life cycle: planula (free-swimming larva), ephyra (immature medusa), and adult medusa. It is likely that all three swimming stages initiate the eruption.[165,181] Another culprit off Long Island, New York, has been the planula larval form (visible at 2 to 3 mm) of the sea anemone *Edwardsiella lineata,* which carries hundreds of nematocysts.[66,67] Given the number of cnidarians that inhabit the oceans of the world and the cross-reactivity of antigens, it is likely that etiologic organisms are numerous.

Clinical Aspects. A swimmer who encounters the stinging forms usually complains of cutaneous discomfort (stinging, tingling, or a pins-and-needles sensation) after contact, often while in the water or soon after exiting. Application of freshwater may intensify the sting. The eruption occurs a few minutes to 12 hours after bathing and consists of erythematous and intensely pruritic wheals, vesicles, or papules that persist for 2 to 14 days and then involute spontaneously. When a bathing suit has been worn by a woman, the areas commonly involved include the buttocks, genital region, and breasts (Figure 74-41). A person at the water's surface (commonly a person who surfaces after a dive) may suffer stings to the exposed neck (Figure 74-42), particularly if there has been recent motorboat activity in the vicinity, which may disturb and fragment the causative jellyfish. Nematocysts adherent to scalp hair may sting the neck as the hair hangs down. Individual lesions resemble insect bites. Coalescence indicates a large inoculum (Figure 74-43). Surfers develop lesions on areas that contact the surfboard (chest and anterior abdomen). The rash may also be seen under bathing caps and swim fins or along the edge of the cuffs of wetsuits, T-shirts, or stinger suits (Figure 74-44).[208] In children with extensive eruptions, fever is common. Low-grade fever may be noted in adults.[210] Other symptoms may include headache, chills, fatigue and malaise, vomiting,

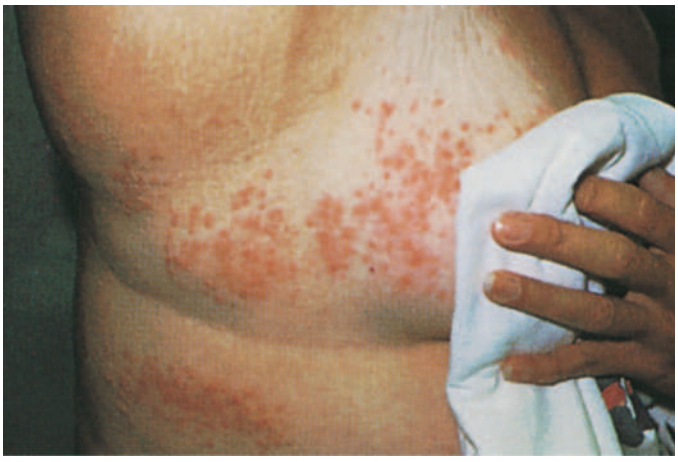


FIGURE 74-41 Seabather's eruption. *(From Wong DE, Meinking TL, Rosen LB, et al: Seabather's eruption,* J Am Acad Dermatol *30:399, 1994.)*

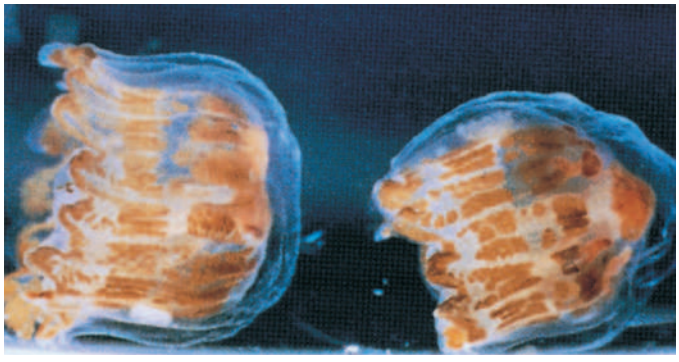


FIGURE 74-40 Mature *Linuche unguiculata,* the causative agents of seabather's eruption. The planula or larvae of these cnidarians were collected from plankton tows and grown to maturity at the University of Miami. Slightly smaller than their brethren found in the open ocean, these specimens are approximately 2 cm in diameter when open and 1 cm when contracted. *(Courtesy David Taplin and Terri L. Meinking.)*

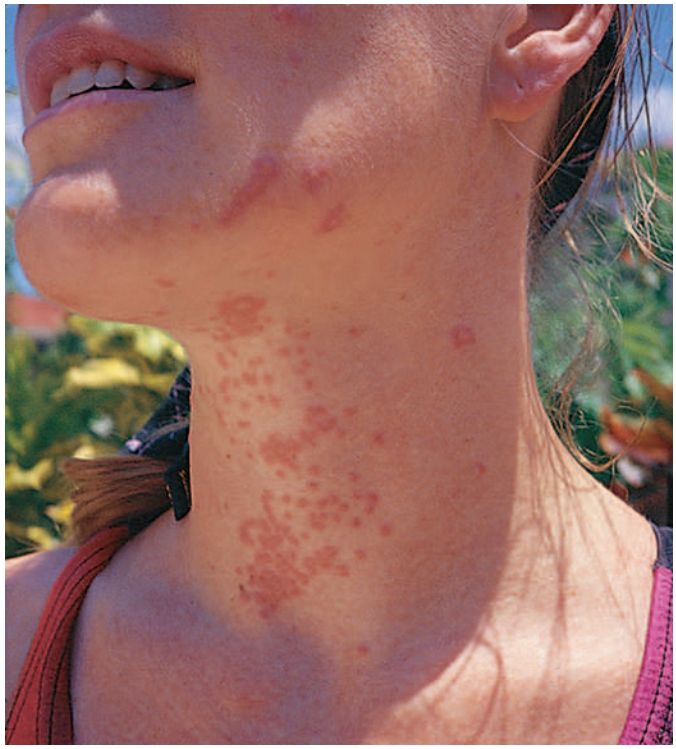


FIGURE 74-42 Seabather's eruption on the neck of a diver in Cozumel, Mexico. *(Courtesy Paul S. Auerbach, MD.)*

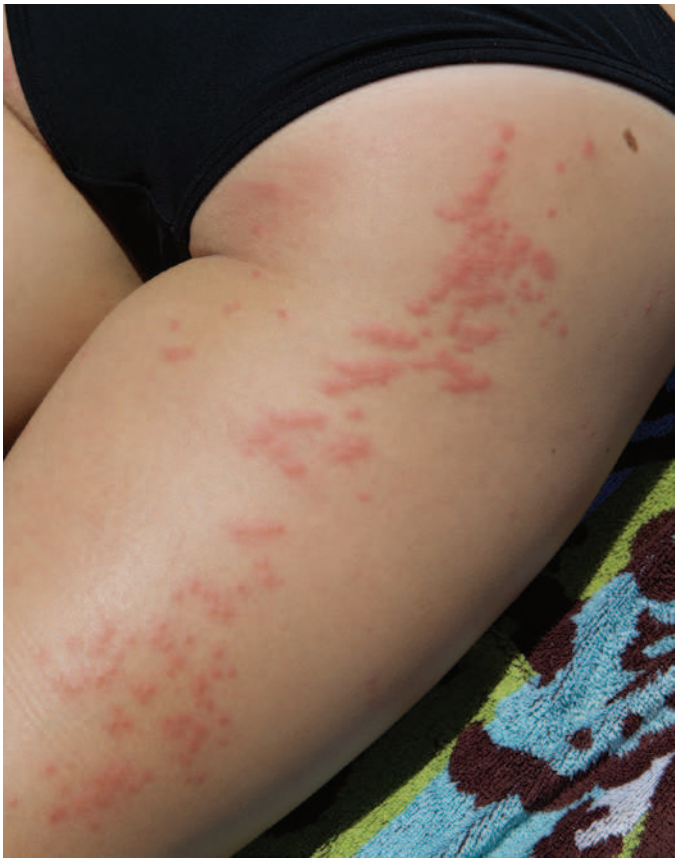


FIGURE 74-43 Seabather's eruption. *(Copyright Stephen Frink.)*

conjunctivitis, and urethritis. Itching is often pronounced at night and awakens the victim from sleep. Burnett and Burnett[22] reported blurred vision and left arm weakness in a teenager stung by an adult *Linuche*. People who note a stinging sensation during the primary contact while still in the water may have a higher incidence of previous sensitization to the antigen or antigens. Persons who wear clothing that has been contaminated with the larvae may suffer recurrent reactions. Prior sensitization may precede prolonged (≤ 6 weeks) reactions (rash and pruritus).

Elevated IgG levels specific for *L. unguiculata* can be measured by ELISA in the sera of victims who have suffered from seabather's eruption. The extent of the cutaneous eruption or sting severity appears to correlate with the antibody titer.[33] In an evaluation of southeastern Florida victims envenomed by *L. unguiculata,* histopathologic examination of inflammatory papules demonstrated superficial and deep perivascular and interstitial infiltrate consisting of lymphocytes, neutrophils, and eosinophils.[234]

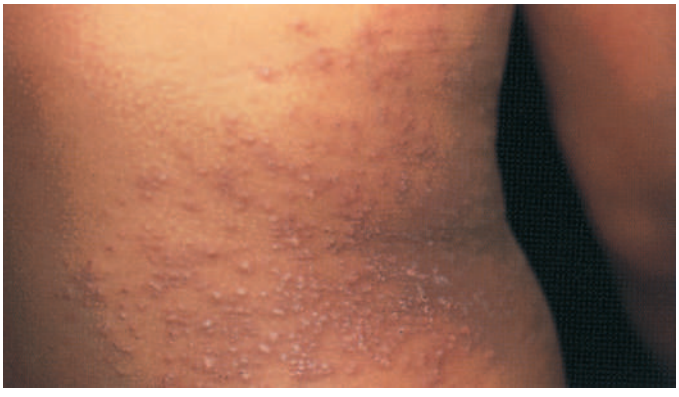


FIGURE 74-44 Seabather's eruption in an area under the weight belt. *(Courtesy Doug Wong, MD.)*

Treatment. Field management is identical to that for any cnidarian sting (see earlier), with the empirical observation that topical papain may be slightly more effective as an initial decontaminant than vinegar, isopropyl alcohol, or other substances. Papain application may be more effective if undertaken with a mildly abrasive scrub pad. Whether the pain relief is due to nematocyst inactivation or counterirritation is not yet known. Substances that are believed to be ineffective include hydrogen peroxide, garlic, antifungal spray, anti–head lice medication, petroleum distillates, fingernail polish, and citrus juice.

The skin eruption is self-limited and usually remits within 10 days. However, in a severe envenomation, the rash may persist for up to 4 weeks and leave atrophic scars.[125] Further treatment is palliative and consists of calamine lotion with 1% menthol. Because the lesions rarely extend into the dermis, a potent topical corticosteroid may be helpful in mild cases, but benefit is not invariably attained. In a more severe case, an oral or parenteral antihistamine or systemic corticosteroid may be used. A thorough soap and water scrub (not a casual rinse) on leaving the water provides partial prophylaxis. Avoidance logically includes advice to ocean bathe in abbreviated swimwear (which may, however, expose a person to other stings), to maintain tightly occlusive cuffs on dive skins and wetsuits, to change swimwear as soon as possible after leaving the water, and to use caution during high season for *L. unguiculata* (April to July off southern Florida) or *E. lineata* (August to November off Long Island) and when there are strong onshore winds. Swimwear worn and suspected to be contaminated with nematocysts should be washed in detergent and fresh water and dried before wearing.[180]

True sea lice are parasites on marine creatures and do not cause this disorder.

Gonionemus Species

These small hydrozoans are distributed worldwide but have been reported as causing severe envenomation only in the Sea of Japan near Vladivostok, Russia, and at the northwestern shores of Honshu Island, Japan.[56] It is a small creature of 5 to 15 mm in diameter across the bell, with a symmetric, right-angled cross visible in the transparent part.

When the reaction is painful, the victim suffers muscle, joint, chest, and pelvic pain for up to 3 days. There may be muscle fasciculations. In a respiratory presentation, the victims suffer rhinitis, tearing, hoarseness, cough, and shortness of breath. In addition, there may be a combination of symptoms, such as sore throat, tachycardia, vomiting, and mild hypertension. Psychiatric depression and hallucinations may occur.[152]

It has been noted that envenomation may occur under a bathing suit. In addition, a similar syndrome was reported after ingestion of raw seaweed, to which was presumably attached the jellyfish.[56]

CLASSES CUBOZOA AND SCYPHOZOA

The classes Cubozoa and Scyphozoa contain the larger medusae or jellyfish, including the deadly box-jellyfish and variably injurious species (e.g., *Chironex, Cyanea, Chiropsalmus,* and *Chiropsella,* which were formerly classified as *Chiropsalmus* spp.). These creatures are armed with some of the most potent venoms in existence. Jellyfish are mostly free-swimming pelagic creatures; however, some can be found at depths of more than 2000 fathoms. They may be transparent or multicolored and range in size from a few millimeters to more than 2 m (6.5 feet) in width across the bell, with tentacles up to 40 m (131 feet) in length. Like physaliae, the scyphozoans depend on wind, currents, and tides for transport and are widely distributed (Figure 74-45). Some vertical motion may be produced by rhythmic contractions of the gelatinous bell, from which originate the feeding tentacles.

Some jellyfish contain less than 5% solid organic matter. Regardless, they can withstand remarkable temperature and salinity variations, although they do not fare well with violent activity and thus may descend to great depths during stormy surface weather. Some scyphozoans avoid sunlight; others follow an

FIGURE 74-45 Schooling jellyfish. *(Copyright iStockphoto.com/Gary Adams.)*

opposite pattern. Certain jellyfish have adapted to local nutrient (largely algal) supply and have lost their ability to sting humans (Figure 74-46).

In eastern coastal waters of the North American continent, the creatures appear to grow larger as they progress north (Figure 74-47), so that true giant jellyfish, typified by *Cyanea capillata* (lion's mane), are found in Arctic waters (Figure 74-48). Tentacles (which may number up to 1200) of larger specimens may exceed 30 m (100 feet) in length.[29] *Pelagia* species (purple-striped or mauve stingers) are commonly found in large numbers off the California coast and appear in the Mediterranean Sea in abundance every 10 to 12 years.[166] *P. noctiluca* (Figure 74-49) phosphoresces at night, hence its name.[139] *Olindias sambaquiensis* is a jellyfish that stings bathers in South American coastal waters. *R. nomadica* is a tropical jellyfish that has invaded the eastern Mediterranean.[61,120,121] As another example, stings from *S. nomurai* in the Bohai waters of China produce severe pulmonary edema, coma, convulsions, psychoses, and death. Australian jellyfish include the blubber jellyfish (*Catostylus* species), hair jellyfish (*Cyanea* species), little mauve stinger *(P. noctiluca),* and the cuboid-shaped jellyfish (*C. fleckeri* and *Chiropsalmus* species). A number of cubomedusan (box-shaped jellyfish) scyphozoans of a highly toxic nature inhabit Indo-Pacific and, less frequently, Caribbean waters. These include *Carybdea rastoni* (jimble) (Figure 74-50) and *Carybdea marsupialis* (sea wasp), *Chiropsella bronzi, Chiropsalmus quadrigatus* and *Chiropsalmus quadrumanus*, and *Chironex fleckeri.*[172] The carybdeids of the order Carybdeida have four tentacles only, whereas the chirodropids of the order Chirodropidae may have up to 60 tentacles. All are frequently called box-jellyfish.

FIGURE 74-46 The author snorkels in Jellyfish Lake in Palau, Micronesia. The jellyfish have evolved to subsist on algae and thus no longer pose a stinging hazard to humans. *(Courtesy Avi Klapfer.)*

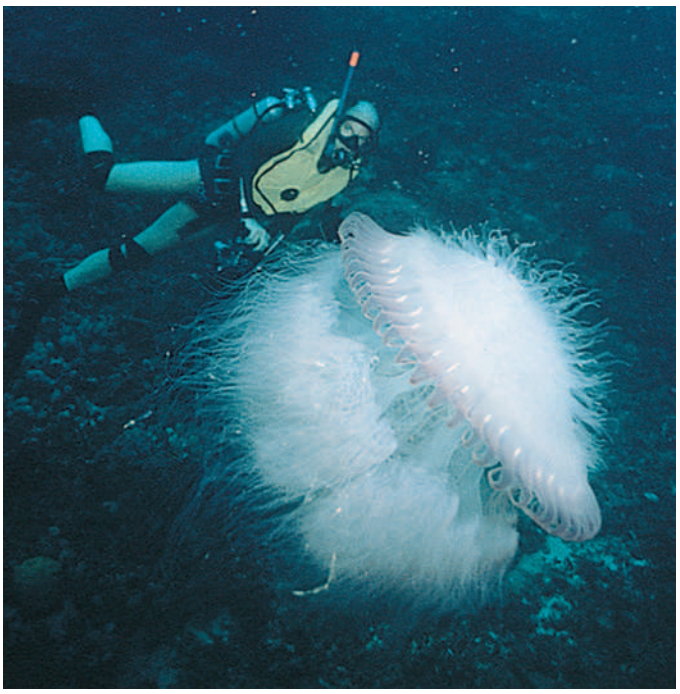


FIGURE 74-47 Lion's mane jellyfish *(Cyanea capillata). (Courtesy Carl Roessler.)*

Chironex (Box-Jellyfish)

The dreaded chirodropid box-jellyfish (*C. fleckeri* Southcott), often misnamed the sea wasp, is a venomous sea creature that can induce death in less than 60 seconds with its potent sting. Like all other scyphozoans, it is a carnivore, adapted to deal rapidly with prey. A member of the group of Cubomedusae jellyfish, it ranges in size from 2 to 30 cm across the bell. Although these creatures seem to prefer quiet, protected, and shallow areas, chiefly in the waters off northern Queensland, Australia, they can be found in the open ocean. A seasonal alternation of polypoid and medusoid generations from winter to summer, respectively, appears to account for the shift in preferred habitat from tidal estuaries to the open eulittoral zone.[86] Stinger season

FIGURE 74-48 Lion's mane jellyfish *(Cyanea capillata)* can reach 3 m (10 feet) in diameter in Arctic waters. *(From Norbert Wu, with permission:* norbertwu.com.*)*

FIGURE 74-49 Mauve stinger *(Pelagia noctiluca). (Courtesy Larry Madin, Woods Hole Oceanographic Institution.)*

FIGURE 74-51 Box-jellyfish *(Chironex fleckeri),* swimming just beneath the surface of the water. *(Courtesy John Williamson, MD.)*

in the Northern Territory of Australia is from October 1 to May 31.[42] Swimming and bathing are precluded in the littoral and estuarine waters of Indonesia, Malaysia, and Northern Australia during this season, which coincides with the hottest tropical months in the Southern Hemisphere.[158] However, it is likely that *Chironex* ("the assassin's hand") may be present year-round in the Northern Territory.[59] *Chironex* are fragile and photosensitive and thus are found submerged during bright sunlight hours (Figure 74-51), seeking the surface in the early morning and late afternoon and evening. The visual system of the box-jellyfish has 24 eyes of different types (eyes with spheric lenses, pigment pit eyes, and pigment slit eyes), which may possibly be used for an avoidance response or attraction to light.[72] Box-jellyfish are swift and graceful travelers, capable of sailing along at a steady 2 knots.

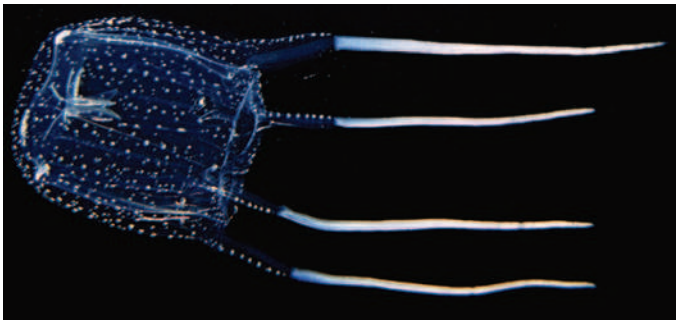


FIGURE 74-50 Jimble box-jellyfish or southern sea wasp *(Carybdea rastoni)* in Southern Australia. *(From Gary Bell:* oceanwideimages.com.*)*

An adult *Chironex* carries up to 15 broad tentacles (Figure 74-52) in each corner (pedalium, or foot) of its bell (up to 60 tentacles total, each with a length of up to 3 m [10 feet]) and has enough venom (> 10 mL) to kill three adults.[44,196] As *Chironex* grows in size, the ratio of mastigophores (nematocysts believed to hold the lethal venom component for prey) to less injurious organelles increases.[37] Two fractions have been isolated from the venom: a "lethal" fraction of molecular weight 150,000, and a lethal-hemolytic-dermatonecrotic fraction of molecular weight 79,000. At least 72 fatalities have been verified in Australian and Southeast Asian waters, with greater numbers probably lacking official documentation. Thus, the box-jellyfish is a much greater true hazard than the more fearsome shark. Other jellyfish, such as *C. rastoni* and *P. noctiluca,* infrequently cause severe prolonged reactions and have rarely been reported to lead to death, but are capable of causing dramatic immediate reactions (Figure 74-53).

Sudden death in a child has followed envenomation by *Chiropsalmus quadrumanus* (also sometimes described as a box-jellyfish) in the Gulf of Mexico at Crystal Beach, Texas.[14] Death was attributed to acute arrhythmia after a catecholamine surge, followed by cardiogenic shock and pulmonary edema.

Clinical Aspects. The extreme example of envenomation occurs with *C. fleckeri* (after Dr. Hugo Flecker) (Figure 74-54).[158] Death is attributed to hypotension, profound muscle spasm, muscular and respiratory paralysis, and subsequent cardiac arrest. Recent evidence suggests that *C. fleckeri* toxin has direct effects on the myocardium and may be cardiotoxic.[40,93] The overall mortality rate after box-jellyfish stings may approach 15% to 20% in select locales. Most commonly, bathers, frequently aboriginal children, are stung in shallow and remote coastal waters. The

FIGURE 74-52 Close-up of the tentacle mass of an adult box-jellyfish *(Chironex fleckeri). (Courtesy Bob Hartwick.)*

FIGURE 74-53 Box-type jellyfish in open water in Tonga. *(Copyright Carl Roessler.)*

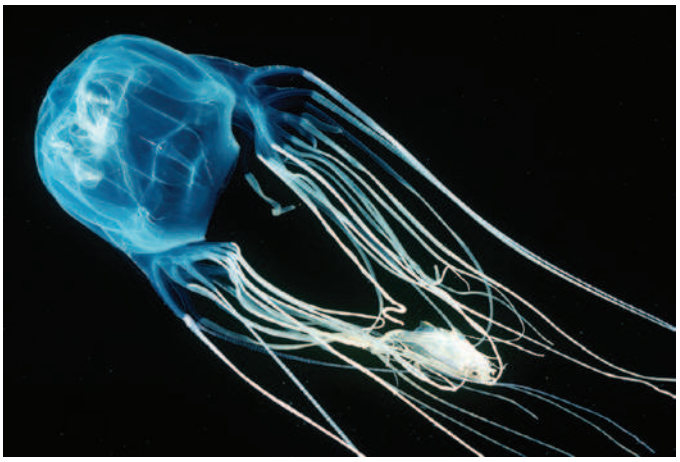


FIGURE 74-54 Box-jellyfish with prey in Australia. *(Copyright David Doubilet.)*

victims do not recognize the small, semitransparent, and submerged creature, which may approach as a member of a small armada. Most stings are minor; severe reaction or death follows skin contact with tentacles longer than 6 to 7 m (20 to 23 feet), although 10 cm of tentacle is capable of delivering a lethal dose of venom.[158,197] The sting is immediately excruciatingly painful, and the victim usually struggles purposefully for only a minute or two before collapse. The toxic skin reaction may be intense, with rapid formation of wheals, vesicles, and a darkened reddish brown or purple whiplike flare pattern with stripes 8 to 10 mm in width (Figures 74-55 and 74-56). With major stings, skin blistering occurs within 6 hours, with superficial necrosis in 12 to

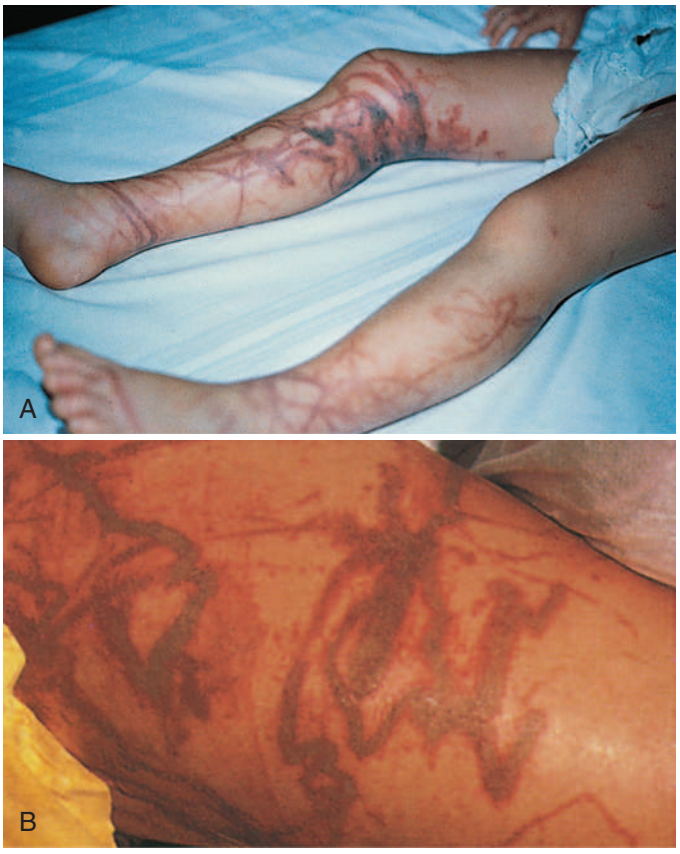


FIGURE 74-55 Intense necrosis (here, at 48 hours) is typical of a severe box-jellyfish *(Chironex fleckeri)* sting. **A,** Involvement of nearly an entire limb. **B,** Skin darkening can be rapid with cellular death. *(Courtesy John Williamson, MD.)*

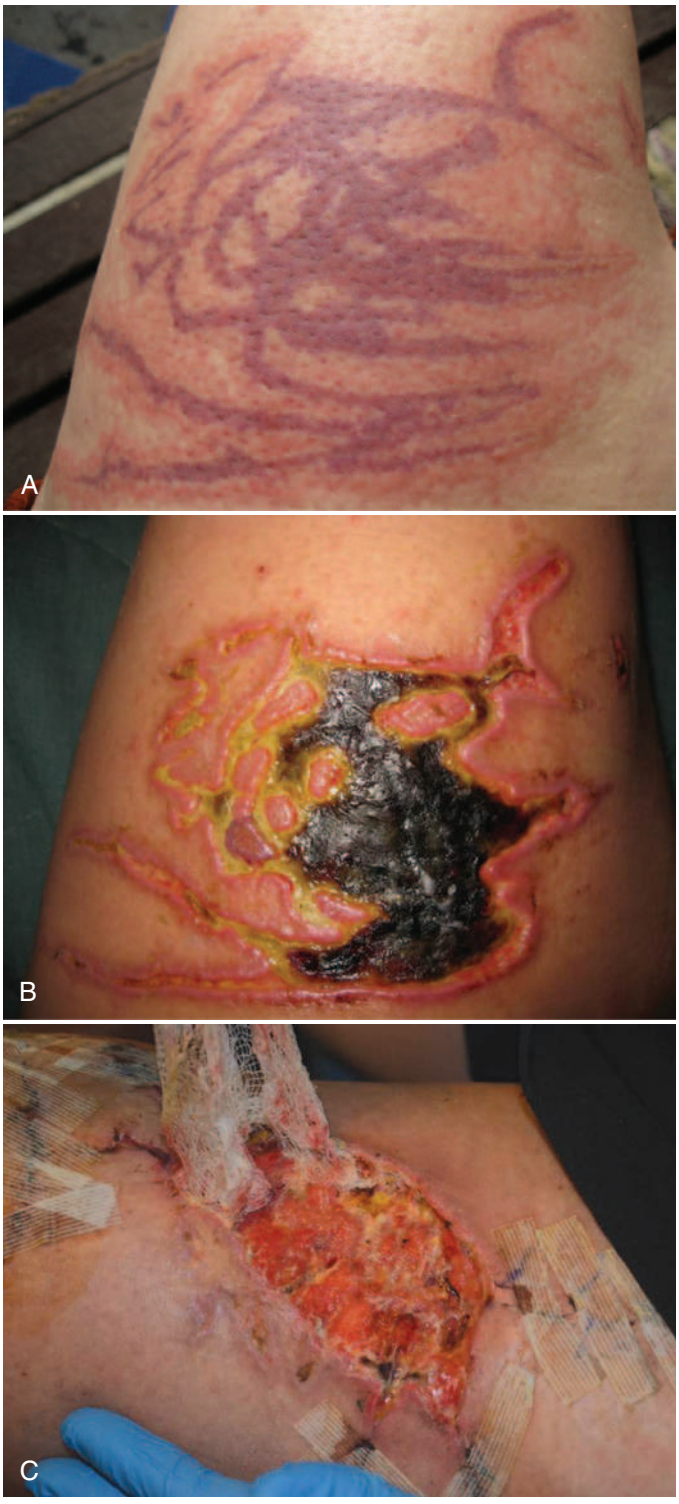


FIGURE 74-56 Progression of a severe jellyfish sting. **A,** Soon after the sting. **B,** Within a few weeks, severe necrosis is evident. **C,** Treatment required excision and skin grafting. *(Courtesy Stefan Caporale.)*

18 hours (Figure 74-57). The skin defects that result from a severe envenomation can be profound (Figure 74-58). On occasion, a pathognomonic frosted appearance with a transverse cross-hatched pattern has been observed (Figure 74-59). This appearance may be primarily the result of the application of aluminum salts used for decontamination. More severe reactions and increased mortality rates in women and small children have been attributed to their greater hairless body surface area and smaller body mass.

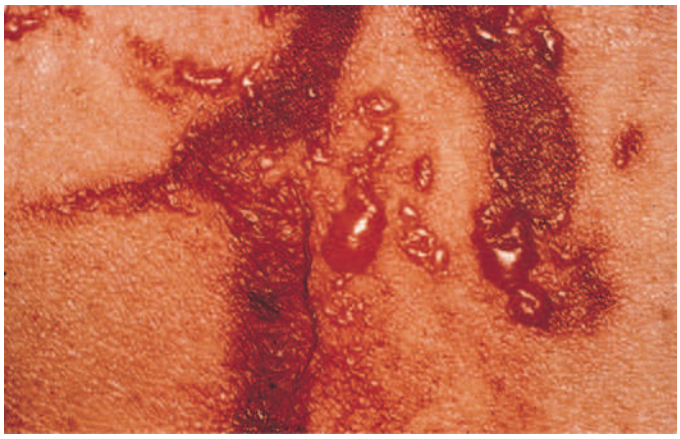


FIGURE 74-57 Incipient necrosis and blistering within 24 hours of box-jellyfish *(Chironex fleckeri)* envenomation. *(Courtesy John Williamson, MD.)*

One case of *Chironex* envenomation in a pregnant woman has been reported.[111,223] A 20-year-old woman in the 34th week of pregnancy suffered apparent respiratory arrest but was successfully revived with rescue breathing at the scene. The victim received antivenom in the hospital and delivered a healthy child at term by cesarean section. It is interesting to note that one rescuer was 37 weeks pregnant and received a sting from tentacles adherent to the victim, but she also delivered uneventfully.

Identification of *Chironex* envenomation is sometimes possible by nematocyst recovery from the skin. This can be done by scraping with a scalpel or by applying sticky tape. In the former technique, the skin is firmly scraped with a sterile scalpel blade, which is then placed in a container. Five to 10 mL of distilled water is added, and the container is sonicated for 5 minutes to remove any nematocysts adherent to the blade. The solution is syringed through a 13-mm Millipore filter, which leaves the nematocysts, debris, and skin cells on the paper. A 0.5% eosin stain is syringed through the filter paper, which is allowed to dry, after which it is placed on a glass slide, fixed, and mounted with a cover slip. In the sticky tape technique, transparent household sticky tape is applied to the sting site, stroked several times to ensure adherence, and then removed and placed sticky side up on a glass slide, with the ends secured to the slide with additional tape.[45]

Treatment. In the case of a known or suspected box-jellyfish envenomation, the victim must be assessed rapidly for adequacy of breathing and supported with an airway and

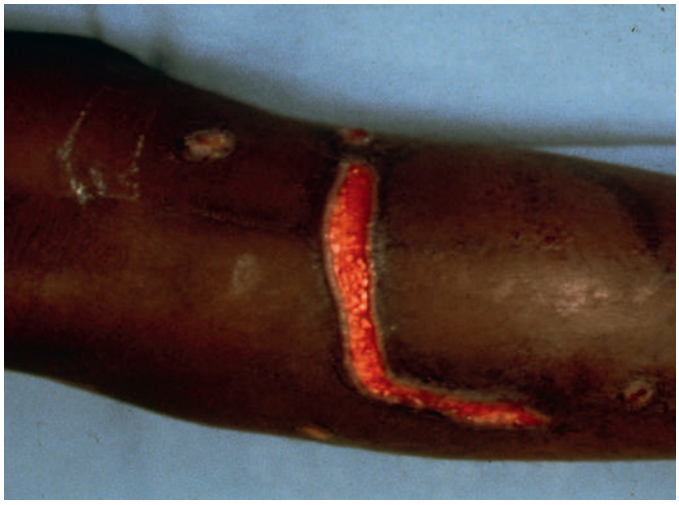


FIGURE 74-58 Skin destruction 3 weeks after an untreated box-jellyfish *(Chironex fleckeri)* envenomation. *(Courtesy John Williamson, MD.)*

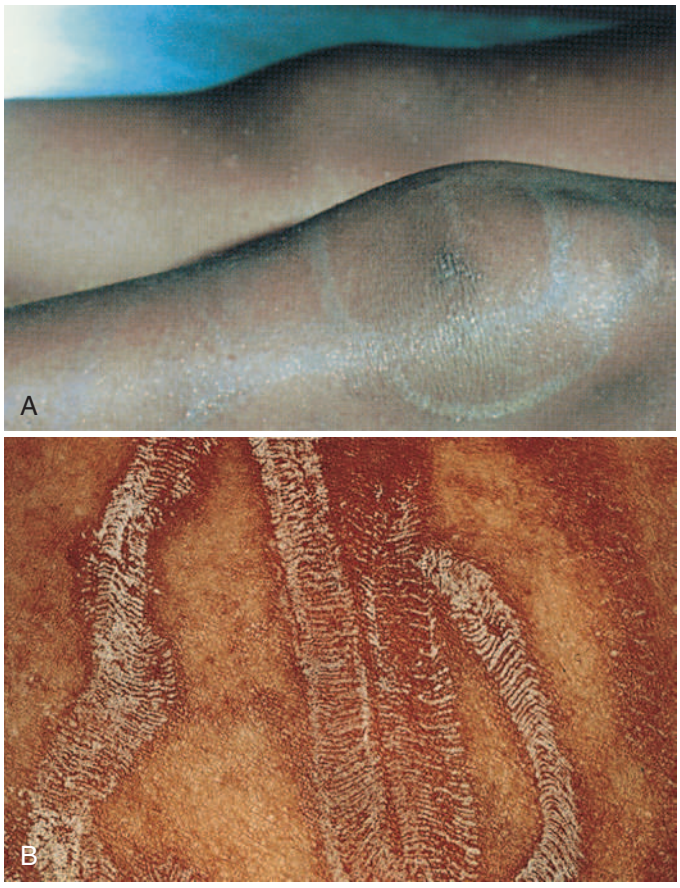


FIGURE 74-59 Frosted cross-hatched pattern pathognomonic for a box-jellyfish envenomation. **A,** The victim of this sting expired rapidly. **B,** The enhanced frosted appearance is a result of application of a spray of aluminum sulfate. *(Courtesy John Williamson, MD.)*

artificial ventilation if necessary. The victim should be moved as little as possible. It is essential to immediately and liberally flood, for a minimum of 30 seconds, the skin surrounding any adherent tentacles with 5% acetic acid (vinegar) before any attempt is made to remove them; this paralyzes the nematocysts and avoids worsening the envenomation (Figure 74-60). Significant pain relief should not be expected from this maneuver, which may actually worsen the pain briefly.[13,218] Although most nematocysts cannot penetrate the thickened skin of the human palm, the rescuer should pay particular attention to his or her own skin protection. If acetic acid is not available, aluminum sulfate surfactant (Stingose) may be substituted, although its efficacy has not been well demonstrated for a *Chironex* envenomation. A number of experts recommend that isopropyl alcohol *not* be used as a topical decontaminant for a box-jellyfish envenomation, based on in vitro observations of inefficacy and nematocyst discharge after application of this detoxicant.[86,197] Clinical confirmation of this recommendation has not been published.

Pressure-immobilization is no longer recommended to prevent absorption of *Chironex* venom.[4,115] Certain experts have questioned its efficacy and noted that large affected skin surfaces cannot be effectively bandaged. Others have noted that application of pressure might promote nematocyst discharge, which is believed to be more harmful than foregoing any attempt to devascularize the area immediately below the bandage in order to prevent distribution of venom into the general circulation.[8,161,182,196,225,226] In any event, it is reasonable to splint or otherwise immobilize the limb to prevent motion.

In the absence of antivenom (see below) and facing a prolonged transport prior to supportive intensive care, a rescuer might apply a constriction bandage proximal to the site of an extremity sting, to impede lymphatic and superficial venous return. Such a bandage should be loosened for 90 seconds every 10 minutes and should be completely removed after 1 hour. In no case should an arterial tourniquet be applied. Use of a proximal constriction band has not been proved to be helpful.

Up until recently, it has been recommended that *Chironex* antivenom be administered intravenously as soon as possible. Following the "antivenom approach," the IM route is less preferred, because peak blood levels may not be obtained for 48 hours after administration by this route. One author has recommended consideration of intraosseous administration if the IV route is not available.[44] The antivenom is supplied in vials (1.5 to 4 mL of liquid) containing 20,000 units by CSL (Figure 74-61). The initial dose is one vial (diluted 1:5 to 1:10 in isotonic crystalloid; dilution with water is not recommended) administered intravenously over 5 minutes, or three vials into three different sites (generally on the thigh) intramuscularly. IM antivenom has been administered successfully over the years by members of the Queensland Surf Life-Saving Association and the Queensland Ambulance Transport Brigade.[62] Although the antivenom is prepared by hyperimmunizing sheep and adverse reactions reported have been rare and mild, the prudent physician is always prepared to treat anaphylaxis or serum sickness.[42] It has been stated that it cannot be overemphasized that timely administration of antivenom might be lifesaving, particularly in light of the fact that most deaths from *Chironex* stings occur in the first 5 to 20 minutes.[223] In addition to its lifesaving properties, early administration of antivenom is felt to markedly reduce pain and decrease

FIGURE 74-60 Surf lifeguards pour vinegar on the leg of a simulated box-jellyfish envenomation. Note how they restrain the victim's arms to prevent him from handling the harmful tentacles. *(Courtesy John Williamson, MD.)*

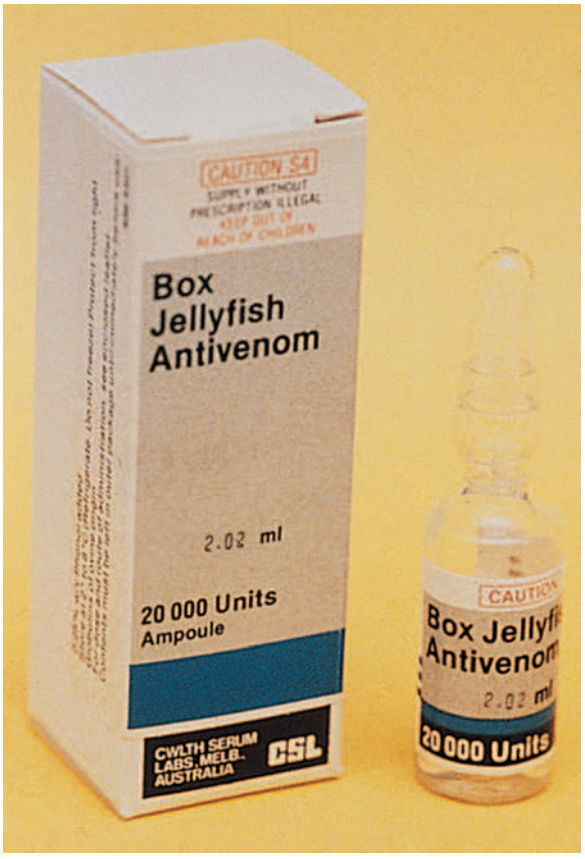


FIGURE 74-61 Box-jellyfish antivenom. *(Courtesy John Williamson, MD.)*

subsequent skin scarring.[224] Antivenom administration may be repeated once or twice every 2 to 4 hours until there is no further worsening of the skin discoloration, pain, or systemic effects. A large sting in an adult may require initial IV administration of up to three vials. The antivenom may also be used to neutralize the effects of a *Chiropsella* (formerly *Chiropsalmus*) envenomation.[167,196,230] Antivenom should be stored in a refrigerator at 2° to 10°C (35.6° to 50°F) and must not be frozen.[29] Concomitant administration of a glucocorticoid (such as hydrocortisone 200 mg intravenously) is often recommended for its antiinflammatory activity but is no substitute for administration of antivenom.

The usefulness of antivenom is under scrutiny and not universally supported. There is not 100% consensus that antivenom is effective for treatment of human envenomations by box-jellyfish. Some of the arguments against its efficacy include in vitro and experimental animal observations of incomplete or lack of efficacy, unless the antivenom is administered for protection prior to venom administration.[51,231] Some have noted that CSL box-jellyfish antivenom, which is raised against "milked" venom derived from electrical stimulation of tentacles stretched over a membrane, may not have complete efficacy against tentacle-derived venom encountered in vivo. In an in vivo (rodent) comparison of the efficacy of CSL box-jellyfish antivenom with antibodies raised against nematocyst-derived *C. fleckeri* venom, antibodies were able to neutralize the cardiovascular collapse produced by the venom, but large amounts of antivenom were required and needed to be preincubated with the venom to be protective. The authors interpreted these results to indicate a very rapid action of the toxins and that antivenom is unlikely to be clinically effective because it cannot be administered early enough.[231] The effectiveness of the antivenom remains the subject of debate, because no controlled trials or observational studies exist to support its effectiveness.[43] Furthermore, administration of antivenom in the actual field situation is often delayed and suboptimal, and deaths have occurred despite its administration. None of these observations mandates that it not be used, but they do call into question whether, in what circumstances, and to what degree antivenom might be effective. Until further notice, its use is still widely recommended.

Another line of inquiry seeks to understand whether there is any benefit to adjunctive therapy if antivenom is used. In an investigation that sought to quantify the in vivo cardiovascular effects of box-jellyfish venom in rats, efficacy of pretreatment with antivenom, verapamil, and magnesium sulfate was undertaken. Box-jellyfish venom was injected intravenously and produced a transient hypertensive response followed by hypotension and cardiovascular collapse. Pretreatment with antivenom did not have any effect on the venom-induced pressor response but prevented cardiovascular collapse in some of the animals. Administration of verapamil alone or in combination with antivenom did not have any beneficial effect; however, verapamil negated the protective effects of antivenom. Magnesium sulfate administration alone was not beneficial; however, combined with antivenom, it prevented cardiovascular collapse in all animals. In a different study in which a cell-based assay for screening of antidotes to and antivenom against *C. fleckeri* venom was deployed, it was determined that box-jellyfish antivenom could neutralize certain effects of the venom only if added prior to administration of the venom, and that felodipine and $MgSO_4$ potentiated detrimental effects of the venom. The extrapolation of these animal data to humans treated with antivenom is theoretical.[168]

Burnett and Calton[17,25,34] discovered that verapamil can prolong the lives of mice challenged with box-jellyfish, sea nettle, or Portuguese man-of-war venom. Verapamil was considered to be inactive or deleterious in anesthetized laboratory pigs envenomed with box-jellyfish venom.[207] Extrapolation of these data to humans is as yet untested. Although there is logic to using verapamil from a theoretical pharmacologic perspective (venom affects calcium influx through voltage-dependent channels; elevated calcium levels may represent cell death), the suitability of using verapamil as an adjunct to therapy in humans has been questioned because of the perceived problem of administering a hypotensive agent during an episode of cardiac decompensation.[89] In a cell-based assay to evaluate antidotes to box-jellyfish venom, verapamil had no effect and felodipine was detrimental.[107] Calcium channel–blocker drug use is currently not recommended for any form of jellyfish sting.

If a sting is mild (not life-threatening), one may use nonmoist ice packs for initial pain relief, along with a parenteral analgesic. Even with successful treatment, skin irritation may persist for months, marked by discolored striae, intermittent desquamation, and pruritus. Type IV hypersensitivity reactions with *Chironex* stings may occur more commonly than previously thought; they may be attributable to retained foreign material.[155]

Irukandji Jellyfish

Carukia barnesi, the carybdeid jellyfish known as Irukandji, is a small (1 to 2.5 cm across the bell) translucent jellyfish with four thin nematocyst-covered tentacles (5 to 7 cm in length at rest, and up to 70 cm [27.5 inches] extended) found off the coast of northern Australia in both inshore and open waters.[11,116,143,191] Barnes demonstrated that *C. barnesi* causes Irukandji syndrome.[11] With this species, most stings occur near shore and during the afternoon.[158] Because the jellyfish tend to aggregate, victims often present in clusters. Furthermore, victims can be stung inside stinger-resistant enclosures, even when the mesh is as small as 2 cm diagonally.[57]

It has been reported that additional species of jellyfish can cause Irukandji syndrome. These include *Alatina mordens, C. alata, Malo maxima, Carybdea xaymacana,* and perhaps others.[118,119,232] Other carybdeid medusae that envenom with varying severity include the jimble *(C. rastoni)* and fire jelly *(Tamoya haplonema).* The morbakka is a stinging creature that resembles the Irukandji but is larger. Its bell, which measures up to 12 by 16 cm, is covered with clumps of nematocysts and may be as dangerous to handle as the meter-long tentacles. This animal may have been previously misidentified as *Tamoya.* An Irukandji-like syndrome has been reported in South Florida divers, but the jellyfish species was not identified.[77]

Clinical Aspects. The immediate skin reaction is characterized by stinging pain that is often not severe, followed by erythema at the sting site. Within minutes, irregularly spaced papules of 2 mm in diameter may develop. The venom may then induce a more severe reaction of restlessness, muscle pain and spasm, severe lumbosacral back pain, lower leg pain, priapism, abdominal pain, pancreatitis, parasympathetic dysautonomia, respiratory difficulty (including painful breathing), headache, shivering, tremor, nausea, and vomiting, which progress to profound weakness and collapse. Localized piloerection and sweating have been reported to occur commonly. Generally, the discomfort remits in 6 to 24 hours; however, it occasionally recurs. The *Irukandji syndrome* (named by Hugo Flecker for an Aboriginal tribe in the Cairns region of Australia) presupposes massive catecholamine release, with abdominal and chest pain, a sensation of chest tightness, pallor or peripheral cyanosis, vomiting, diaphoresis, hypertension (diastolic blood pressure to 140 mm Hg), oliguria, tachycardia, ventricular tachycardia, cardiomyopathy, severe pulmonary edema, cerebral edema, troponin leak, and hypokinetic heart failure.[44,63,130,148,177] This resembles what might be seen with a pheochromocytoma. Papilledema and coma in a child have been described.[60] Although the systemic syndrome can be quite distinctive, there may be minimal cutaneous signs of envenomation.[83,148] Two deaths have been reported, both attributed to intracerebral hemorrhage associated with hypertension.[58]

It is interesting to note that many Irukandji-like stings occur inside stinger enclosures (bathing nets) designed to exclude *C. fleckeri*. Although residents of Irukandji-endemic areas are often aware that stinger-resistant enclosures do not prevent entry of the smaller jellyfish, many tourists, particularly those from countries other than Australia, are not aware.[85,148]

Treatment. It is not determined whether or not there is a suitable topical decontaminant for an Irukandji sting, and it has been noted that the skin manifestations may be comparatively innocuous, so rapid field therapy may not be undertaken. In addition to the standard cnidarian measures and supportive therapy, IV phentolamine (5 mg initially, followed by 5- to 10-mg doses as needed) may be administered to control high blood pressure. However, because acute cardiac failure may be a feature of envenomation, administration of an α-adrenergic blocking drug should be undertaken with close cardiovascular monitoring and perhaps preliminary echocardiography, supplemented as needed in a case of severe or rapidly progressive illness.[117] Administration of box-jellyfish antivenom does not significantly relieve symptoms. Propranolol or other β-adrenergic blockers should not be used to control tremor, as these might precipitate catastrophic hypotension, or might contribute to unopposed α-adrenergic stimulation predisposing to myocardial ischemia.[57] Fentanyl has been suggested for pain relief because it does not cause cardiac depression.[117] One report noted resolution of agitation and sympathetic features, and significant resolution of pain, in a victim of Irukandji syndrome treated with magnesium sulfate (loading dose 10 mmol [≈ 2.5 g or 20 mEq], followed by an infusion of 5 mmol/hr).[41]

Chrysaora (Sea Nettles)

Sea nettles (such as *C. quinquecirrha* and *C. capillata*) are considerably less lethal animals and can be found in both temperate and tropical waters, particularly in the Chesapeake Bay, where they are found in seasonal plague proportions.[139] Not as dangerous as the Indo-Pacific box-jellyfish, they are still capable of inducing a moderately severe sting. *C. quinquecirrha* and similar species carry a proteinaceous venom that contains at least seven enzymes, with at least one antigenic and thermolabile component that is cardiotoxic, neurotoxic, and dermatonecrotic.[73] The venom also contains histamine, histamine releasers, prostaglandins, serotonin, and kinin-like factors (kinin-like factors have also been found in venoms of *C. fleckeri* and *P. physalis*).[23] Large intradermal injections of crude sea nettle venom in normal saline produced immunosuppression (T cells) for several days, with a homologous reaction against the same cnidarian antigen and a heterologous reaction against antigens contained within vaccinia and herpes simplex viruses and tetanus bacillus.[212]

Clinical Aspects. The clinical presentation of a sea nettle envenomation is similar to that of *Physalia* species, with perhaps a greater incidence of systemic complications. Death is exceedingly rare. Elevated levels of serum anti–sea nettle venom IgM, IgG, and IgE may persist for years in victims who suffer exaggerated reactions to *C. quinquecirrha* stings. These antibodies cross-react with *Physalia* venom and have been postulated to be of value in identifying victims at risk for a severe reaction.[24] This technique is not widely available or frequently used, and its reliability and reproducibility require further verification.

The reaction after a sting by the blubber jellyfish (*Catostylus* species) is relatively mild, with the formation of wheals, erythema, and pruritus limited to the areas of contact. Systemic effects are exceedingly rare. *Cyanea* species carry long thin tentacles that induce a similar effect, with occasional muscle aching, nausea, and drowsiness, particularly in small children. *Pelagia* species also induce wheals, which are more circinate or irregularly shaped and may not follow a linear pattern. The venom is sufficiently toxic to cause a severe generalized allergy, with bronchospasm and pruritus.

Treatment. Treatment for a sea nettle envenomation is similar to that for the sting of *Physalia* species. Baking soda may be the most effective commonly available initial detoxicant, followed by papain and Stingose. One study found that ammonia, ethanol, and vinegar may increase the sensation of pain from sea nettle envenomation and cause discharge of nematocysts.[16] Topical lidocaine is the anesthetic of choice if a patient presents with painful lesions. Monoclonal antibodies to jellyfish venoms have been developed that demonstrate cross-reactivity among venoms of a variety of cnidarians, which may allow development of a single protective antivenom or vaccine.

CLASS ANTHOZOA

The class Anthozoa includes sea anemones, stony (true) corals (subclass Zoantharia), and soft corals (subclass Alcyonaria). Anemones are considered here because they envenom.

Actinaria (Anemones)

Actinarians (sea anemones) are abundant (1000 species) multicolored animals with sessile habits and a flower-like appearance (Figures 74-62 and 74-63). They are composed of stalked, finger-like projections capable of stinging and paralyzing passing fish. Their sizes range from a few millimeters to more than 0.5 m (1.7 feet); they are found at depths of up to 5303 m (2900 fathoms). The insides of some anemones can be eaten after they are dried.

Anemones can be colorful creatures and may be found in tidal pools, where the unwary brush up against them or inquisitively

FIGURE 74-62 Detail of grape-like vesicles of sea anemone (*Actinaria* species). *(From Gary Bell:* oceanwideimages.com.*)*

FIGURE 74-63 Orange stinging anemone. *(Copyright Lynn Funkhouser.)*

FIGURE 74-65 Clownfish in peaceful coexistence with a sea anemone. *(Courtesy Paul Auerbach, MD.)*

touch them. Other anemones burrow into bottom mud or sand. Like other cnidarians, they possess tentacles loaded with one of two variations of the nematocyst, either the sporocyst or the basitrichous isorhiza (basitrich). These wreak havoc once stimulated by an unfortunate victim. Some sporocysts are adhesive and act to hold and envenom prey. To present a greater number of nematocysts to the victim, an exposed anemone inflates the tentacles by filling them with water. Many anemones also secrete mucus, which covers the anemone's body and may contain cytolytic and hemolytic protein toxins. These may serve to repel potential predators.

Although a number of sea animals, such as clownfish (anemonefish) of the genera *Amphiprion* and *Premnas,* live in symbiosis with certain anemones *(Heteractis* species, *Stichodactyla* species, *Macrodactyla doreensis, Entacmaea quadricolor,* and *Cryptodendrum adhaesivum),* humans are not so fortunate and are frequently stung when attempting to handle these not so delicate "flowers." The clownfish have evolved resistance to the anemone's sting by repeated contact and development of a mucous coat (Figures 74-64 and 74-65), and perhaps by immunity.[137]

Sea anemones contain biologically active substances, including neurotoxins (sodium channel inactivation, stabilizing the open state conformations), cardiotoxins, hemolysins (for erythrocytes and platelets), and proteinase inhibitors.[138,186] A ubiquitous and well-studied class of sea anemone toxins is composed of cytolytic polypeptides of four known groups based on differing molecular properties and modes of action.[195] Cytolytic toxins elaborated by anemones include cytolysins, which are thought to exert their effect by damaging membranes via pore or channel formation. A cytolytic toxin has been isolated from the Indo-Pacific sea anemone *Stoichactis kenti*.[15] The anemone *Actinia equina* elaborates cytolytic polypeptide toxins known as equinatoxins, which may induce hemolysis and cardiorespiratory arrest in animals, attributed by some to coronary vasospasm.[124] Tenebrosin-C from the anemone *Actinia tenebrosa* is a positive inotrope that can be inhibited by the cyclooxygenase blockers indomethacin and aspirin, a lipooxygenase blocker and leukotriene antagonist, and mepacrine (a phospholipase A_2 inhibitor).[69] Potassium channel toxins have been isolated from the sea anemones *Bunodosoma granulifera* and *Stichodactyla helianthus*.[88,151] Palytoxin has been found in the sea anemone *Radianthus macrodactylus*.[126] Granulitoxin is a lethal neurotoxic peptide isolated from *B. granulifera*.[178]

FIGURE 74-64 Clownfish nestled in anemone. *(Copyright 2011 Norbert Wu:* norbertwu.com*.)*

Clinical Aspects. Most victims are stung when they handle or accidentally brush against an anemone in shallow water. Nudists may acquire genital injuries; small children may accidentally or intentionally ingest tentacles. The dermatitis caused by contact with an anemone is similar in all regards to that from fire coral or a small man-of-war; it is often likened to a bee sting. The variation in skin reaction is related to the specific toxicity of the venom, so that while *Actinia* species produce painful urticarial lesions, *Anemonia* species induce paresthesias, edema, and erythema. Most commonly, the initial skin lesion is centrally pale with a halo of erythema and petechial hemorrhage. This is soon followed by edema and diffuse ecchymosis. If the envenomation is severe, intense local hemorrhage, vesiculation, necrosis, skin ulceration, and secondary infection may occur, particularly after the stings of certain species *(Sagartia, Actinia, Anemonia, Actinodendron,* and *Triactis).* In Floridian waters, the turtle grass anemone *Viatrix globulifera,* translucent-white and less than 2.5 cm (1 inch) in diameter, is very hazardous, particularly for fishermen wading on grass flats. The Hell's fire sea anemone *(Actinodendron plumosum)* is aptly named. Systemic reactions are less likely after the sting of an anemone than after that of a man-of-war; reactions include fever, chills, somnolence, malaise, weakness, nausea, vomiting, and syncope. Fulminant fatal hepatic failure 3 days after a sea anemone sting of approximately 3 cm (just greater than 1 inch) in diameter on the scapula and complicated by coma, severe coagulopathy, and renal failure has been attributed to *Condylactis* (Figure 74-66) (commonly found in reefs and lagoons of south Florida, the Bahamas, and the Caribbean) on the basis of a positive serum test of IgG by ELISA at a dilution of 1:450.[70]

In most cases, mild envenomations resolve within 48 hours. More severe reactions, characterized by discoloration and vesicle formation, may become indolent, with eschar leading to residual hyperpigmentation, hypopigmentation, or keloid formation.

FIGURE 74-66 Giant anemone *(Condylactis gigantea). (From Norbert Wu, with permission:* norbertwu.com*.)*

Sponge fisherman's (diver's) disease is caused by contact with an anemone *(Sagartia* or *Actinia)* that attaches itself symbiotically to the base of a sponge. A few minutes after contact with the sponge, the victim's skin begins to itch and burn, with development of erythema and small vesicles. As described previously, this transforms to a darkened purple appearance, with frequent systemic components (headache, nausea, vomiting, fever, chills, and muscle spasm).

Treatment. Treatment for an anemone envenomation is similar to that for the sting of *Physalia* species. The dermatitis is frequently more severe and may require prolonged wound care consisting of debridement and antibiotic therapy for secondary infection. The healing process is generally slower after an anemone sting than after a man-of-war envenomation.

PHYLUM ECHINODERMATA

The phylum Echinodermata ("spiny skin") has five classes: sea lilies, brittle stars, starfish, sea urchins, and sea cucumbers. Only the last three are of medical interest in humans, although some brittle stars carry toxins capable of causing paralysis and death in small animals.

STARFISH

Life and Habits

Starfish are simple, free-living, stellate echinoderms covered with thorny spines of calcium carbonate crystals held erect by muscle tissue. The creatures move on the ocean floor by means of tube feet located under the arms (rays). They eat other echinoderms, mollusks, coral, worms, and poisonous shellfish. Starfish proliferation and the destruction of coral beds within the Great Barrier Reef off the coast of Australia is a conservation issue of international concern. The starfish everts its membranous stomach through its mouth and secretes digestive enzymes that destroy coral polyps. Only the stark white coral skeleton remains. The crown-of-thorns starfish *(Acanthaster planci)* is found in the coral reef communities of the Great Barrier Reef, throughout the Pacific and Indian Oceans, in the Red Sea, and in the Gulf of California.

Venom and Venom Apparatus

Glandular tissue interspersed in or lying underneath the epidermis (integument) produces a slimy venomous substance. The carnivorous *A. planci* is a particularly venomous species, normally 25 to 35 cm (10 to 14 inches) in diameter but up to 70 cm (27.5 inches) in diameter, with 7 to 23 arms (Figure 74-67). The sharp, rigid, and venomous aboral spines of this animal may grow to 4 to 6 cm (1.6 to 2.4 inches) (Figure 74-68). Potentially toxic saponins and histamine-like compounds have been isolated from the spine surfaces; crude venom extracts demonstrate hemolytic, capillary permeability–increasing, myotoxic (via phospholipases A_2-I and -II), myonecrotic, and anticoagulant effects. The *A. planci* lethal factor is a potent hepatotoxin in laboratory animals.[185,187] A case report described abnormal liver function after *A. planci* envenomation of a 19-year-old.[113] Plancinin is an anticoagulant purified from the crown-of-thorns starfish. This peptide shows activity in mice that suggests a longer duration of action than heparin.[100] Severe systemic hypotension, thrombocytopenia, and leukopenia were induced by *A. planci* venom in dogs.[188] Indomethacin, a cyclooxygenase inhibitor, suppressed the hypotension. *A. planci* venom caused smooth (uterine) muscle contraction in rats, which was blocked by inhibitors of prostaglandin synthesis but not by atropine.[101]

Other starfish that might envenom humans are those of the genus *Echinaster*. The slime (cushion) star *Pteraster tessalatus,* which inhabits Pacific coastal waters from Puget Sound to Alaska,

FIGURE 74-67 Crown-of-thorns starfish *(Acanthaster planci). (Courtesy Paul S. Auerbach, MD.)*

FIGURE 74-68 Spines of the crown-of-thorns starfish *(Acanthaster planci). (Courtesy Paul S. Auerbach, MD.)*

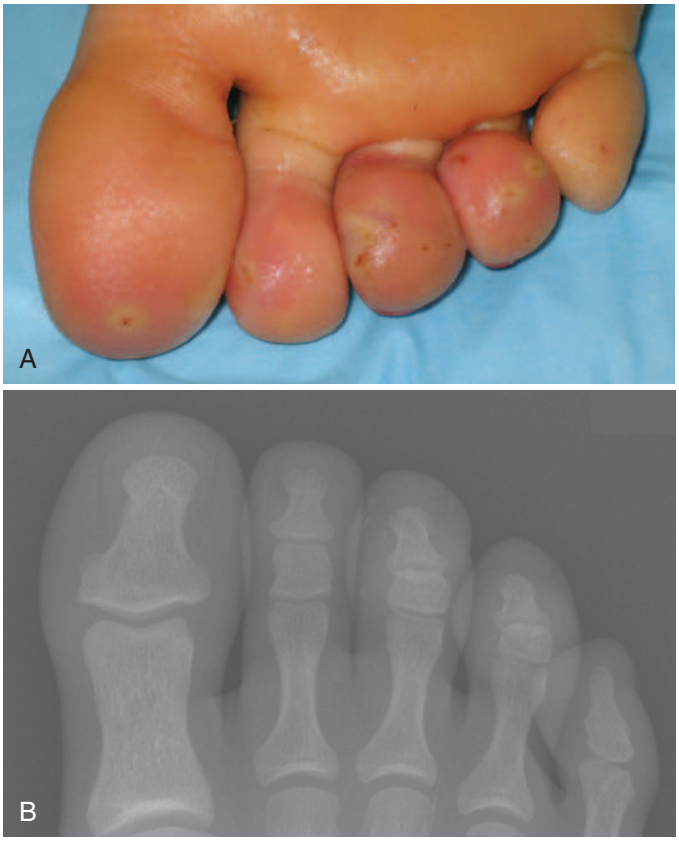


FIGURE 74-69 **A,** Crown-of-thorns starfish spine punctures to the toes. **B,** X-ray of foot of the same patient demonstrates retained spine fragments. *(Courtesy Brian Lin, MD.)*

generates the unique defense of copious gelatinous or rubbery, poisonous mucus to repel natural enemies. No human injuries have been reported to date.

Clinical Aspects

The ice pick–like spine of *A. planci* can penetrate the hardiest of diving gloves. Most spines are composed of porous crystalline magnesium calcite, articulated at the base and extremely sharp, with three raised cutting edges at the tips. As the spine enters the skin, it carries venom into the wound, with immediate pain, copious bleeding, and mild edema. The pain is generally moderate and self-limited, with remission over a period of 30 minutes to 3 hours. However, it may be of a severity to require narcotic analgesia (Figure 74-69). The wound may become dusky or discolored. Multiple puncture wounds may result in acute systemic reactions, including paresthesias, nausea, vomiting, lymphadenopathy, and muscular paralysis. If a spine fragment is retained, a granulomatous lesion may develop akin to that seen after a sea urchin puncture wound. A previously sensitized victim may suffer a prolonged reaction lasting for weeks or even months and consisting of local edema and pruritus. Tenosynovitis may affect multiple fingers simultaneously after a single puncture wound.[3] Contact with other, less injurious starfish may induce a pruritic papulourticarial eruption (irritant contact dermatitis).

Treatment

Immersion therapy may provide some relief from the pain. The wound should immediately be immersed into nonscalding hot water to tolerance (45°C [113°F]) for 30 to 90 minutes or until there is significant pain relief. The pain is occasionally severe enough to require local anesthetic infiltration. The puncture wound should be irrigated and explored to remove all foreign material. Because of the stout nature of the spines, retainment of a fragment is rarer than with sea urchin puncture. However, if a victim steps on a starfish and creates a shearing motion, the tips of spines may remain in the wound(s). If any question of a foreign body exists, a soft tissue radiograph often identifies the fractured spine. Not infrequently, the victim suffers an indolent contact dermatitis from handling a starfish such as Solaster papposus, the sun (Figure 74-70) or rose star. The dermatitis may be managed in standard fashion with topical solutions, such as calamine with 0.5% menthol, or a corticosteroid preparation. Systemic therapy is supportive. Granulomas from retained spine fragments may require excision. Starfish that have ingested poisonous shellfish are themselves toxic on ingestion.

SEA URCHINS

Life and Habits

Sea urchins are free-living echinoderms that have an egg-shaped, globular, or flattened body. A hard skeleton (test) composed of fused calcareous plates surrounds the viscera and is covered by regularly arranged spines and triple-jawed (pincerlike) pedicellariae. These pedicellariae (globiferous, or glandular) are sometimes used for defense (Figure 74-71). Urchins are nocturnal and omnivorous (mostly in pursuit of algae) eaters, yet are shy, nonaggressive, and slow-moving animals found on rocky bottoms or burrowed in sand and crevices (Figure 74-72). Their bathymetric range extends from the intertidal zone to great depths. The raw or cooked gonads of several species are eaten as a great delicacy by humans.

Venom and Venom Apparatus

Of the approximately 600 species of sea urchins, roughly 80 may be venomous to humans.[114] The venom apparatuses of sea urchins consist of the hollow, venom-filled spines and the triple-jawed globiferous pedicellariae. Venom may also be released from within a thin integumentary sheath on the external surface of the spines of certain urchins.

The spines of sea urchins, formed by calcification of a cylindric projection of subepidermal connective tissue, may be non–venom bearing, with solid blunt and rounded tips (Figure 74-73), or venom bearing (as in the families Echinothuridae and Diadematidae [Figure 74-74]), with hollow, long, slender, and sharp needles (Figure 74-75). These are extremely dangerous to handle. The spines, which are attached to the shell with a modified ball-and-socket joint, are brittle and break off easily in the flesh, lodging deeply, and removal is difficult. They are keen enough to penetrate rubber gloves and fins. *Diadema setosum* (black sea urchin) spines may exceed 1 foot in length. *Echinothrix* species also carry lengthy spines. The purple sea urchin *Strongylocentrotus purpuratus* (Figure 74-76) of California has much shorter spines. The genera *Astbenosoma* (Figures 74-77 and 74-78) and *Aerosoma* have special venom organs (sacs) on the sharp tips of the aboral spines (Figure 74-79), which introduce the potent venom.

Pedicellariae are small, delicate seizing organs attached to the stalks scattered among the spines. These are considered to be

FIGURE 74-70 Sun starfish *(Solaster). (From Norbert Wu, with permission:* norbertwu.com.*)*

FIGURE 74-71 Globiferous pedicellariae are equipped with venom glands. *(Courtesy Dietrich Mebs.)*

modified spines with flexible heads.[173] Globiferous pedicellariae, typified by those found in *Toxopneustes pileolus* (flower urchin) (Figure 74-80) and *Tripneustes* species, have globe-shaped heads that contain the venom organs (Figure 74-81). The terminal head, with its calcareous pincer jaws (two to four, but usually three), is attached by the stalk to the shell plates of the sea urchin. The outer surface of each opened "jaw" is covered by a large venom gland, which is triggered to contract with the jaw on contact. When the sea urchin is at rest in the water, the jaws are extended, slowly moving about (Figure 74-82). Anything that touches them is seized. As long as the object is moving, the pedicellariae continue to bite and envenom. Once a pedicellaria attaches to a victim, it will be torn from the shell rather than let go. Detached pedicellariae may remain active for several hours. The *Toxopneustes* sea urchin also has solid spines, but these are nonvenomous.

The venom of sea urchins contains various toxic fractions, including steroid glycosides, hemolysins, proteases, serotonin,

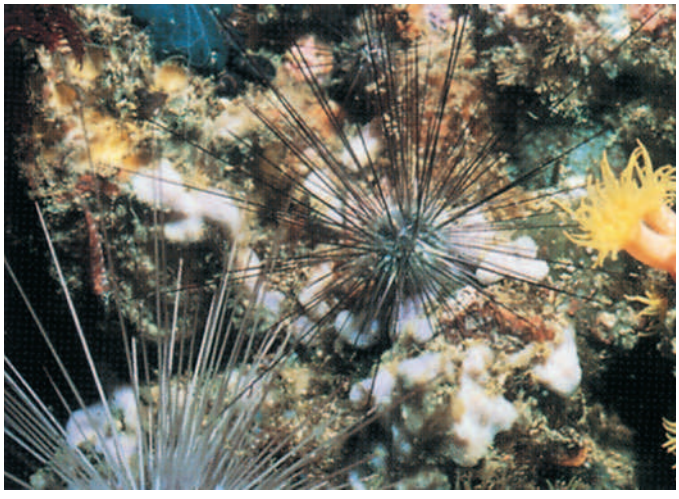


FIGURE 74-72 Needle-like spines of sea urchins in their natural habitat. *(Courtesy Kenneth Kizer, MD.)*

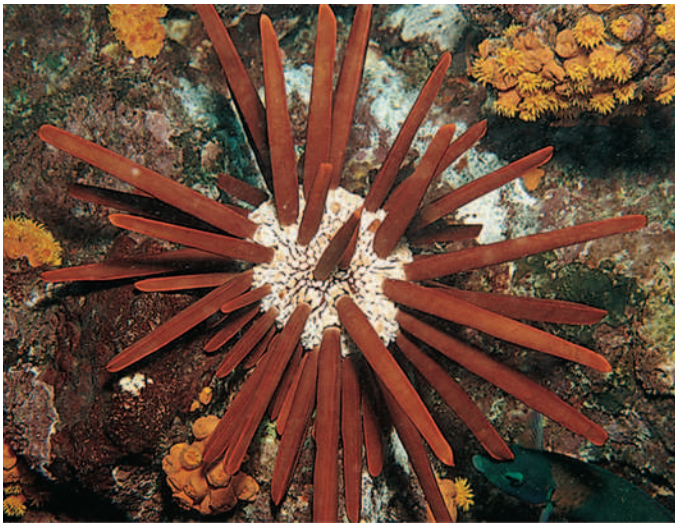
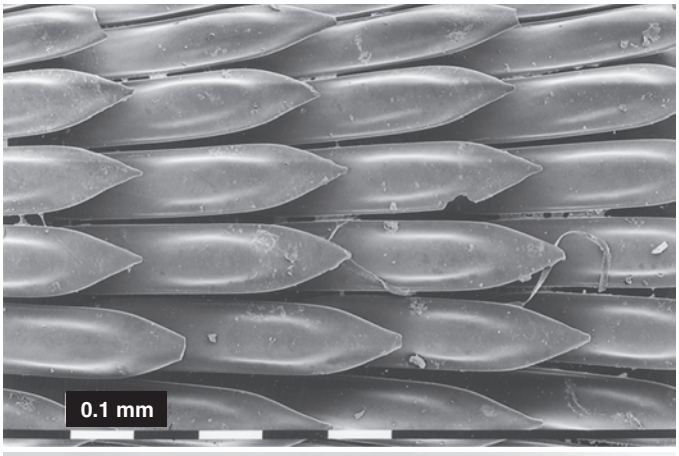


FIGURE 74-73 Nontoxic "pencil" urchin with blunt, rounded tips. *(Courtesy Paul S. Auerbach, MD.)*



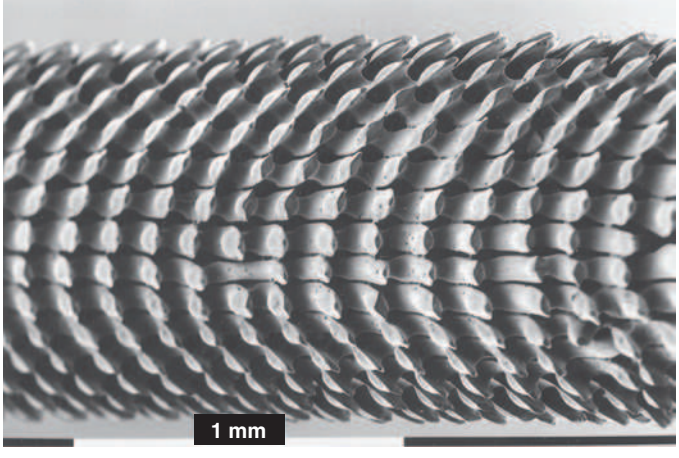


FIGURE 74-74 The spines of the diadematid sea urchin (*Diadema* species) are covered with small, tilelike structures. *(From Meier J, White J:* Handbook of clinical toxicology of animal venoms and poisons, *Boca Raton, Florida, 1995, CRC Press. Courtesy Dr. J. Meier.)*

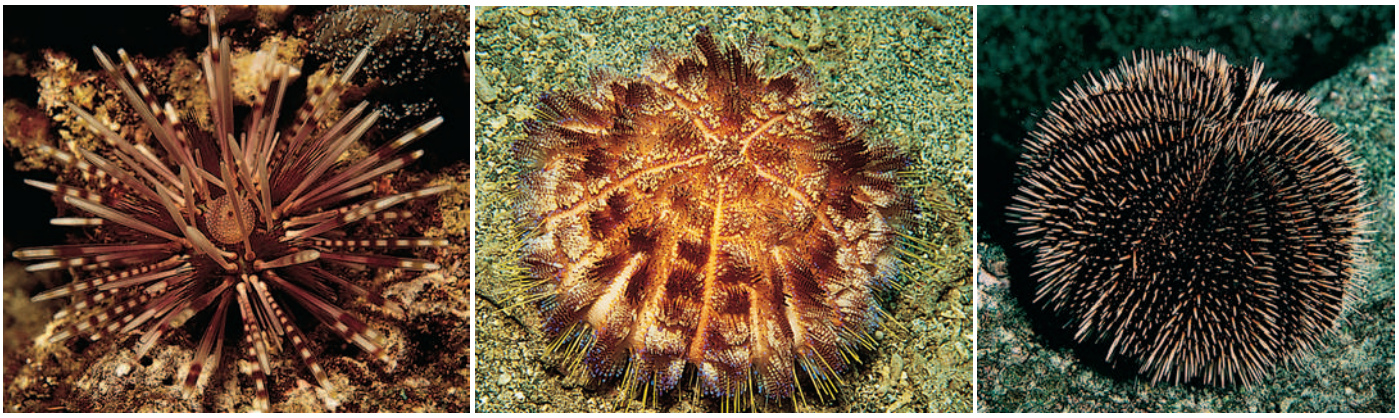


FIGURE 74-75 Three examples of sharp-spined (venomous) sea urchins. *(Courtesy Paul S. Auerbach, MD.)*

and cholinergic substances. The Pacific *Tripneustes* urchin carries a neurotoxin with a predilection for facial and cranial nerves. A toxic substance from the sea urchin *T. pileolus* induces histamine release from rat peritoneal mast cells.[202] Contractin A (a mannose-containing glycoprotein) from the pedicellariae of the same species causes contraction of isolated guinea pig tracheal smooth muscle.[145] Other substances that have been identified from sea urchin spines or pedicellariae include D-galactose–binding lectins and heparin-binding and hemolytic lectins.[144]

Clinical Aspects

Most victims are envenomed when they step on, handle, or brush up against a sea urchin.[54] Because the creatures tend to be nocturnal, divers are most commonly injured in dark waters during night diving activities, particularly in small caves or shallow turbulent waters. Young inquisitive children who explore tide pools frequently handle urchins incorrectly and may be injured. If a diver moves a hand slowly toward a spiny (venomous) sea urchin, the spines may align to offer the greatest defense.

Venomous spines inflict immediate and intensely painful stings.[110] The pain is initially characterized by burning, which

FIGURE 74-76 Purple sea urchins. *(Courtesy Howard Hall.)*

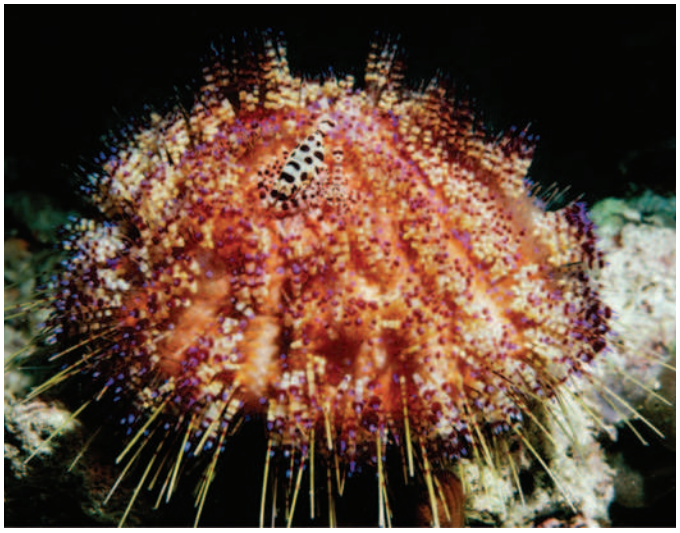


FIGURE 74-77 Pair of shrimp on an *Asthenosoma* anemone. *(Copyright Carl Roessler.)*

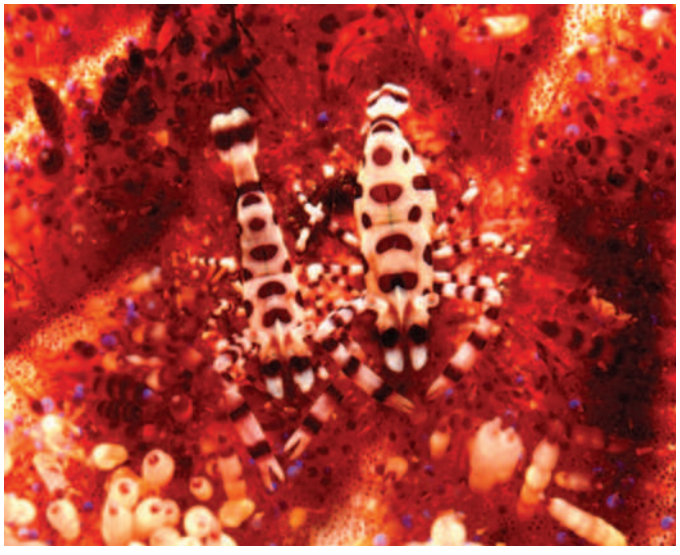


FIGURE 74-78 Porcelain shrimp in fire urchin. *(Courtesy Paul S. Auerbach, MD.)*

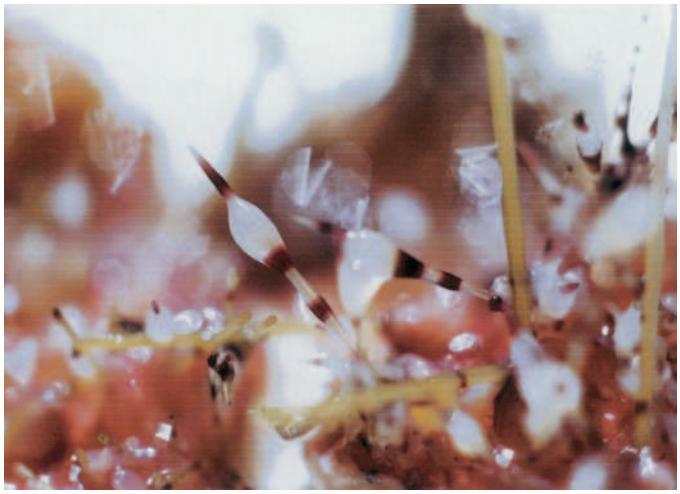


FIGURE 74-79 The tips of the short spines of the leather urchin (e.g., *Asthenosoma* from the Indo-Pacific) are encased by a venom gland. *(Courtesy Dietrich Mebs.)*

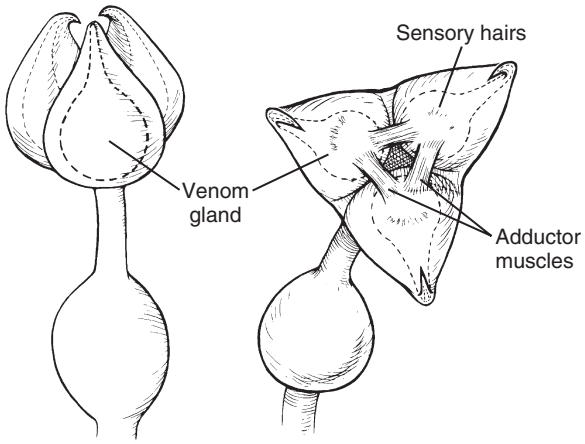


FIGURE 74-81 Globiferous pedicellaria of a sea urchin, used to hold and envenom prey.

rapidly evolves into severe local muscle aching with visible erythema and swelling of the skin surrounding the puncture site or sites (Figure 74-83). Frequently, a spine breaks off and lodges in the victim. Some sea urchin spines (such as those of *D. setosum* or *S. purpuratus*) contain black-purplish dye, which may give a false impression of spines left in the skin (Figures 74-84 to 74-86). Soft tissue density x-ray techniques, ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) may reveal a radiopaque foreign body. If a spine enters a joint, it may rapidly induce severe synovitis. Over time, if the spine remains embedded in or near the joint, this may progress to arthritis.[114] There may be a symptom-free period of 1 to 2 months between the initial injury and the onset of fusiform swelling, limited motion, and pain of the affected joint, which reflect joint effusion and soft tissue thickening, followed by osteolysis, sharply demarcated bone erosion, and periosteal reaction. Radiography may not reveal a visible spine but may show soft tissue swelling and osteolysis.[213] Gadolinium-enhanced MRI may be useful to identify subtle changes, such as synovial proliferation.[114] If multiple spines have penetrated the skin, particularly if they are deeply embedded, systemic symptoms that may rapidly develop include nausea, vomiting, paresthesias, numbness and muscular paralysis, abdominal pain, syncope, hypotension, and respiratory distress. The presence of a frank neuropathy may indicate that the spine has lodged in contact with a peripheral nerve. The pain from multiple stings may be sufficient to cause delirium. Secondary infections and indolent ulceration are common. A delayed hypersensitivity–type reaction (flare-up) at the sites of the punctures has been described, in which the victim demonstrates erythema and pruritus in a delayed fashion, 7 to 10 days after primary resolution from the initial envenomation.[6] The sensitizing antigen in such cases has yet to be identified. Hepatic transaminasemia after a relatively minor puncture has been reported, which may have been caused by the envenomation or by therapy with cephradine and mefenamic acid.[235] Eosinophilic pneumonia has been associated with, but not proved to be related to, foot injury from a sea urchin.[108]

Three separate unusual cases have been reported to the lead author since 1993 by neurologists. In each case, the victim sustained multiple punctures from one or several black sea urchins in Hawaiian waters. The immediate clinical reaction was typical, but it was followed in 6 to 10 days by severe bulbar polyneuritis with respiratory insufficiency. In two cases, the victims were hyporeflexic and appeared to suffer a Guillain-Barré variation with elevated protein levels in the cerebrospinal fluid. In the other case, the victim manifested meningoencephalitis documented by MRI. The temporal relationship to the urchin stings suggests an autoimmune phenomenon.

A spine that enters a finger in proximity to the nail apparatus may cause a subungual or periungual granulomatous nodular lesion. Excision may cause permanent nail plate dystrophy. Small, firm, and erythematous chronic inflammatory cutaneous nodules (granulomas) of the palms, dorsa of the hands, elbows, knees, and other areas of skin contact may be persistent.[97]

FIGURE 74-80 Flower urchin *(Toxopneustes pileolus). (Courtesy Ken Kizer, MD.)*

FIGURE 74-82 Close-up of opened flower urchin *(Toxopneustes pileolus)* pedicellariae seeking prey. *(Courtesy Ken Kizer, MD.)*

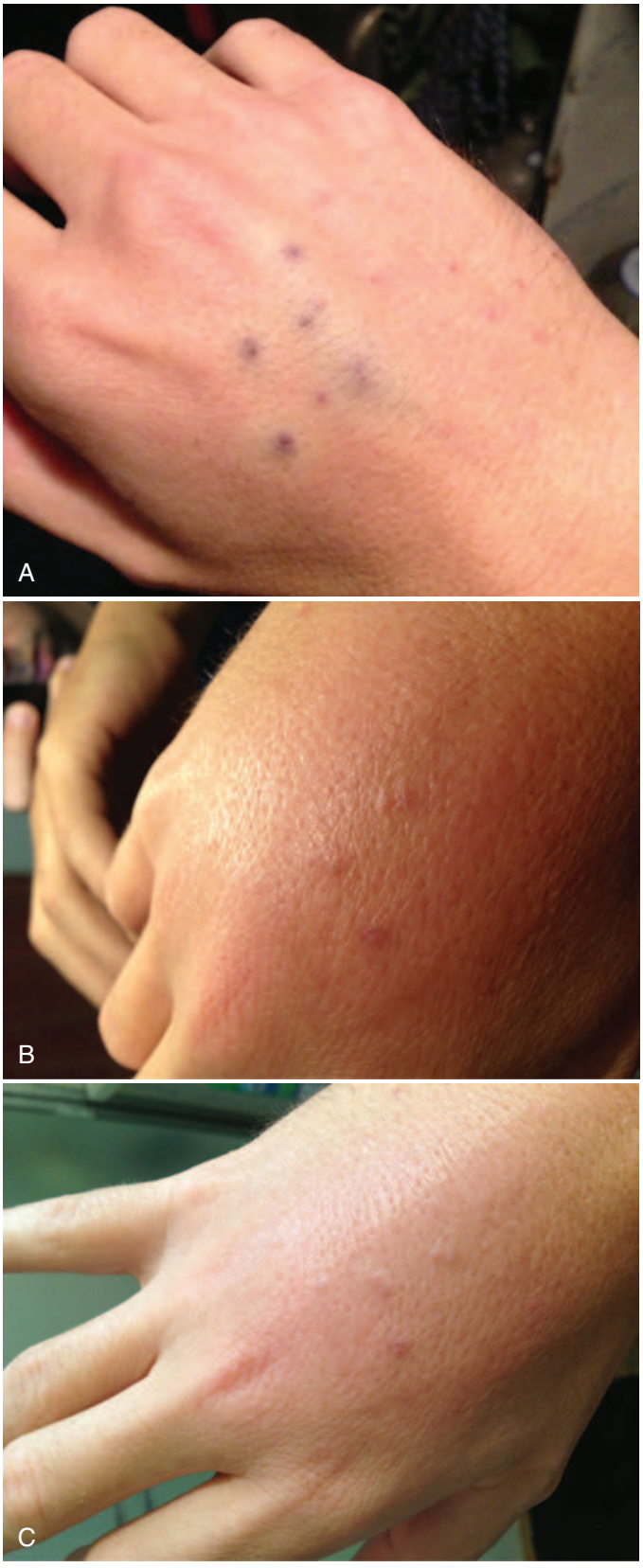


FIGURE 74-83 Swelling of the hand associated with sea urchin punctures. **A,** Soon after the injury. **B,** 24 hours after the injury. **C,** Resolving swelling. *(Courtesy John Martin.)*

The stings of pedicellariae are often of greater magnitude, causing immediate intense radiating pain, local edema and hemorrhage, malaise, weakness, paresthesias, hypesthesia, arthralgias, aphonia, dizziness, syncope, generalized muscular paralysis, respiratory distress, and hypotension; death is a rare occurrence. In some cases, the pain disappears within the first hour, but the localized muscular weakness or paralysis persists for up to 6 hours.

Treatment

The envenomed body part should immediately be immersed in nonscalding hot water to tolerance (upper limit, 45°C [113°F]) for 30 to 90 minutes in an attempt to relieve pain. Hot candle wax application has been used successfully. Any pedicellariae still attached to the skin must be removed or envenomation will continue. This may be accomplished by applying shaving foam and gently scraping with a razor. Embedded spines should be removed with care because they easily fracture. Black or purplish discoloration surrounding the wound after spine removal is often merely spine dye and therefore may be of no consequence. Although some thin venomous spines may be absorbed within 24 hours to 3 weeks, it is best to remove those that are easily reached. All thick spines (calcium carbonate, magnesium carbonate, and silica) should be removed because of the risk of infection, foreign body encaseation granuloma, or dermoid inclusion cyst.

Although some persons recommend crushing embedded spines in situ, external percussion to achieve fragmentation may prove disastrous if a chronic inflammatory process is initiated in sensitive tissue of the hand or foot. If the spines have acutely entered joints or are closely aligned to neurovascular structures, the surgeon should take advantage of an operating microscope in an appropriate setting to remove all spine fragments. The extraction should be performed as soon as possible after the injury. If the spine has entered an interphalangeal joint, the finger should be splinted until the spine is removed to limit fragmentation and further penetration. This also may control the fusiform finger swelling (Figure 74-87) commonly noted after a puncture in the vicinity of the middle or proximal interphalangeal joint. It is inappropriate to rummage about in a hand wound in the emergency department, virtually looking for a needle in a haystack. After a spine has been embedded in soft tissue for 24 to 48 hours, the spine dye may be absorbed, and the spine becomes flesh colored and very difficult to locate. If the spine is lodged

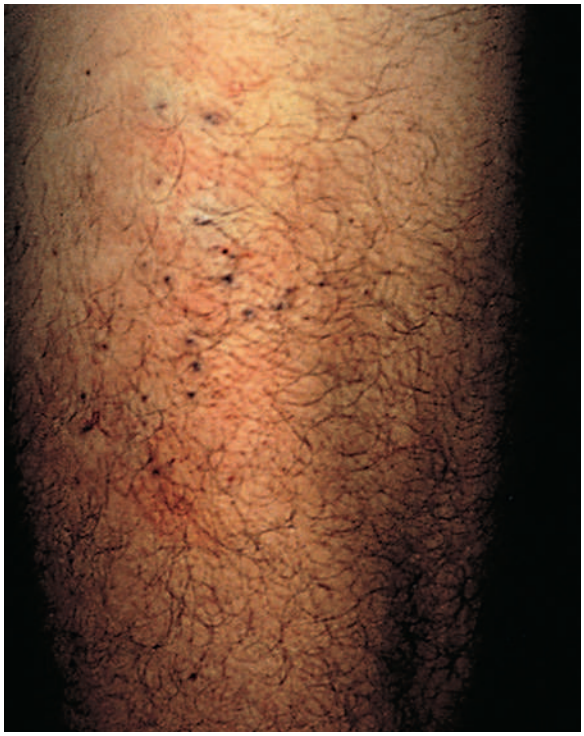


FIGURE 74-84 Thigh of the author demonstrating multiple sea urchin punctures from black sea urchins *(Diadema)*. Within 24 hours, the black markings were absent, indicative of spine dye without residual spines. *(Courtesy Ken Kizer, MD.)*

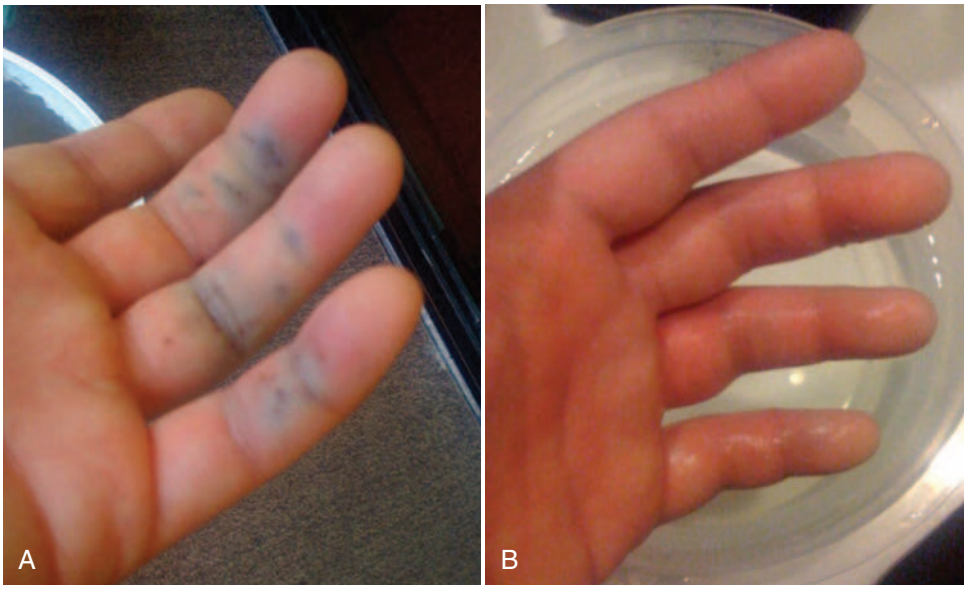


FIGURE 74-85 **A,** Multiple sea urchin punctures to hand soon after injury and following a soak in hot water. **B,** Same hand after 6 days without intervening therapy other than soaking. Lack of discoloration indicates absorption of dye from sea urchin spines and probable absence of retained fragments.

in avascular tendon or ligament, the spine dye may persist for a longer period, allowing easier identification of the foreign body. If surgery is undertaken to remove a spine, particularly of the hand, an elliptical skin incision may allow better visualization with magnification to aid in complete spine removal.[146]

If the presence of a spine is in question, soft tissue density radiographic techniques for a radiopaque foreign body may be diagnostic. CT or MRI (Figure 74-88) may be quite useful to locate spine fragments. Although the calcium carbonate is relatively inert, it is accompanied by slime, bacteria, and organic epidermal debris. Therefore, secondary infections are common (Figure 74-89), and deep puncture wounds are an indication for prophylactic antibiotics.

Some sea urchin spines are phagocytosed in the soft tissues and ultimately dissolve. The granulomas caused by retained sea urchin spine fragments have sarcoidal histologic features and generally appear as flesh- or dye-colored surface or subcuticular nodules 2 to 12 months after the initial injury (Figure 74-90).[171] In thin-skinned areas, these nodules are erythematous and rubbery, painless, and infrequently umbilicated. In thicker-skinned areas (palms, soles, and knees) that are frequently abraded, they have a keratinized appearance. Although necrosis and microabscess formation may be evident microscopically, suppuration is unusual. Rarely, the destructive nature of the inflammatory process may be severe enough to necessitate amputation of a digit. If a spine cannot be removed and becomes a nidus for cyst or granuloma formation, the lesion may be removed surgically. Intralesional injection with a corticosteroid (triamcinolone hexacetonide, 5 mg/mL) is less efficacious but may be successful. Erbium-YAG laser (emission wavelength 2940 nm) ablation has been used to destroy multiple sea urchin spines in the sole of the foot, with resulting circumscribed crater

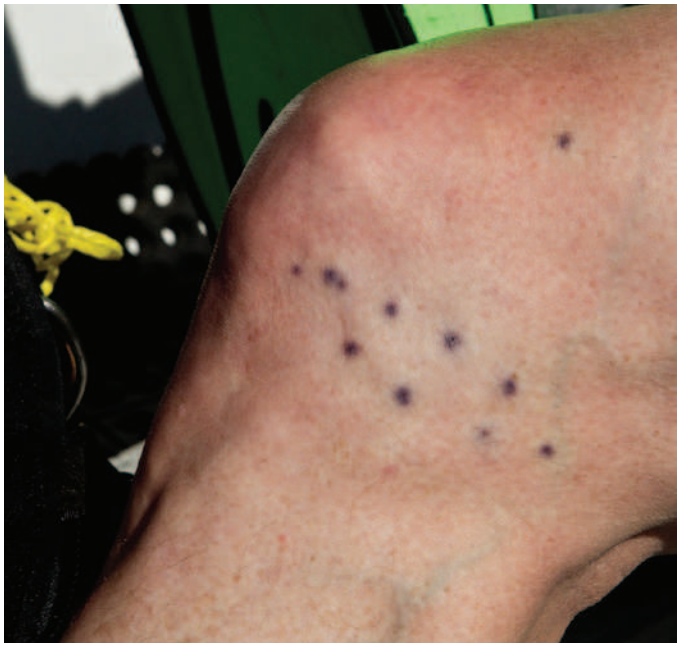


FIGURE 74-86 Sea urchin spines that have punctured the knee. *(Copyright Stephen Frink.)*

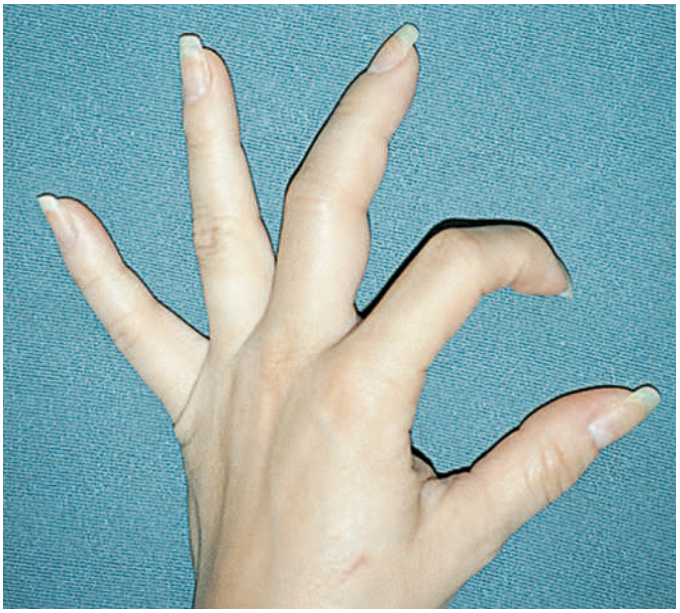


FIGURE 74-87 Finger swelling from sea urchin puncture. A single spine entered the palm over the mid–third metacarpal bone. Swelling was severe in the second and third digits. *(Courtesy Paul S. Auerbach, MD.)*

FIGURE 74-88 Magnetic resonance imaging of the hand of a victim of multiple sea urchin spine punctures, demonstrating the presence of spine fragments in the soft tissues. *(Courtesy Paul S. Auerbach, MD.)*

lesions with tiny pinpoint areas of bleeding and scattered focal hyperkeratosis without scarring but with some delayed (2 years) granulomatous reactions.[183] Systemic antiinflammatory drugs may be minimally helpful but are not substitutes for removal of the spine. A diffuse delayed reaction, consisting of cyanotic induration, fusiform swelling in the digits, and focal phalangeal bony erosion, may be treated with a systemic corticosteroid and

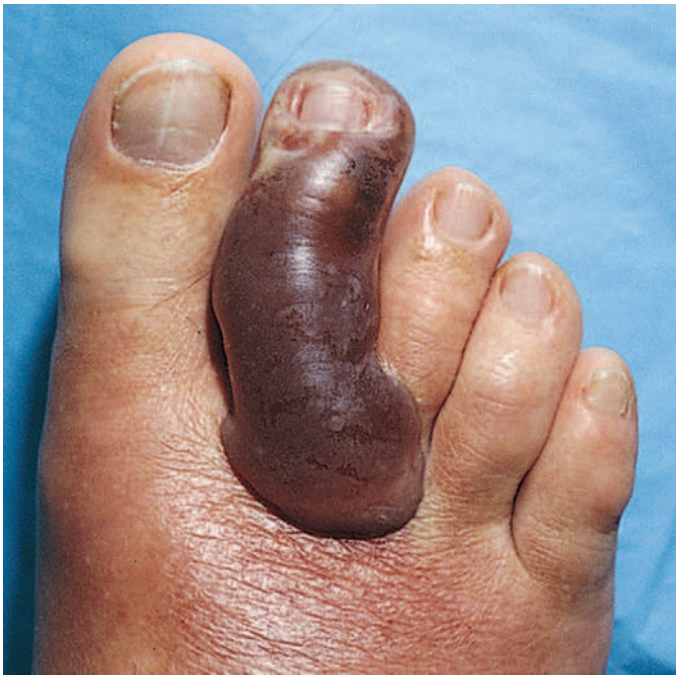


FIGURE 74-89 Infection after sea urchin puncture. The rapid-onset, gas-containing hemorrhagic blister and severe cellulitis with sepsis are common features of infection with *Vibrio* species. *(Courtesy Paul S. Auerbach, MD.)*

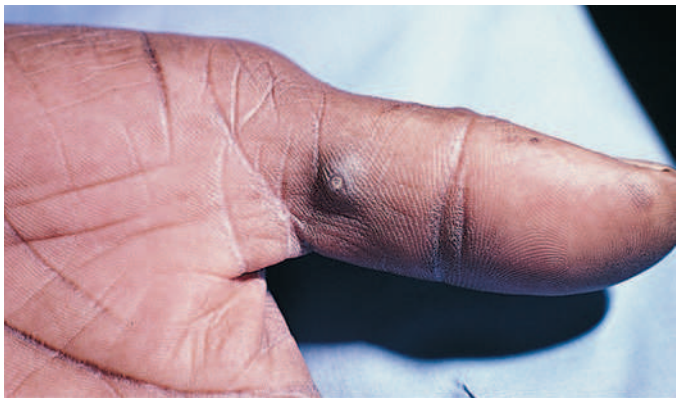


FIGURE 74-90 Subcuticular nodule after sea urchin puncture. *(Courtesy Paul S. Auerbach, MD.)*

antibiotics. Sea urchin spine arthritis of the hand in the proximal interphalangeal joint not responsive to antibiotics or nonsteroidal antiinflammatory agents has been successfully treated with synovectomy of the joint combined with removal of granulation tissue around the joint.[213]

SEA CUCUMBERS

Life and Habits

Sea cucumbers are free-living worm- or sausage-shaped bottom feeders of diverse external patterns and coloration (Figure 74-91) that are essentially scavengers. They are cosmopolitan in distribution, found in both shallow and deep waters. Cucumbers are harvested as a food (trepang, bêche-de-mer) in the South Pacific.

Venom and Venom Apparatus

Cucumbers produce in their body walls a visceral cantharidin-like liquid toxin (holothurin). Holothurin is concentrated in the tentacular organs of Cuvier, which can be projected and extended anally when the animal mounts a defense (Figure 74-92). Toxic genera include *Actinopyga, Stichopus,* and *Holothuria*. Some cucumbers dine on nematocysts and thus can secrete cnidarian venom as well.

Clinical Aspects

Holothurin may induce contact dermatitis when the tentacular organs directly contact the skin. Generally, the substance is diluted in the surrounding ocean water and the reaction is minimal; however, persons who dissect sea cucumbers topside in the preparation of food products may inadvertently handle the toxin and develop papular skin irritation. The major risk for

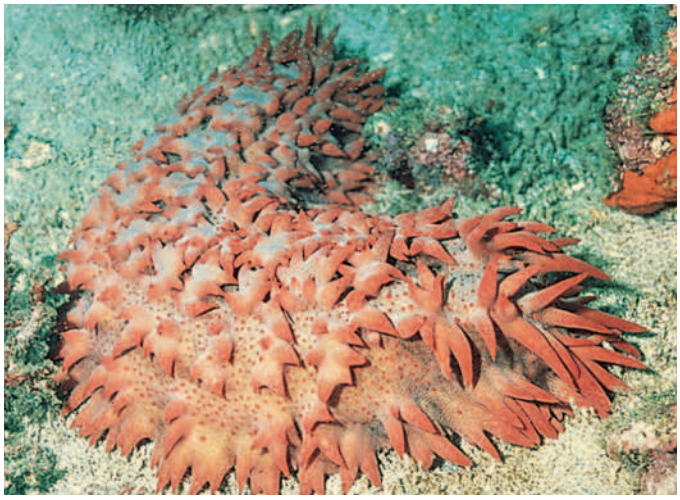


FIGURE 74-91 Sea cucumber. *(Courtesy Paul S. Auerbach, MD.)*

FIGURE 74-92 Extruded tentacular organs of Cuvier from within a sea cucumber. *(Courtesy Paul S. Auerbach, MD.)*

divers is to the corneas and conjunctivae, which may become intensely inflamed if directly contacted by tentacular fragments or high concentrations of the toxin. This may occur if the mask is cleared in the immediate vicinity of recent sea cucumber manipulation. A severe reaction may lead to blindness. Holothurin is a potent cardiac glycoside and may cause severe illness or death on ingestion.

Treatment

The management of holothurin-induced contact dermatitis is similar to that for starfish dermatitis. A topical or systemic corticosteroid may be necessary to manage a severe reaction. Because cucumbers that dine on nematocysts may secrete cnidarian venom, the initial skin detoxification should include topical application of 5% acetic acid (vinegar), papain, or 40% to 70% isopropyl alcohol. If an eye is involved, it should be anesthetized with 1 or 2 drops of 0.5% proparacaine and then irrigated with 100 to 250 mL of normal saline to remove any residual foreign matter. The cornea should be stained with fluorescein to identify corneal defects. A proper slit-lamp examination is optimal to determine whether inflammation extends into the anterior chamber or involves the iris. If there is no sign of infection, a moderate approach to the inflammatory keratitis includes regular instillation of cycloplegic, mydriatic, and corticosteroid ophthalmic solutions. Prompt referral to an ophthalmologist is essential.

PHYLUM ANNELIDA

ANNELID WORMS

Life and Habits

There are 6200 species of segmented marine worms (phylum Annelida, class Polychaeta), either free-moving or sedentary. Some free-moving members are considered toxic and may attain 30 cm (1 foot) in length. The worms are predominantly carnivorous and exist in the tidal zone to depths of 5000 m (16,405 feet), mostly as bottom feeders. Each segment of the worm possesses paddle-like appendages (parapodia) for locomotion. From these project numerous silky or bristle-like setae, which are capable of puncturing the victim (Figures 74-93 to 74-97).

The chitinous urticating bristles are arranged in soft rows about the body. When a worm is stimulated, its body contracts and the bristles are erected. There are no associated venom-producing cells. Easily detached, the bristles penetrate skin like cactus spines and are difficult to remove. The ubiquitous bottom-dwelling bristleworm *Hermodice carunculata* is frequently handled in Floridian and Caribbean waters by snorkelers and divers. This worm can attain a length of one foot and a width of 2.54 cm (1 inch). It is found on coral, under rocks, and moving among sponges. The body is green or reddish with tufts of white bristles. *Chloeia flava* is found along the Malayan coast, *Chloeia viridis* in the West Indies, Gulf of California, and Gulf of Mexico south to Panama, and *Eurythoe complanata* in Australia and other tropical seas. Other worms, such as *Chloeia euglochis,* are free swimming. Some marine worms possess strong chitinous jaws with pharyngeal teeth and can inflict painful bites.

FIGURE 74-93 The chitinous spines of a bristleworm are easily dislodged into the skin of an unwary diver. *(Copyright Stephen Frink.)*

Clinical Aspects

The bite or sting of an annelid worm may induce intense inflammation typified by a burning sensation with a raised, erythematous, and urticarial rash, most frequently on the hands and fingers (Figure 74-98). Edema and papules ensue, with rare necrosis. The setae are easily fractured into the skin and are generally not visible on external inspection, although the victim may report a

FIGURE 74-94 Bristleworm I. *(Copyright Stephen Frink.)*

FIGURE 74-95 Bristleworm. *(Copyright Stephen Frink.)*

FIGURE 74-96 Bristleworm. *(Copyright Stephen Frink.)*

sensation of pricking or abrasion. Untreated, the pain is generally self-limited over the course of a few hours, but the inflammatory component of erythema and urticaria may last for 2 to 3 days, with total resolution of the skin discoloration over 7 to 10 days. With multiple stings, marked local soft tissue edema and pruritus may develop. Secondary infections and cellulitis may occur if the eczematous component is severe.

Treatment

All large visible bristles should be removed with forceps. The skin should be dried (without scraping, to avoid breaking or embedding the spines further into the skin) so that a layer of adhesive tape may be applied to remove the remaining smaller spines, which are too tiny for individual extraction. Application of tape may force spines into the tissue, causing pain. Alternatively, a facial "peel" or thin layer of rubber cement may be applied and removed. After this maneuver, 5% acetic acid (vinegar), 40% to 70% isopropyl alcohol, or a paste or solution of unseasoned meat tenderizer (papain) or application of a papain-impregnated scrub brush may provide some pain relief. If the inflammatory reaction becomes severe, the victim may benefit from administration of a topical or systemic corticosteroid.

FIGURE 74-97 Bristleworm. *(Courtesy Marty Snyderman.)*

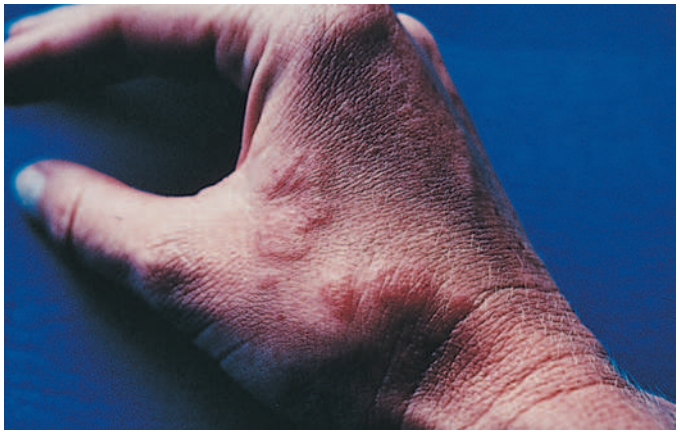


FIGURE 74-98 Skin rash caused by a bristleworm. *(Courtesy Paul S. Auerbach, MD.)*

PHYLUM MOLLUSCA

MOLLUSKS

The phylum Mollusca (45,000 species) encompasses a group of unsegmented, soft-bodied invertebrates, many of which secrete calcareous shells. Generally, a muscular foot is present with various modifications. Of the five main classes, three predominate in their hazard to humans: the pelecypods (such as scallops, oysters, clams, and mussels), the gastropods (such as snails and slugs), and the cephalopods (such as squids, octopuses, and cuttlefish [Figures 74-99 and 74-100]). Mollusks are often implicated as the transvectors in poisonous ingestions.

CONE SNAILS (CONE SHELLS)

Life and Habits

There are approximately 500 species of these circumtropical, beautiful, yet potentially lethal, univalve and cone-shaped shelled

FIGURE 74-99 Giant cuttlefish in the Coral Sea. *(Copyright Carl Roessler.)*

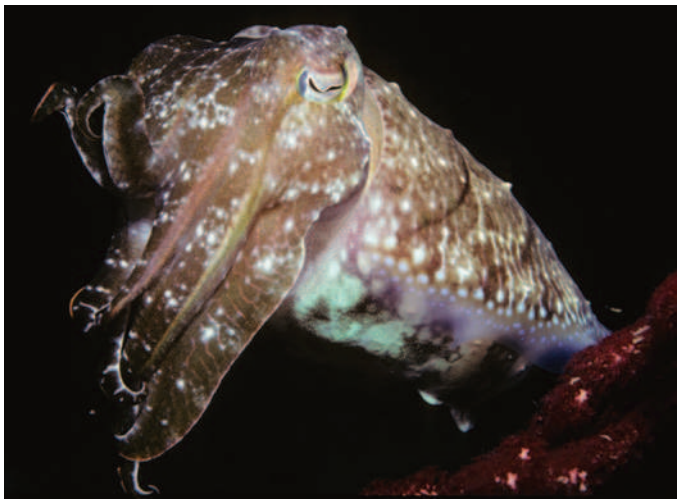


FIGURE 74-100 Curious cuttlefish in Papua, New Guinea. *(Copyright Carl Roessler.)*

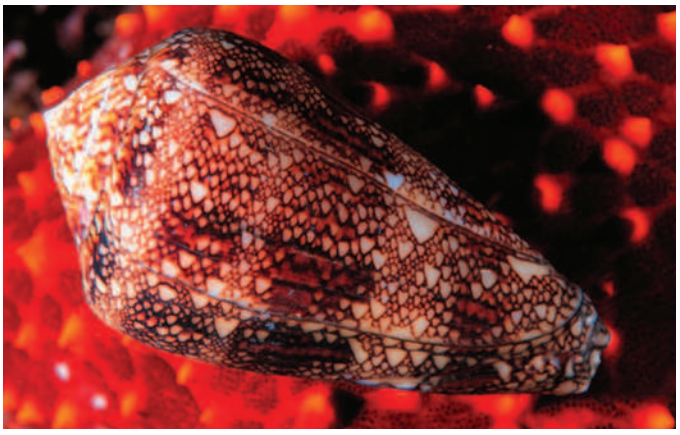


FIGURE 74-102 *Conus dalli*, in the Sea of Cortez. *(From Norbert Wu, with permission:* norbertwu.com.*)*

mollusks of the class Gastropoda, family Conidae, genus *Conus* (Figures 74-101 and 74-102).[136] Most of these carnivores carry a highly developed venom apparatus, and at least 18 species have been implicated in human envenomations, with occasional fatalities (≈ 16 to 30 have been recorded).[78] These include *Conus aulicus* (court), *Conus geographus* (geographer), *Conus gloria-maris* (glory of the sea), *Conus marmoreus* (marbled), *Conus omaria* (pearled), *Conus striatus* (striated) (Figure 74-103), *Conus textile* (textile) (Figure 74-104), and *Conus tulipa* (tulip).

Most harmful cone snails (cones) are creatures of shallow Indo-Pacific waters; variance in feeding habits and venom production accounts for varying toxicity. Atlantic species, such as *Conus ermineus* (turtle) are less toxic. *Conus regius* (crown or queen) and *Conus spurius* (Chinese alphabet) are found in Florida waters. Apparently, cones that feed on fish or mollusks are the most dangerous. Less toxic stings are attributed to cones that feed on marine worms. Predominantly nocturnal creatures, cones burrow in the sand and coral during the daytime, emerging at night to feed. They have two eye stalks, but vision is poor, so chemosensory prowess is required to identify and approach prey.[204]

Venom and Venom Apparatus

Cone snails are predators that feed by injecting rapid-acting venom by means of a detachable, dartlike radular tooth (or radula) (Figure 74-105). To do this, the head of the animal must extend out of the shell. The venom apparatus is composed of a set of minute, harpoon-like, chitinous, and hollow radular teeth associated with a venom bulb, a long convoluted duct, and a radular sheath (Figure 74-106).[139] The barbed teeth, which may attain a length of 1 cm (0.34 inch), are housed within the radular sheath. The act of envenomation is performed by release of a radular tooth from the sheath into the pharynx, where it is "charged" with venom from the venom duct and then transferred to the extensible proboscis. This appendage, which may extend in some species as far back as the spire of the shell, grasps the venom-impregnated and barbed tooth and thrusts it into the flesh of the victim. In normal small fish prey, the cone snails may deploy a hunting method of initial rigid paralysis with fin tetanus to tether the prey to the radular tooth, and then flaccid paralysis to allow consumption. This has been observed in the fish-hunting snail *C. purpurascens*.[205] Remarkably, cone snails can switch rapidly between venom distinct for predation (high in prey-specific toxins) and venom for defense (high in paralytic toxins).[50]

The venom is composed of biologically active peptides (> 100 conotoxins have been identified) of 13 to 35 amino acids in length.[153] The majority of the unique *Conus* peptides appear to be derived from a few gene superfamilies (A, M, and O), which results in the biologically active venom components.[52] Peptide families in the A-superfamily include the α-conotoxins and the αA-conotoxins, which antagonize the nicotinic acetylcholine receptor, as well as the κA-conotoxins, which may act by blocking voltage-gated potassium channels. The μ-conotoxins, in the M-superfamily, block voltage-gated sodium channels. The ψ-conotoxins are noncompetitive antagonists of the nicotinic

FIGURE 74-101 Assorted cone snails. *(Courtesy Vidal Haddad, Jr.)*

FIGURE 74-103 Conus striatus. *(From Norbert Wu, with permission:* norbertwu.com.*)*

FIGURE 74-104 Cone snail, *Conus textile,* from the Red Sea. *(Courtesy Dietrich Mebs.)*

acetylcholine receptor. In the O-superfamily are the ω-conotoxins, which block voltage-sensitive calcium channels; δ-conotoxins, which delay inactivation of voltage-sensitive sodium channels; μO-conotoxins, which block voltage-gated sodium channels; and κ-conotoxins, which block voltage-gated potassium channels.[136]

Smaller peptides are probably strategic from an evolutionary perspective because of the speed of diffusion through a poisoned

FIGURE 74-105 Radula of *Conus textile. (Courtesy Dietrich Mebs.)*

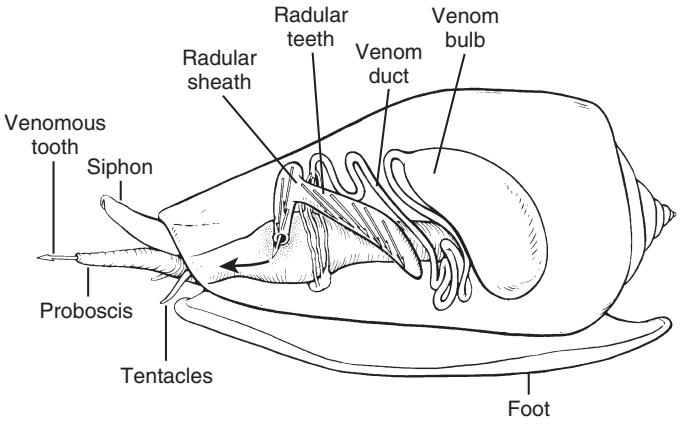


FIGURE 74-106 Venom apparatus of the cone snail.

fish. The venom targets are neuromuscular transmission and ion channels. Because there is a redundancy of sites of action at the neuromuscular junction, presynaptically and postsynaptically, minute amounts of conotoxins effect neuromuscular blockade.[216]

At the same site as tetrodotoxin and saxitoxin, μ-conotoxins bind and modify muscle sodium channels.[84] Voltage-dependent calcium uptake at the presynaptic cleft, and cholinergic transmission in avian and mammalian neuromuscular junctions are inhibited by ω-conotoxins, such as that from *C. geographus*.[48] These ω-conotoxins bind to neuronal (N-type) rather than the cardiac (L-type) calcium channels, which prevents the calcium influx necessary for neurotransmitter release. N-type calcium channels are expressed almost exclusively on neurons, and they are implicated in synaptic release of neurotransmitters such as substance P and calcitonin gene–related peptide within nociceptive sensory neurons. Ziconatide, a synthetic form of the ω-conopeptide MVIIa, is a potent analgesic intended for human application directly to the spinal cord and to prevent cell death in the brain after head trauma and ischemic events.[216] The α-conotoxins block the nicotinic acetylcholine receptor.[78,145] A subset of the α-conotoxins known as α-conotoxins RgIA and Vc1.1 produces both acute and long-lasting analgesia, and accelerates recovery of function after nerve injury, perhaps through immune-mediated mechanisms.[134] A sleeper peptide in *C. geographus* venom causes test animals to enter a deep sleeplike state.[78] Conantokins G and T, which are selective inhibitors of certain subtypes of the *N*-methyl-D-aspartate (NMDA) receptor, exhibit potent antinociceptive effects in several models of injury-induced pain, which holds promise as a novel therapeutic approach for the control of pain.[127] Furthermore, if conotoxins targeting NMDA receptors can be translated into effective drugs, this may lead to another approach to the treatment of epilepsy.[96] A novel conotoxin isolated from *Conus virgo* inhibits vertebrate voltage-sensitive potassium channels.[102] Serotonin is present in venom from the cone snail *Conus imperialis,* which is a worm feeder.[135] In the act of envenomation, milky venom from the venom duct is transformed into a clear product, which may indicate conversion from an ineffective to an effective toxin.

Clinical Aspects

Most stings occur on the fingers and hand, as the unknowledgeable fossicker (i.e., a prospector, or collector) incorrectly handles a hazardous specimen. Mild stings are puncture wounds that resemble bee or wasp stings, with associated burning or a sharp stinging sensation. Initial pain is followed by localized ischemia, cyanosis, and numbness in the area surrounding the wound. Numbness may occur without preceding pain, or in a rare case, the envenomation may be without any specific dermal sensation. More serious envenomations induce paresthesias at the wound site, which rapidly encompass the limb and then become perioral before becoming generalized. Partial paralysis transitions to generalized muscular paralysis, causing diaphragmatic dysfunction and respiratory failure; bronchospastic respiratory distress is not commonly seen. Coma has been observed, and death is

attributed to diaphragmatic paralysis or cardiac failure. Other symptoms include dysphagia, syncope, weakness, failing coordination, areflexia, aphonia, dysarthria, diplopia, ptosis, absent gag reflex, blurred vision, and pruritus. The sting of *C. geographus* may be rapidly toxic, with progression to cerebral edema, coma, respiratory arrest, and cardiac failure within a few hours, perhaps even 1 hour. Although mild stings may cause symptoms of nausea, blurred vision, malaise, and weakness for only a few hours, severe envenomation may induce symptoms that require 2 to 3 weeks to achieve total resolution. *C. textile* and *C. marmoreus* have been reported to kill humans. A fatality has been attributed to *C. gloriamaris,* but this has not been confirmed.[139]

Treatment

No antivenom is available for cone shell envenomation. Numerous therapies have been recommended, including the pressure-immobilization technique (see Figure 35-30 in Chapter 35), application of a proximal lymphatic–venous occlusive bandage, incision and suction, soaking in nonscalding hot water to tolerance (upper limit, 45°C [113°F]) until pain is relieved, injection of a local anesthetic (1% to 2% lidocaine without epinephrine), and local excision. The pressure-immobilization technique makes sense and should be applied.

Cardiovascular and respiratory support are the usual priorities after severe envenomation. The wound should be inspected for the presence of a foreign body (the radula). Edrophonium (10 mg intravenously for an adult) has been suggested as empirical therapy for paralysis. A rational approach would be to administer an edrophonium (Tensilon) test to determine effectiveness. The clinician should choose a weak muscle group for which strength can be objectively measured, then inject edrophonium (2 mg intravenously). If there is improvement, this is followed by edrophonium (8 mg intravenously). Adverse reactions to edrophonium (an anticholinesterase inhibitor) include salivation, nausea, diarrhea, and muscle fasciculations. These can be ameliorated with atropine, 0.6 mg intravenously.

Cone shells should be handled only when wearing proper gloves; if the proboscis protrudes, the cone should be dropped. If the animal must be carried, it should always be lifted by the large posterior end of the shell, although this does not afford complete protection. A collector should never carry a live cone inside a wetsuit, clothing pocket, or buoyancy compensator pocket.

OCTOPUSES

Life and Habits

Octopuses and cuttlefish are cephalopods that are usually harmless and retiring. On occasion, they are noted to manifest "curiosity" or "play behavior," by navigating mazes or manipulating objects without intent to feed or create a habitat. True octopuses are inhabitants of warmer waters and have little tolerance for extremes in salinity. They prefer rocky bottoms and rock pools in the intertidal zones. The entertainment media have created the image of a giant creature that envelops its victim in a maze of tentacles and suction cups. However, most dangerous (envenoming) creatures are smaller than 10 to 20 cm (4 to 8 inches) and do not squeeze their victims at all. On the other hand, there are reports in the South Pacific of breath-hold spearfishermen drowned while hunting octopuses. The method used to kill the animals was to allow an octopus to cling to a diver, who would bite the animal between the eyes as the combatants surfaced. Apparently, the octopuses were large enough (4-m [13-foot] tentacle span) to resist the technique. *Octopus apollyon* can be pugnacious and may bite, in one case causing an immediate reaction of bradycardia and hypotension.[20]

Octopus bites are rare but can result in severe envenomations. Fatalities have been reported from the bites of the Australian blue-ringed (or "spotted") octopuses, *Octopus (Hapalochlaena) maculosa* and *Octopus (Hapalochlaena) lunulata.* These small creatures, which rarely exceed 20 cm (8 inches) in length with tentacles extended, are found throughout the Indo-Pacific (Australia, New Zealand, New Guinea, Japan) in rock pools, under discarded objects and shells, and in shallow waters,

FIGURE 74-107 Extremely venomous temperate blue-ringed octopus *(Hapalochlaena maculosa),* in Southern Australia. *(From Gary Bell: oceanwideimages.com.)*

posing a threat to curious children, tidepoolers, fossickers, and unwary divers.[199] Divers rarely spot them in water deeper than 3 m (10 feet). The bodies are oblong and pyriform, with a pointed tail and conspicuous excrescences on the upper surface.[18] In Australian waters, *H. maculosa,* the southern species, is smaller and yellow. *H. lunulata* is found in the north; larger, darker, and predominantly brownish, it favors the warmer tropical water. A third species, the blue-lined octopus *(Hapalochlaena fasciata)* has been described along the east coast (New South Wales) of Australia.[149] It has blue lines on the body and blue rings on the arms. When any of these animals is at rest, it is covered with dark brown to yellow-ochre bands over the body and arms, with superimposed blue patches or rings.[196] When the animal is excited or angered, the entire body darkens and the blue circles or stripes glow iridescent peacock blue, a trait shared by other animals, such as the peacock flounder *(Bothus lunatus).* The colorful appearance is attractive to small children, who can easily handle the 25- to 90-g animal (Figure 74-107). The smallish *Octopus joubini* of the Caribbean, which lives in small shells and empty containers, such as submerged bottles, is dangerous to a lesser degree; envenomation causes pain followed by numbness, fever, and nausea. The large common octopus, *Octopus vulgaris,* is nontoxic (Figure 74-108). Many octopuses can release inky fluid into the water, which is used to confuse attackers, but this mechanism is not present in the blue-ringed octopus. The chameleon-like changing of colors to match the surroundings is accomplished with pigment cells (chromatophores) (Figures 74-109 to 74-112).

Venom and Venom Apparatus

The venom apparatus of the blue-ringed octopus consists of the salivary glands (anterior and posterior), salivary ducts, buccal mass, and beak. The mouth is located ventrally and centrally at the base of the tentacles and is surrounded by a circular lip fringed with finger-like papillae, leading into a muscular pharyngeal cavity. This anatomic complex (buccal mass), concealed by the tentacles, is fronted by two parrot-like, powerful, and chitinous jaws (the beak), which bite and tear with great force at food held by the suckers. The salivary glands, particularly the posterior ones, secrete toxin (sometimes called maculotoxin or cephalotoxin)–containing venom via the salivary ducts into the pharynx. This venom, normally released into the water to subdue crabs, may be injected into the victim with great force through the dermis down to the muscle fascia.[199] The venom of *H. maculosa* has been extensively studied. The toxin, maculotoxin (molecular weight less than 5000), contains at least one fraction identical to

FIGURE 74-108 *Octopus vulgaris. (Copyright Stephen Frink.)*

FIGURE 74-109 Octopus posed atop coral in the Coral Sea. *(Copyright Carl Roessler.)*

tetrodotoxin (TTX, with the chemical formula $C_{11}H_{17}O_8N_3$) of molecular weight 319.3, which blocks peripheral nerve conduction by interfering with sodium conductance in excitable membranes by blocking voltage-gated sodium channels.[99,184] The toxin, as well as the tetrodotoxin precursor anhydrotetrodotoxin,

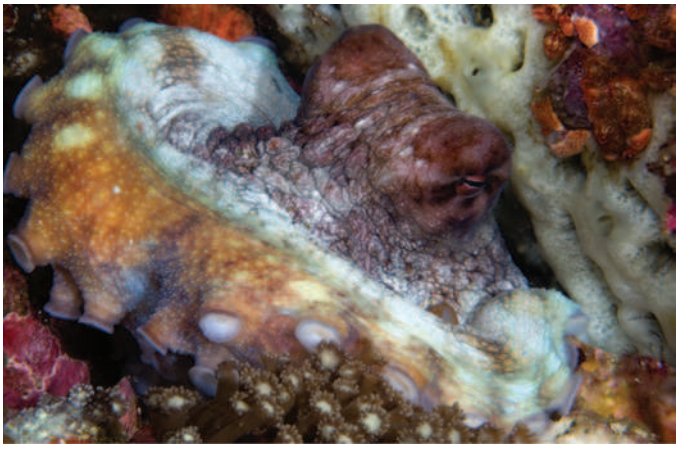


FIGURE 74-110 *Octopus vulgaris. (Copyright Stephen Frink.)*

FIGURE 74-111 *Octopus vulgaris. (Copyright Stephen Frink.)*

is produced by bacteria of the Vibrionaceae family, and is passed along the food chain to the octopus.[216] In a study of the intraorganismal distribution of tetrodotoxin in two species of blue-ringed octopuses (*H. fasciata* from New South Wales, Australia, and *H. lunulata* from Indonesia), TTX was detected in posterior salivary gland, arm, mantle, anterior salivary glands, digestive gland, testes contents, brachial heart, nephridia, gill, and oviductal gland of *H. fasciata*, but only in the posterior salivary gland, mantle tissue, and ink of *H. lunulata*. The highest concentrations of TTX reside in the posterior salivary gland. The distributional data suggest both offensive and defensive functions of TTX.[219]

FIGURE 74-112 Mimic octopus. *(Copyright Lynn Funkhouser.)*

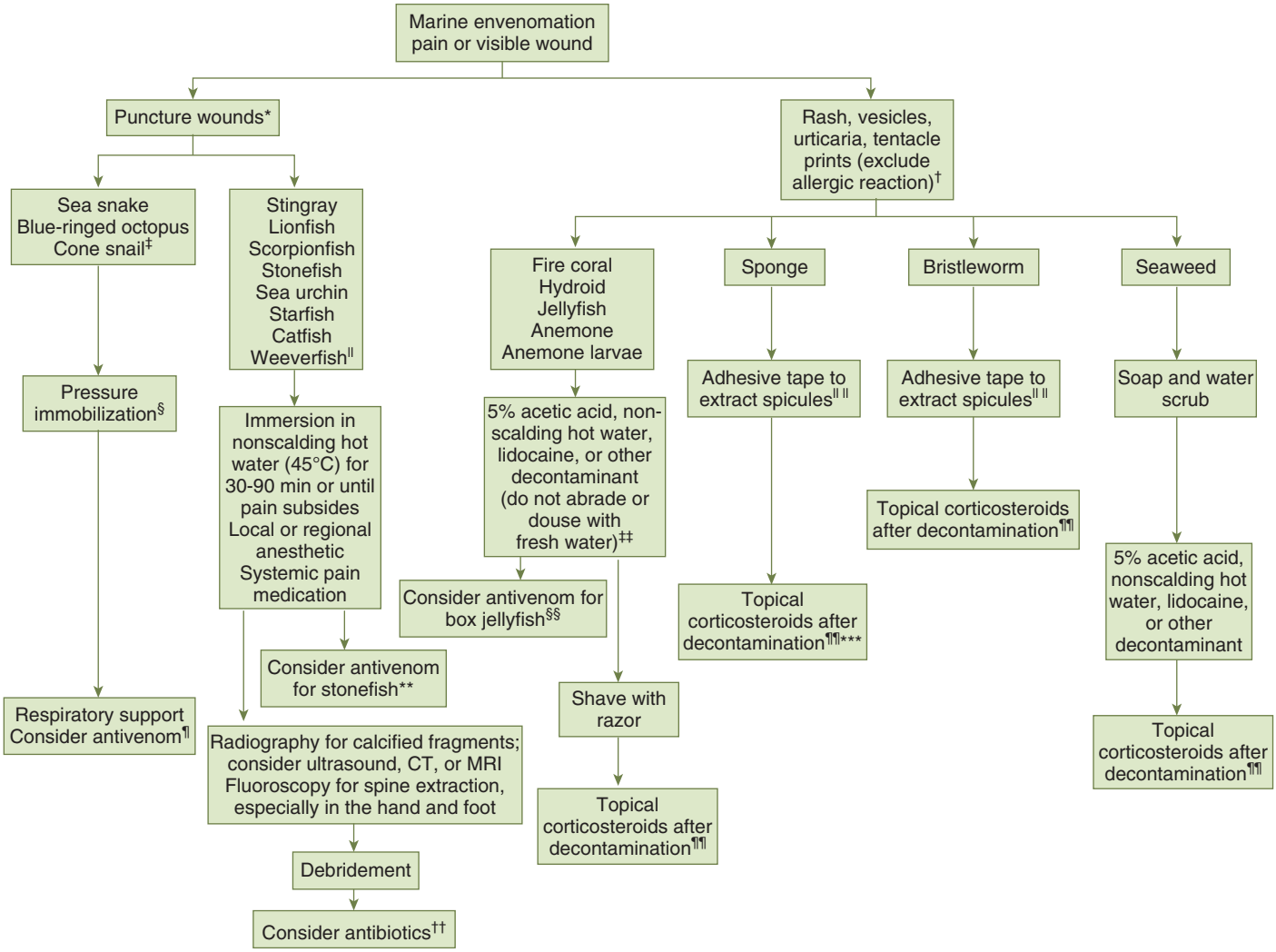


FIGURE 74-113 Algorithmic approach to marine envenomation. *A gaping laceration, particularly of the lower extremity, with cyanotic edges suggests a stingray wound. Multiple punctures in an erratic pattern with or without purple discoloration or retained fragments are typical of a sea urchin sting. One to eight (usually two) fang marks are usually present after a sea snake bite. A single ischemic puncture wound with an erythematous halo and rapid swelling suggests scorpionfish envenomation. Blisters often accompany a lionfish sting. Painless punctures with paralysis suggest the bite of a blue-ringed octopus; the site of a cone shell sting is punctate, painful, and ischemic in appearance. †Wheal-and-flare reactions are nonspecific. Rapid onset (within 24 hours) of skin necrosis suggests an anemone sting. Broad "tentacle prints" with cross-hatching or a frosted appearance after application of aluminum-based salts suggests a box-jellyfish *(Chironex fleckeri)* envenomation. Ocular or intraoral lesions may be caused by fragmented hydroids or cnidarian tentacles. An allergic reaction must be treated promptly. ‡Sea snake venom causes weakness, respiratory paralysis, myoglobinuria, myalgias, blurred vision, vomiting, and dysphagia. The blue-ringed octopus injects tetrodotoxin, which causes rapid neuromuscular paralysis. §As soon as possible, venom should be sequestered locally with a proximal venous-lymphatic occlusive band of constriction or (preferably) the pressure-immobilization technique, in which a cloth pad is compressed directly over the wound by an elastic wrap that should encompass the entire extremity at a pressure of 70 mm Hg or less. Incision and suction are not recommended. ¶Early ventilatory support has the greatest influence on outcome. The minimal initial dose of sea snake antivenom is 1 to 3 vials; up to 10 vials may be required. ‖The wounds range from large lacerations (stingrays) to minute punctures (stonefish). Persistent pain after immersion in hot water suggests a stonefish sting or a retained fragment of spine. The puncture site can be identified by forcefully injecting 1% to 2% lidocaine or another local anesthetic agent without epinephrine near the wound and observing the egress of fluid. Do not attempt to crush the spines of sea urchins if they are present in the wound. Spine dye from sea urchin spines that have already been extracted will disappear (be absorbed) in 24 to 36 hours. **The initial dose of stonefish antivenom is one vial per two puncture wounds. ††The antibiotics chosen should cover *Staphylococcus, Streptococcus,* and microbes of marine origin, such as *Vibrio.* ‡‡Acetic acid 5% (vinegar) is a good all-purpose decontaminant and mandated for the sting from a box-jellyfish. Alternatives, depending on the geographic region and indigenous jellyfish species, include isopropyl alcohol, bicarbonate (baking soda), lidocaine, papain, and preparations containing these agents. Application of water heated to 45° C may be effective for relieving pain. §§The initial dose of box-jellyfish antivenom is one ampule intravenously or three ampules intramuscularly. ¶¶If inflammation is severe, steroids should be given systemically (beginning with at least 60 to 100 mg of prednisone or its equivalent), and the dose should be tapered over a period of 10 to 14 days. ‖‖An alternative is to apply and remove commercial facial peel materials. ***An alternative is to apply and remove commercial facial peel materials followed by topical soaks of 30 mL of 5% acetic acid (vinegar) diluted in 1 L of water for 15 to 30 minutes, several times a day, until the lesions begin to resolve. Anticipate surface desquamation in 3 to 6 weeks.

This paralytic agent rapidly produces neuromuscular blockade, notably of the phrenic nerve supply to the diaphragm, without any apparent direct cardiotoxicity. It has been estimated that enough venom (25 g) may be present in one adult octopus to paralyze 750 kg of rabbits or 10 adult victims.[196,199] An adult blue-ringed octopus can inject a second fatal dose of toxin after a 1-hour interval. The venom is active on ingestion or by parenteral administration, the latter being much more effective. Other components of the venom, which include hyaluronidase, histamine, 5-hydroxytryptamine, tyramine, serotonin, and hapalotoxin (believed to derive from tyrosine, but still not confirmed as being present), are not believed to be major contributors to the clinical effects of an octopus bite.[179] Because most venoms and toxins with molecular weights less than 30,000 are poor antigens, octopus venom elicits no good antivenom.[199]

Clinical Aspects

Most victims are bitten on the hand or arm as they handle the creature or "give it a ride." No blue-ringed octopus bites have yet been reported from an animal in the water.[221] An octopus bite usually consists of two small puncture wounds produced by the chitinous jaws. The bite goes unnoticed or causes only a small amount of discomfort, described as a minor ache, slight stinging, or pulsating sensation. Occasionally, the site is initially numb, followed in 5 to 10 minutes by discomfort that may spread to involve the entire limb, persisting for up to 6 hours. Local urticarial reactions occur variably, and profuse bleeding at the site is attributed to a local anticoagulant effect or may rarely be a harbinger of coagulation abnormalities. Within 30 minutes, considerable erythema, swelling, tenderness, heat, and pruritus develop. By far the most common local tissue reaction is absence of symptoms, a small spot of blood, or a tiny blanched area.[220] More serious symptoms are related predominantly to the neurotoxic properties of the venom. Within 10 to 15 minutes of the bite, the victim notices oral and facial numbness, rapidly followed by systemic progression.[221] Voluntary and involuntary muscles are involved, and the illness may rapidly progress to total flaccid paralysis and respiratory failure. Other symptoms include perioral and intraoral anesthesia (classically, numbness of the lips and tongue), diplopia, blurred vision, aphonia, dysphagia, ataxia, dizziness, myoclonus, weakness, sense of detachment, nausea, vomiting, peripheral neuropathy, absent deep tendon reflexes, flaccid muscular paralysis, sensation of chest tightness, and respiratory failure, which may lead to death. Ataxia of cerebellar configuration may occur after envenomation that does not progress to frank paralysis. Jerking limbs have been mentioned, as have poorly reactive or unreactive pupils. The victim may collapse from weakness and remain awake, so long as oxygenation can be maintained. When breathing is disturbed, respiratory assistance may allow the victim to remain mentally alert despite being paralyzed. Cardiac arrest is probably a complication of the anoxic episode.[214] Although tetrodotoxin is a potent vascular smooth muscle depressant, it does not appear to often produce significant hypotension in humans; however, hypotensive crisis has been mentioned in the literature as a complicating factor.

Treatment

First aid at the scene might include the pressure-immobilization technique (see Fig. 35-30, Chapter 35), although this is as yet unproved for management of octopus bites. A monoclonal rabbit serum IgG antibody has been effective against tetrodotoxin injected into mice.[131,135,170] This raises the possibility of the practical use of passive immunotherapy in the event of tetrodotoxin poisoning.

Treatment is based on symptoms and is supportive. Prompt mechanical respiratory assistance has by far the greatest influence on the outcome. Respiratory demise should be anticipated early, and the rescuer should be prepared to provide artificial ventilation, including endotracheal intubation and application of a mechanical ventilator. The duration of the intense clinical venom effect is 4 to 10 hours, after which the victim who has not suffered an episode of significant hypoxia shows rapid signs of improvement. If no period of hypoxia occurs, mentation may remain normal. Complete recovery may require 2 to 4 days. Residua are uncommon and related to anoxia rather than venom effects.

Management of the bite wound is controversial. Some clinicians recommend wide circular excision of the bite wound down to the deep fascia, with primary closure or an immediate full-thickness free skin graft, whereas others advocate observation and a nonsurgical approach. Because the local tissue reaction is not a significant cause of morbidity, excision is presumably recommended to remove any sequestered venom. Kinetic studies of radiolabeled venom absorption are necessary to track the movement of octopus bite–introduced tetrodotoxin. Based on review of the literature, this author would favor a nonsurgical approach with supportive therapy. As previously mentioned, there is no antivenom. Granuloma annulare of the hand developing over a 2-week period after an octopus (presumed to be *O. vulgaris* of the Florida Gulf Coast) bite of the hand has been reported.[68] On biopsy, histologic sections demonstrated superficial and deep dermal foci of altered dermis, presumably degenerated collagen, surrounded by histiocytes, lymphocytes, and fibroblasts. Intralesional triamcinolone acetonide injections were temporarily successful in treating the primary lesion.[132]

Prevention

All octopuses, particularly those less than 20 cm (8 inches) in length (including *O. joubini* of the Caribbean), should be handled with gloves. Divers need to be familiar with the lethal creatures in their domain. Giving an octopus a ride on one's back, shoulder, or arm is not recommended.

SUMMARY

A summary algorithmic approach to marine envenomation (Figure 74-113) can be followed when the causative agent cannot be definitively identified.

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CHAPTER 75

Envenomation by Aquatic Vertebrates

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See Chapter 74 for a discussion of infections associated with aquatic wounds and the relevant antimicrobial therapy. An analysis that compared DNA sequences from 233 fish species was used to create a family tree for spiny-rayed fishes. This indicates that previous estimates of approximately 200 venomous fishes should be revised to suspect at least 1200 fishes in 12 clades (a group of biologic taxa or species that share features inherited from a common ancestor) as perhaps venomous.[97]

A common clinical question is how best to image embedded spines, such as those from stingrays, scorpionfishes, or sea urchins. Some prove to be radiopaque and some are not. One limited study evaluated intraarticular foreign bodies using sea urchin spines and chicken thigh-leg combinations.[61] Pending further evidence, computed tomography (CT) and magnetic resonance imaging (MRI) appear to be more reliable modalities for imaging than plain radiography, ultrasonography, or fluoroscopy. However, for reasons of limiting radiation exposure or expense, one of the latter three may be chosen as the initial imaging technique.

STINGRAYS

Stingrays are the most commonly incriminated group of fish involved in human envenomations. They have been recognized as venomous since ancient times, known as "demons of the deep" and "devil fish." Aristotle (384 to 322 BC) made reference to their stinging ability. Stingray spines were used in certain Mayan bloodletting procedures and rituals.[55]

Stingrays are members of the class Chondrichthyes (cartilaginous fish), subclass Elasmobranchii (plates and gills; with sharks and chimaeras), order Rajiformes (which contains stingrays [Dasyatidae], guitarfish [Rhinobatidae], skates [Rajidae], electric rays [Torpedinidae], eagle rays [Myliobatidae], mantas [Mobulidae], and freshwater rays [Potamotrygonidae]). Twenty-two species of stingrays are found in U.S. coastal waters, 14 in the Atlantic and 8 in the Pacific. The family Dasyatidae includes most of the species that cause human envenomation. It is likely that at least 2000 stingray injuries take place each year in the United States. On the west coast of the United States, the round stingray *(Urolophus* [or *Urobatis*] *halleri)* is a frequent stinger; along the southeastern coast, it is the southern stingray *(Dasyatis americana)*. Most attacks occur during the summer and autumn months as vacationers venture into surf that may be laden with congregating (for spawning purposes) rays. Freshwater species do not inhabit U.S. waters. They are found in South America, Africa, and Southeast Asia. Skates are related to rays and look similar, but do not carry a sting, so are harmless to humans.

LIFE AND HABITS

Stingrays are cartilaginous fish that are usually found in tropical, subtropical, and warm temperate oceans, generally in shallow (intertidal) water areas, such as sheltered bays (Figure 75-1), shoal lagoons, river mouths, and sandy areas between patch reefs (Figure 75-2).[76] Although rays are generally found above moderate depths, at least one deep-sea species has been discovered. Rays can enter brackish and freshwaters as well. For instance, freshwater stingrays are common in rivers and tributaries in South America (Figure 75-3).[52]

Rays are small (several inches) to large (up to 4 m × 2 m [12 feet × 6 feet]) creatures observed lying on top of the sand and mud or partially submerged, with only the dorsally placed eyes and spiracles and part of the tail exposed (Figure 75-4). Their dorsoventrally flattened bodies are round-, diamond-, or kite-shaped, with wide pectoral fins that look like wings (Figure 75-5). The large fleshy cephalic lobes that appear to extend from the front of the head in manta rays are continuations of modified and enlarged pectoral fins. Rays are nonaggressive scavengers and bottom feeders that burrow into the sand or mud to feed on worms, mollusks, and crustaceans. The mouth and gill plates are located on the ventral surface of the animal (Figure 75-6). The flattened shape is largely configured by the modified pectoral fins, or "wings," of the animal. These wings ripple or flap to propel the animal through the water (Figure 75-7).

VENOM AND VENOM APPARATUS

The venom organ of stingrays consists of one to four venomous stings on the dorsum of an elongate, whip-like caudal appendage. Anatomic types of stingray venom organs, and thus stinging ability, are differentiated into four groups based on their adaptability as a defense organ (Figure 75-8): (1) the gymnurid type (butterfly rays, or Gymnuridae), with a poorly developed sting of up to 2.5 cm (1 inch) placed at the base of a short tail; (2) the myliobatid type (eagle and bat rays, or Myliobatidae), with a sting of up to 12 cm (4.7 inches) placed at the base of a cylindrical caudal appendage that terminates in a long whip-like tail; (3) the dasyatid type (stingrays and whip rays, or Dasyatidae), with a sting of up to 37 cm (14.5 inches) placed at the base or further out on the caudal appendage that terminates in a long whip-like tail; and (4) the urolophid type (round stingrays, or Urolophidae), with a sting of up to 4 cm (1.5 inches) located at the base of a short, muscular, and well-developed caudal appendage. The efficiency of the apparatus is related to the length and musculature of the tail and to the location and length of the sting. Eagle rays and some mantas (Atlantic *Mobula mobular* and Pacific *Mobula japanica*) have a stinging apparatus, but it is less of a threat because the spine is located at the base of the tail and is not well adapted as a striking organ. Although the Pacific manta *(Manta birostris)* may grow to a width ("wingspan") of 6 m (20 feet) and weight of 1800 kg (4000 lb), it dines on small fish, crustaceans, and microorganisms (Figures 75-9 and 75-10). There is some DNA evidence and a prevailing opinion that all mantas may be of the same species *(M. birostris),* which will in time render other Latin names and some common names obsolete. Many divers have "hitched" a ride on the wings of a manta; there are no reports of envenomation. However, manta skin is rough and can abrade unprotected human skin. A stingray "hickey" is a mouth-bite created by powerful grinding plates that produces superficial erosions and ecchymosis in an oral pattern. People who hand-feed stingrays may incur this type of injury.[37] The suction force generated by a stingray is sufficient to pull in a large amount of soft tissue, for example, from an obese thigh. This may result in a large and painful contusion or hematoma.

In all cases, the venom apparatus of stingrays consists of a bilaterally retroserrate spine or spines and the enveloping integumentary sheath or sheaths. The elongate and tapered vasodentine (modified dentin permeated by blood and capillaries) spine is

FIGURE 75-1 Stingrays gliding in shallow reef waters. *(Copyright Stephen Frink.)*

FIGURE 75-2 Stingray glides along the sandy ocean bottom. *(Courtesy Marty Snyderman.)*

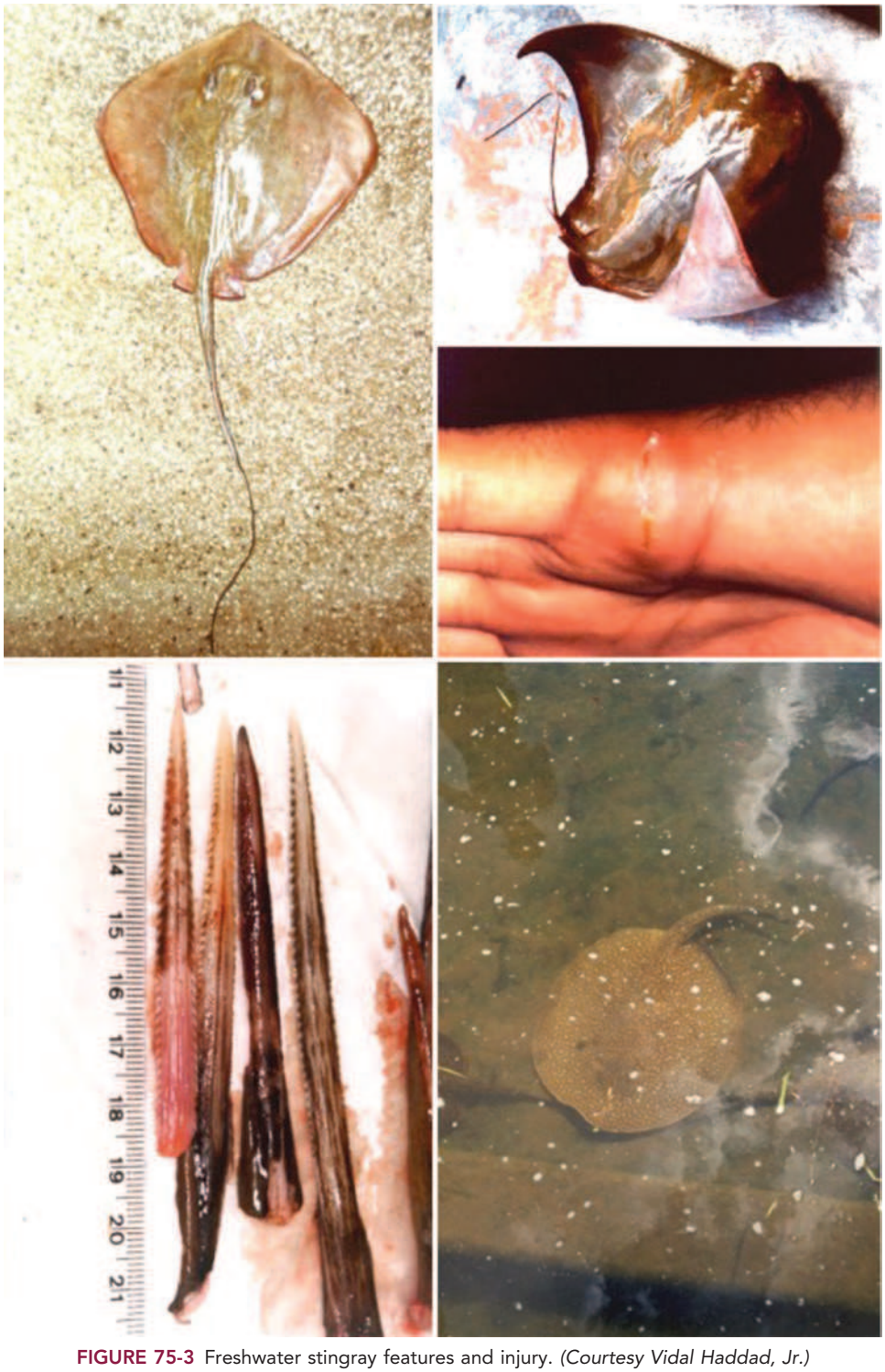

FIGURE 75-3 Freshwater stingray features and injury. *(Courtesy Vidal Haddad, Jr.)*

FIGURE 75-4 Stingray nestled in the sand. Only the eyes and spiracles are visible. *(Copyright Stephen Frink.)*

FIGURE 75-5 Diver cavorting with a large stingray. *(Courtesy Howard Hall.)*

FIGURE 75-6 Ventral surface of a stingray, demonstrating mouth and gill plates. *(Courtesy Paul S. Auerbach, MD.)*

FIGURE 75-7 Large stingray lifts off the bottom and prepares to move away. *(Copyright Stephen Frink.)*

firmly attached to the dorsum of the tail (whip) by dense collagenous tissue and is edged on either side by a series of sharp retrorse teeth. Along either edge on the underside of the spine are the two ventrolateral grooves, which house the soft venom glands. The entire spine is encased by the integumentary sheath, which also contains some glandular cells. The sting is often covered with a film of venom and mucus. The spine is replaced if detached.

The venom contains various toxic fractions, including serotonin, 5′-nucleotidase, and phosphodiesterase. Russell and others have investigated the pharmacologic properties of stingray venoms.[33,90] In animal studies, they demonstrated significant

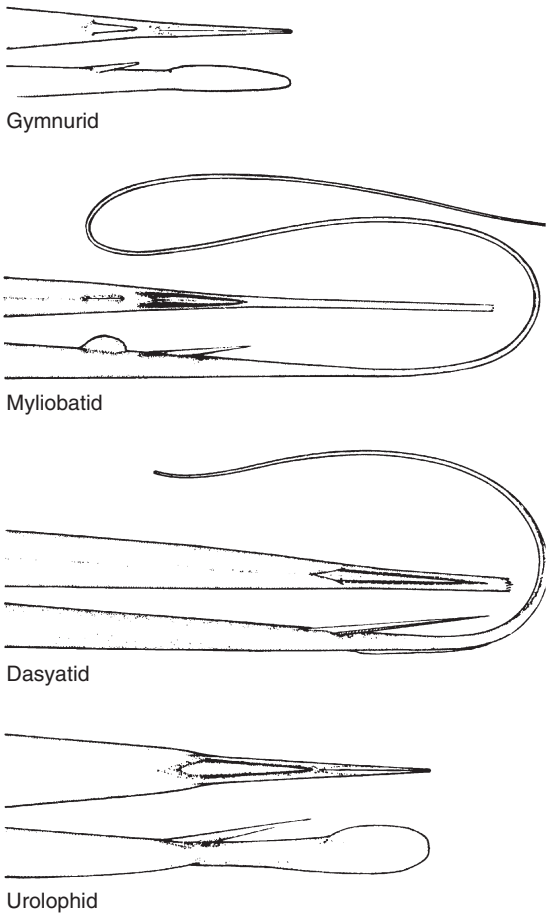

FIGURE 75-8 Four anatomic types of stingray venom organs.

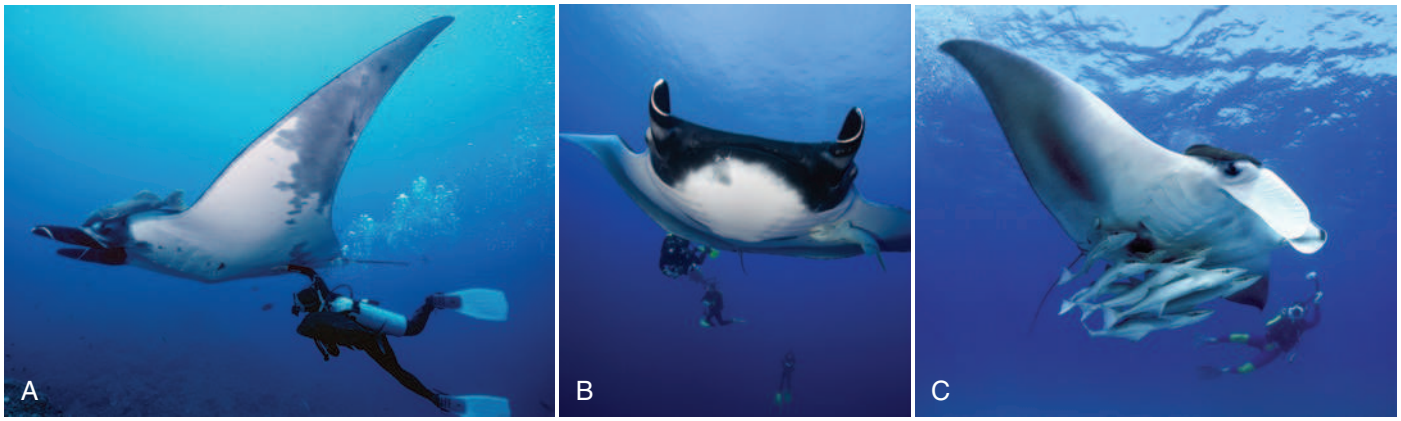

FIGURE 75-9 Manta rays. **A,** Diver strokes the belly of a manta ray. **B,** Pacific manta ray. **C,** Atlantic manta ray. (**A** *copyright Carl Roessler;* **B** *and* **C** *copyright Stephen Frink.)*

FIGURE 75-10 Manta ray. *(Copyright 2011 Norbert Wu:* norbertwu.com.*)*

venom-induced peripheral vasoconstriction, bradycardia, tachycardia, atrioventricular block, ischemic Q and ST-T wave abnormalities, asystole, central respiratory depression, seizure activity, ataxia, coma, and death. The venom did not appear to be a paralytic neuromuscular agent. Research on stingray venom from the 1950s observed that heating the venom to a temperature above 50°C (122°F) diminished some biologic effects. Haddad analyzed proteins from freshwater stingray *(Potamotrygon falkneri)* venom using SDS-polyacrylamide gel electrophoresis and identified components with gelatinolytic, caseinolytic, and hyaluronidase activities.[52] Others have identified hyaluronidase from the freshwater stingray *Potamotrygon motoro* and fibrinolytic activity from the venom of *Dasyatis sephen* and *Aetobatus narinari*.[77,70] A novel bioactive peptide, Porflan, from the stingray *Potamotrygon gr. orbignyi* induces leukocyte rolling and adherent cells, and is proinflammatory in mice.[29]

Electric rays are discussed in Chapter 73.

CLINICAL ASPECTS

Stingray "attacks" are purely defensive gestures that occur when an unwary human wading in shallow waters handles, corners, or steps on a camouflaged creature (Figure 75-11). A frequently cited estimate of annual stingray injuries incurred in U.S. coastal waters is 750 to 1500, although there is no reliable reporting system for these injuries. Estimates are higher in tropical regions. The tail of the ray reflexively whips upward and accurately thrusts the caudal spine or spines into the victim, producing a puncture wound or jagged laceration (Figure 75-12). The integumentary sheath covering the spine is ruptured and venom is released into the wound, along with mucus, pieces of the sheath, and fragments of the spine. On occasion, the entire spine tip is broken off and remains in the wound (Figure 75-13).[91] "Domesticated" stingrays, such as those that congregate at "Stingray City" in the waters off Grand Cayman Island (Figures 75-14 to 75-16), are habituated to the presence of humans and apparently pose less hazard for a spine puncture, but may still be induced to bite. It has been observed that there are hematologic differences between stingrays at tourist and nonvisited sites that reflect suboptimal stingray health in response to stress.[94]

A stingray wound from a spine puncture is both a traumatic injury and an envenomation. The former involves the physical damage caused by the sting itself. Because of the retrorse serrated teeth and powerful strikes, significant lacerations can result. Secondary bacterial infection is common. Osteomyelitis may occur if the bone is penetrated. Most injuries occur when the victim steps on a ray; another common cause is handling a ray during its extraction from a fishing net or hook.[35] The lower extremities, particularly the ankle and foot, are involved most often, followed by the upper extremities, abdomen, and thorax. In a rare case, the heart may be directly injured.[88] The tragic death in September 2006 of 44-year-old naturalist Stephen Irwin

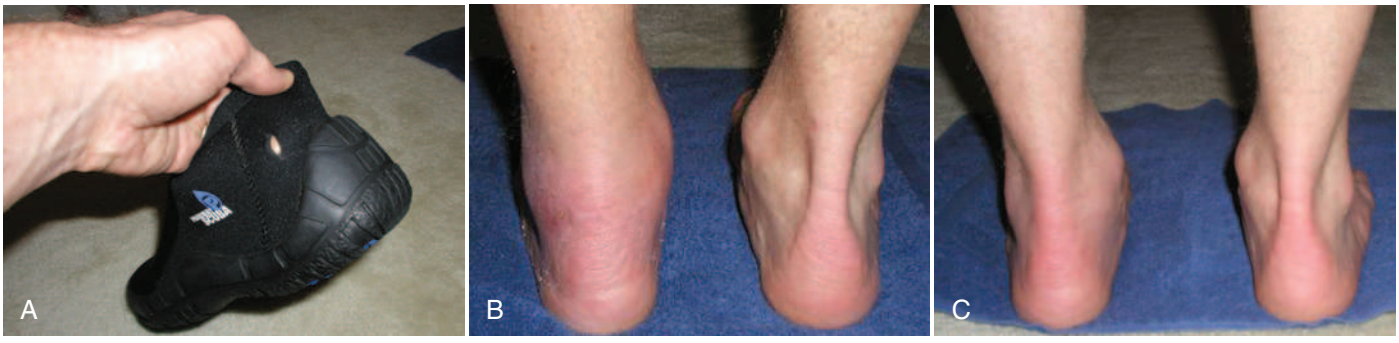

FIGURE 75-11 Stingray puncture wound. **A,** Puncture through neoprene boot in a typical location near the Achilles tendon. **B,** Stingray wound compared with normal foot 2 months following injury. **C,** Stingray wound compared with normal foot 6 months following injury. *(Courtesy Bob Luce.)*

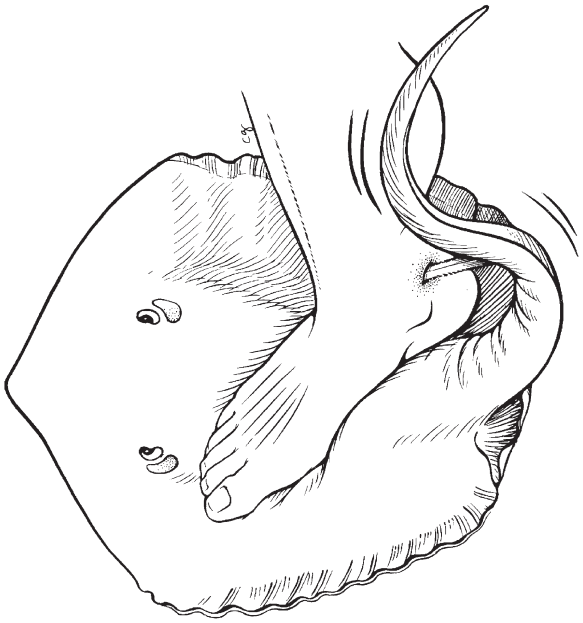

FIGURE 75-12 The stingray lashes its tail upward into the leg and generates a deep puncture wound.

occurred at Batt Reef off the remote coast of northeastern Queensland, Australia, when he swam directly over a stingray that thrust a stingray spine into his chest. Death was attributed to a direct heart puncture. He was filming a documentary titled *Ocean's Deadliest*. Fatalities have occurred after abdominal penetration and from exsanguination from the femoral artery. There have been reported cases of survival following cardiac injury, including one from the sting of a blue-spotted stingray *(Dasyatis kuhlii*; now *Neotrygon kuhlii)* that leaped into the boat of a 75-year-old man.[84] Pseudoaneurysms of the superficial femoral artery and posterior tibial artery caused by stingray envenomation have been reported.[18,57] One death has been attributed to tetanus

FIGURE 75-14 Snorkeler in Stingray City. *(Copyright Stephen Frink.)*

FIGURE 75-15 Stingrays in Stingray City. *(Copyright Stephen Frink.)*

FIGURE 75-13 Stingray spine tip broken off into the heel of a victim. *(Courtesy Robert D. Hayes.)*

FIGURE 75-16 Paired stingrays in Stingray City. *(Copyright Stephen Frink.)*

complicating a leg wound. In one rare case, a women experienced vocal cord paralysis while eating raw stingray after ingesting a barb that lodged in her arytenoid.[71] A spine partially or totally denuded of its sheath and venom glands may not cause an envenomation.[38] A detached stingray spine may be used as a weapon. A man stabbed between the shoulder blades with stingray spine suffered a direct spinal cord injury at the level of T7-T8. He was extremely fortunate to make nearly a complete recovery after delayed operative removal.[49]

The envenomation classically causes immediate local intense pain, edema, and variable bleeding. The pain may radiate centrally, peaks at 30 to 60 minutes, and may last for up to 48 hours. The wound is initially dusky or cyanotic and rapidly progresses to erythema and hemorrhagic discoloration, with rapid fat and muscle hemorrhage and necrosis.[11,62] Although the mechanisms causing pain, edema, and necrosis are not definitively determined, it is possible that the mucus covering the animal might contribute to the injury.[70] If discoloration around the wound edge is not immediately apparent, within 2 hours it often extends several centimeters from the wound. Hemorrhagic blisters resembling a severe thermal burn or frostbite may occur and may be worsened by overzealous therapeutic hot-water immersion.[93,103] Minor stings may simulate bacterial cellulitis. Delayed healing seen following stingray injuries is usually attributed to direct venom toxicity and infections. One analysis of the tissue surrounding a necrotic center 96 hours after envenomation revealed a perivascular and interstitial mononuclear cell infiltrate with numerous eosinophils and rare neutrophils. The phenotype of the lymphoid population was predominately $CD3^+$ T cells that coexpressed $CD4^+$ and contained T cell–restricted intracellular antigen (TIA^+) granules corresponding to the NK1.1 subpopulation of $CD4^+$ T cells. Abundant eosinophils in the vicinity of a stingray soft tissue wound have been noted.[87] All of these findings indicate a possible immunologic reaction, which, if present, might contribute to delayed healing of stingray injuries.[45]

Systemic manifestations include weakness, nausea, vomiting, diarrhea, diaphoresis, vertigo, tachycardia, headache, syncope, seizures, inguinal or axillary pain, muscle cramps, fasciculations, generalized edema (with truncal wounds), paralysis, hypotension, arrhythmias, and death.[48,60] The paralysis may represent spastic muscle contractures induced by pain, which are a tremendous hazard for a diver or swimmer. The clinical syndrome associated with freshwater stingray envenomation may in general be more severe than that associated with marine stingray envenomation.[9]

When handled, a stingray may place its underside adjacent to a human limb or even wrap itself around a leg. The stingray may then bite the victim with a powerful crushing force sufficient to sever a digit or to create a substantial hematoma (Figure 75-17). A lesser wound may amount to a "stingray hickey."[36,37] Rays will sometimes soar ("fly") out of the water, particularly in the vicinity of a motorized boat. This behavior is attributed to a defensive maneuver, although rays will also jump in the act of birth and to dislodge parasites. In 2008, a woman in a boat was killed from head injuries from the blunt impact of a spotted eagle ray that landed in the boat.

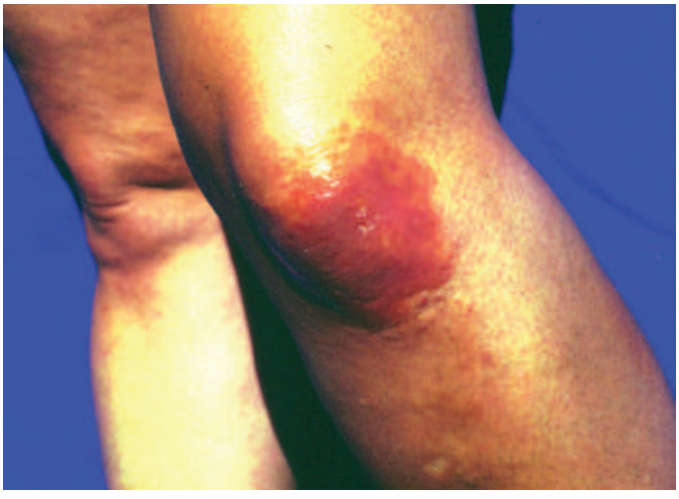

FIGURE 75-17 Stingray suction bite incurred at Stingray City, Grand Cayman Island.

TREATMENT

The success of therapy is largely related to the rapidity with which it is undertaken. Treatment is directed at combating the effects of the venom, alleviating pain, and preventing infection. As soon as possible, the wound should be soaked in nonscalding hot water to tolerance (upper limit 45°C [113°F]) for 30 to 90 minutes. This might attenuate some of the thermolabile components of the protein venom (although this has never been proved in vivo) or interrupt nerve impulse transmission, and, in some envenomations, it relieves pain.[31] Hot water immersion likely has minimal or no effect on the ultimate degree of soft tissue necrosis. If hot water for immersion and irrigation (see below) is not immediately available, the wound should be irrigated immediately with nonheated water or saline. If sterile saline or water is not available, tap water may be used. This removes some venom and mucus and may provide minimal pain relief.

There is no indication for addition of ammonia, magnesium sulfate, potassium permanganate, or formalin to the soaking solution. Under these circumstances, they are toxic to tissue and may obscure visualization of the wound. During the hot water soak (or at any time, if soaking is not an option), the wound should be explored and debrided of any readily visible pieces of the spine or its integumentary sheath, which would continue to envenom the victim. Although the standard recommendation is to remove the spine and fragments as soon as possible (to limit the extent of envenomation and pain), if a spine is seen to be lodged in the victim and has acted as a dagger deeply into the chest, abdomen, or neck (this is extremely rare) and may have penetrated a critical blood vessel or the heart, it should be managed as would be a weapon of impalement (e.g., a knife). In this case, the spine should be left in place (if possible) and secured from motion until the victim is brought to a controlled operating room environment where emergency surgery can be performed to guide its extraction and control bleeding that may occur upon its removal.[84]

Cryotherapy may be disastrous by causing or exacerbating local tissue damage, and no data yet support the use of antihistamines or steroids. One local remedy, application of the cut surface of one-half a bulb of onion directly to the wound, has been reported to decrease the pain and perhaps inhibit infection after a sting from the blue-spotted stingray *N. kuhlii* (Figure 75-18).[104] The author noted that this approach is used in the Northern Territory of Australia for other fish spine stings, and that the medicinal use of the Liliaceae plant family has been recorded in many cultures. No other folk remedy, including application of macerated cockroaches, cactus juice, "mile-a-minute" leaves, fresh human urine, or tobacco juice, has been proved effective.[80]

Local suction, if applied in the first 15 to 30 minutes, has been suggested by some clinicians to be of potential value (this is controversial), as may a proximal constriction band (also controversial) that occludes only superficial venous and lymphatic return. If a constriction band is deployed, it should be released for 90 seconds every 10 minutes to prevent ischemia.

Pain control should be initiated during the first debridement or soaking period. Narcotics may be necessary. Local infiltration of the wound with 1% to 2% lidocaine (Xylocaine) or bupivacaine 0.25% (not to exceed 3 to 4 mg/kg total dose in adults; not approved for children under the age of 12 years) without epinephrine may be useful. A regional nerve block may be necessary.

After the soaking procedure, the wound should be x-rayed (Figures 75-19 and 75-20) or otherwise imaged, then prepared in a sterile fashion, reexplored, and thoroughly debrided, particularly of hemorrhagic fat and obviously necrotic tissue. Wounds may be packed open for delayed primary closure or sutured

FIGURE 75-18 Blue-spotted stingray. *(Copyright Stephen Frink.)*

loosely around adequate drainage in preference to tight closure, which might increase the likelihood of wound infection. Another approach that has been mentioned is wound excision followed by packing with an alginate-based wick dressing.[39,80] Prophylactic antibiotics are recommended because of the high incidence of ulceration, necrosis, and secondary infection. Necrotizing fasciitis caused by *Vibrio alginolyticus* has followed stingray injury in a victim with preexisting hepatic cirrhosis.[59] It has also been attributed to *Photobacterium damsela* (formerly *Vibrio damsela*) in a person with normal immunity punctured by a stingray in the tibialis anterior muscle.[10] If the abdominal cavity is penetrated, the victim should receive cefoxitin, clindamycin-gentamicin, or another intravenous regimen intended to cover bowel flora in addition to any antibiotic(s) chosen to cover marine microbes.

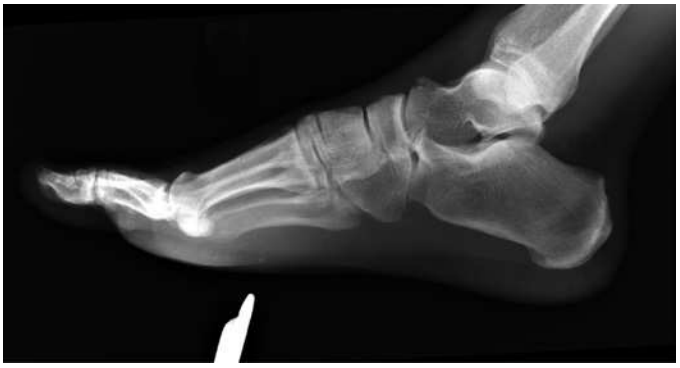

FIGURE 75-20 X-ray of a foot shows tiny fragment of stingray spine that caused inflammatory response. *(Photo courtesy Mathias Schar.)*

If the treatment plan is to treat and release, the victim should be observed for at least 3 to 4 hours for systemic side effects. Properly treated wounds may require a few months to fully heal with complete resolution of local tissue swelling (Figure 75-21). Wounds that are not properly debrided or explored and cleansed of foreign material may fester for weeks or months.[41] Such wounds may appear infected, but what really exists is a chronic draining ulcer initiated by persistent retained organic matter. Within the first few weeks after an envenomation, a foreign body can sometimes be observed by soft tissue radiograph, ultrasound, CT, or MRI. After a few weeks, exploration may reveal erosion or necrosis of adjacent soft tissue structures, synovitis, and/or the formation of an epidermal inclusion cyst or other related foreign body reaction.[12,101] As with other marine-acquired wounds, indolent infection should prompt a search for unusual microorganisms. A case of invasive fusariosis *(Fusarium solani)* after stingray

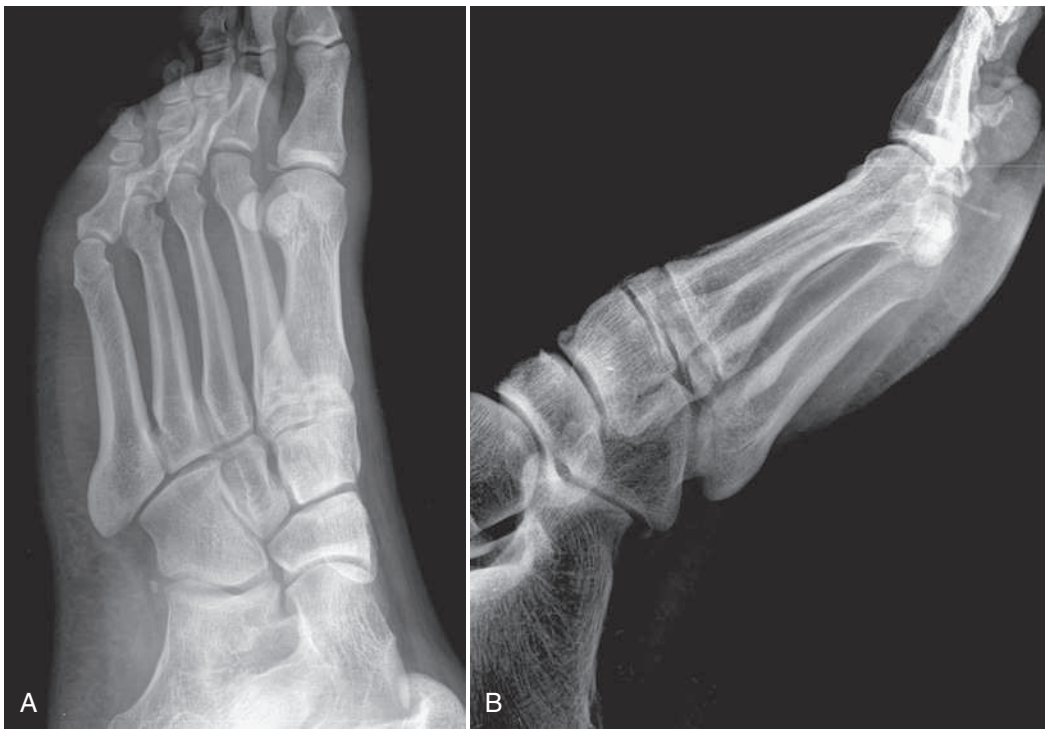

FIGURE 75-19 Radiographs demonstrating stingray spine tip at level of the first metatarsophalangeal joint. **A,** Oblique view. **B,** Lateral view. *(Courtesy Chris Fee.)*

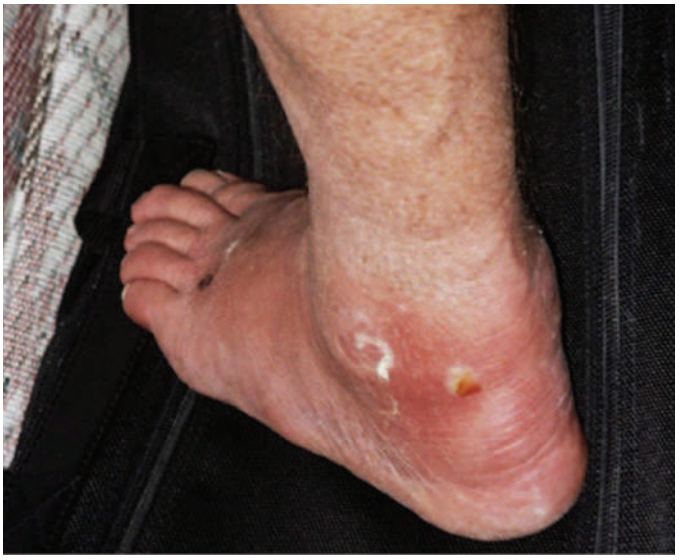

FIGURE 75-21 Initial severe inflammatory response from stingray puncture near the Achilles tendon. This injury required many weeks to heal. *(Courtesy Bob Luce.)*

envenomation responsive to sequential debridement and ketoconazole (the latter of indeterminate effect) has been reported.[58] Necrotizing fasciitis due to *Photobacterium (Vibrio) damsela* followed a leg laceration caused by a stingray. Notably, the patient had the wound sutured primarily and was not prescribed an antibiotic at the time of the repair.[10] Hyperbaric oxygen therapy has been cited to contribute to wound healing in a refractory case of stingray-induced soft tissue necrosis and postulated infection.[87] Another treatment to accelerate wound healing in a refractory case is topical recombinant human platelet-derived growth factor-BB (becaplermin gel 0.01%) every 12 hours underneath a moist dressing.[7]

PREVENTION

A stingray spine can penetrate a wetsuit, leather or rubber boot, and even the side of a wooden boat; therefore, a wetsuit or pair of athletic sneakers is not adequate protection. People walking through shallow waters known to be frequented by stingrays should shuffle along and create enough disturbance to frighten off any nearby stingrays. The same precautions hold true when one is accompanied by animals such as horses.[86]

SCORPIONFISH AND SIMILAR VENOMOUS FISH

Scorpionfish are members of the family Scorpaenidae and follow stingrays as perpetrators of piscine vertebrate stings. Distributed in tropical and less commonly in temperate oceans, several hundred species are divided into three groups typified by different genera on the basis of venom organ structure: (1) *Pterois* (zebrafish, lionfish, and butterfly cod), (2) *Scorpaena* (scorpionfish, bullrout, and sculpin), and (3) *Synanceja* (stonefish). All have a bony plate (stay), which extends across the cheek from the eye to the gill cover. Each group contains a number of different genera and species; at least 80 species of the family Scorpaenidae have been implicated in human injuries or studied anatomically, biochemically, or physiopharmacologically.

Other venomous fish that sting in a manner similar to scorpionfish include the Atlantic toadfish (family Batrachoididae, genus *Thalassophyrne*) (Figure 75-22), with two venomous dorsal fin spines and venomous spines on the gill covers, and the Pacific ratfish *(Hydrolagus colliei)* (Figure 75-23) and European ratfish *(Chimaera monstrosa),* both with a single dorsal venomous spine.[51] Toadfish hide in crevices and burrows, under rocks and debris, or in seaweed, sand, or mud. They may change coloration

FIGURE 75-22 Toadfish. *(Courtesy Marty Snyderman.)*

rapidly and remain superbly camouflaged. Rabbitfish (family Siganidae) (Figure 75-24) and leather jacks (leather backs or leather jackets, family Carangidae) carry venomous spines or fins and pose additional risks. Stargazers (family Uranoscopidae) have spines but do not appear to be venomous (Figures 75-25 and 75-26).

LIFE AND HABITS

Zebrafish (lionfish, firefish, or turkeyfish) are beautiful, graceful, and ornate coral reef fish generally found as single or paired free

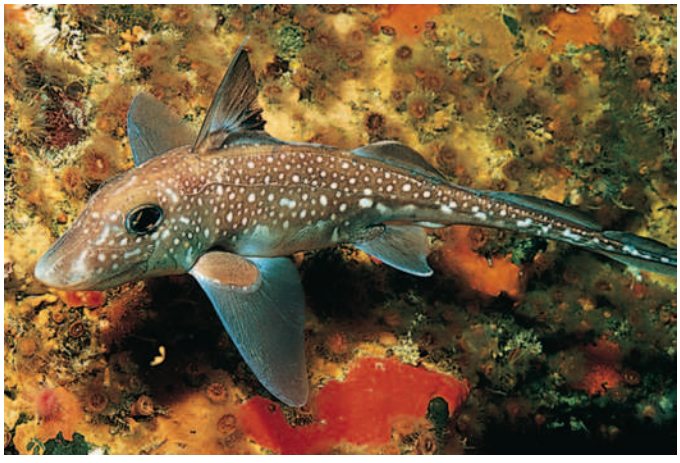

FIGURE 75-23 Ratfish *(Hydrolagus colliei). (Courtesy Howard Hall.)*

FIGURE 75-24 Rabbitfish. *(Courtesy Marty Snyderman.)*

FIGURE 75-25 Stargazer. *(Copyright Lynn Funkhouser.)*

swimmers or hovering in shallow water (Figure 75-27). They are increasingly popular as aquarium pets and are imported illegally as part of the "underground zoo." They have relatively recently been introduced to the Atlantic Ocean, perhaps released from aquaria, and have been spotted from North Carolina to South Florida.[4] They are proliferating in areas such as the Bahamas (Figure 75-28). To date, introduction of "exotic" (sometimes referred to as alien, nonnative, nonindigenous, or introduced) species of fishes has not resulted in the extinction of native species in marine habitats, but this has been mentioned as a concern because of the feeding behavior of zebrafish. The western red lionfish *Pterois volitans* is a recently introduced species.[89]

Scorpionfish proper *(Scorpaena)* dwell on the bottom in shallow water, bays, coral reefs and along rocky coastlines to a depth of 50 fathoms. Their shape and coloration provide excellent camouflage, allowing them to blend in with the ambient debris, rocks, and seaweed (Figures 75-29 to 75-33). They can be captured by hook and line and serve as important food fish in many areas. The protective coloration and concealment in bottom structures make scorpionfish difficult to visualize. Some species bury themselves in the sand, and most dangerous types lie motionless on the bottom. In the United States, they are found in greatest concentration around the Florida Keys and in the Gulf of Mexico, off the coast of southern California, and in Hawaii.

Stonefish live in shallow waters, often in tide pools and among reefs (Figures 75-34 to 75-35). They frequently pose motionless and absolutely fearless under rocks, in coral crevices or holes, or buried in the sand or mud. The fish use their pectoral fins to dredge sand or mud from beneath themselves, so that they can settle with only the mouth and eyes exposed.[63] They are so sedentary that algae frequently take root on their skin (Figures 75-36 and 75-37). They are usually 15 to 20 cm (6 to 8 inches) in length, but can grow to 30 cm (12 inches). Stonefish are not indigenous to North American coastal waters.

FIGURE 75-26 Stargazer. *(Copyright Lynn Funkhouser.)*

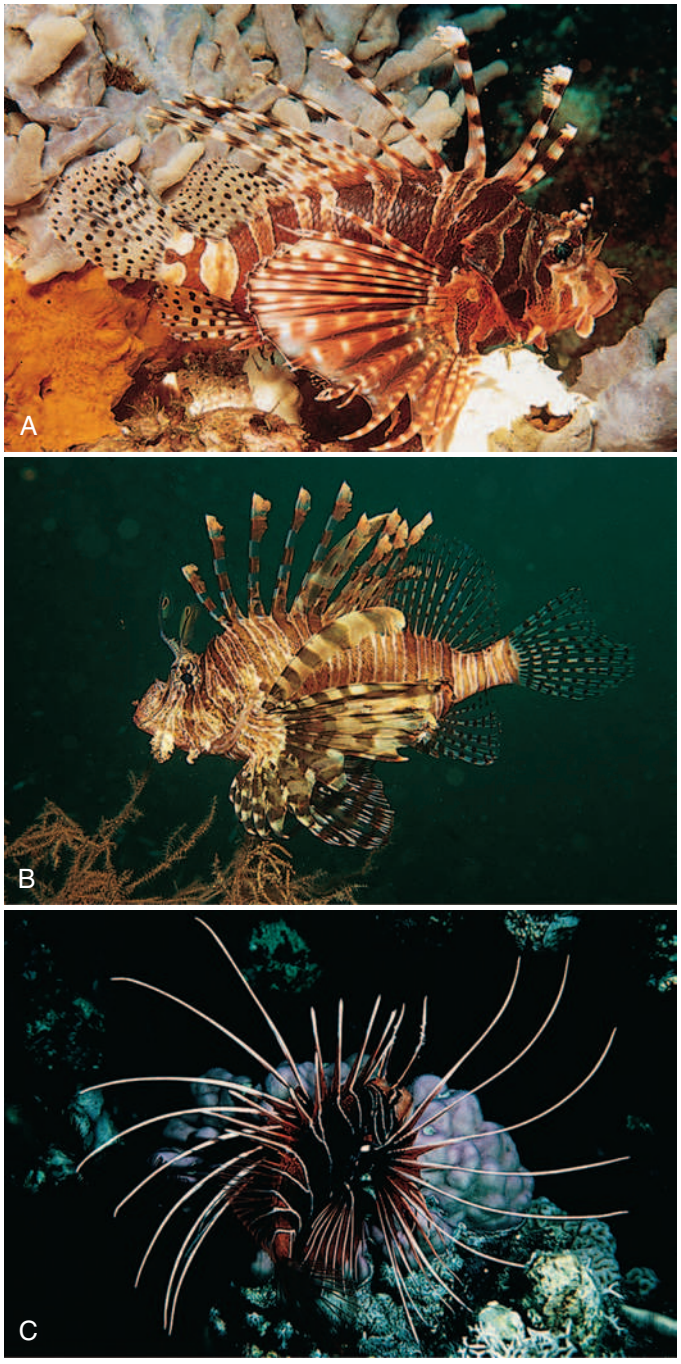

FIGURE 75-27 Three examples of lionfish. **A,** Juvenile lionfish from Sulawesi, Indonesia. **B,** Adult lionfish. **C,** Lionfish from the Red Sea. *(Courtesy Paul S. Auerbach, MD.)*

VENOM AND VENOM APPARATUS

The venom organs are the 12 or 13 (of 18) dorsal (Figure 75-38), 2 pelvic, and 3 anal spines, with associated venom glands. Although they are frequently large, plume-like, and ornate, the pectoral spines are not associated with venom glands. Each spine is covered with an integumentary sheath, under which venom filters along grooves in the anterolateral region of the spine from the paired glands situated at the base or in the mid-portion of the spine. It is estimated that the two venom glands of each dorsal stonefish spine carry 5 to 10 mg of venom, closely associated with antigenic proteins of high molecular weight (between 50,000 and 800,000).[22] Scorpionfish venom contains multiple toxic fractions and, in the case of stonefish venom, has been likened in potency to cobra venom. It contains a mixture

FIGURE 75-28 Invasive lionfish with Caribbean reef shark in the Bahamas. *(Copyright David Doubilet.)*

of proteins containing several enzymes, including hyaluronidase.[63] Hyaluronidase is a spreading factor in venoms because it degrades hyaluronate, which helps structure connective tissue. The major toxic component of *Synanceja* venom (stonustoxin) is a protein of molecular weight 148,000 (comprising alpha and beta subunits of molecular weights 71,000 and 79,000, respectively) that is both antigenic and heat labile. Similar purified toxins from other species are trachynilysin from *Synanceja trachynis* (Australian estuarine stonefish) and verrucotoxin (a glycoprotein) from *Synanceja verrucosa* (reef stonefish).[92] The principal action of stonefish venom appears to be direct muscle toxicity, resulting in paralysis of cardiac, involuntary, and skeletal muscles.[46] In an analysis of biologic activity, stonefish (*Synanceja horrida,* the Indian stonefish) venom exhibited edema-inducing, hemolytic, hyaluronidase, thrombin-like, alkaline phosphomonoesterase, 5′-nucleotidase, acetylcholinesterase, phosphodiesterase, arginine esterase, and arginine amidase activities.[65] In a recent evaluation, chromatographic analysis with electrochemical detection showed the presence of substances comigrating with norepinephrine, dopamine, and tryptophan. Serotonin (5-hydroxytryptamine) was not detected.[44] Crude venom of the stonefish *S. verrucosa* possesses numerous enzymatic properties, including hyaluronidase, 8 esterases, and 10 aminopeptidases.[43] Intracellular Ca^{2+} levels are increased by venoms of the soldierfish *(Gymnapistes marmoratus),* lionfish *(P. volitans),* and stonefish *(S. trachynis),* possibly via formation of pores in the cellular membrane, which, under certain conditions in experimental animals, may lead to necrosis.[27] In addition, trachynilysin activity on the heart, often noted as negative inotropy, may also be a function of Ca^{2+} influx.[92] The hemolytic activity of stonustoxin may in some part depend on surface tryptophan residues.[106] The cardiovascular effects of stonefish venom have been attributed in part to its activity at muscarinic receptors and adrenoceptors, and pain effects perhaps to its activity at bradykinin receptors.[23] Similar receptor activity, neutralized by stonefish antivenom, has been noted with lionfish venom.[25] The pain-causing protein in bullrout *(Notesthes robusta)* venom is an algesic protein (169.8 to 174.5 kDa) called nocitoxin.[54]

Stonefish venom causes pulmonary edema in laboratory animals, which may reflect general vascular permeability.[65,68] It also causes species-restricted (nonhuman) hemolysis and platelet aggregation.[64] Scorpionfish venom also causes acute inflammatory lung injury in mice, with hemorrhage and alveolar macrophage activation.[13] Profound endothelial relaxation may contribute directly to hypotension.[73] The neuromuscular toxicity appears to be a consequence of the venom's dose-dependent presynaptic and postsynaptic actions at the myoneural junction, which include release and depletion of neurotransmitter from the nerve terminal, followed by irreversible depolarization of muscle cells and microscopically observable muscle and nerve damage.[69] Hypotension observed in envenomed laboratory animals may be due in part to binding to receptors on endothelial cells, causing production of nitrous oxide and activation of potassium channels.[99] The nondialyzable opalescent venom retains full potency for at least 24 to 48 hours after the death of a scorpionfish.[67] Extrapolating from the LD_{50} of 0.36 mcg/g in mice, it is estimated that 18 mg relayed by six intact spines might cause death in a 60-kg (132-lb) human.[65]

Pterois species carry long, slender spines with small venom glands covered by a thin integumentary sheath. An extract of lionfish spine tissue contains acetylcholine and a toxin that affects neuromuscular transmission.[28] *Scorpaena* species carry longer heavy spines with moderate-sized venom glands covered by a thicker integumentary sheath. *Synanceja* species carry short, thick spines with large, well-developed venom glands covered by an extremely thick integumentary sheath (Figures 75-39 and

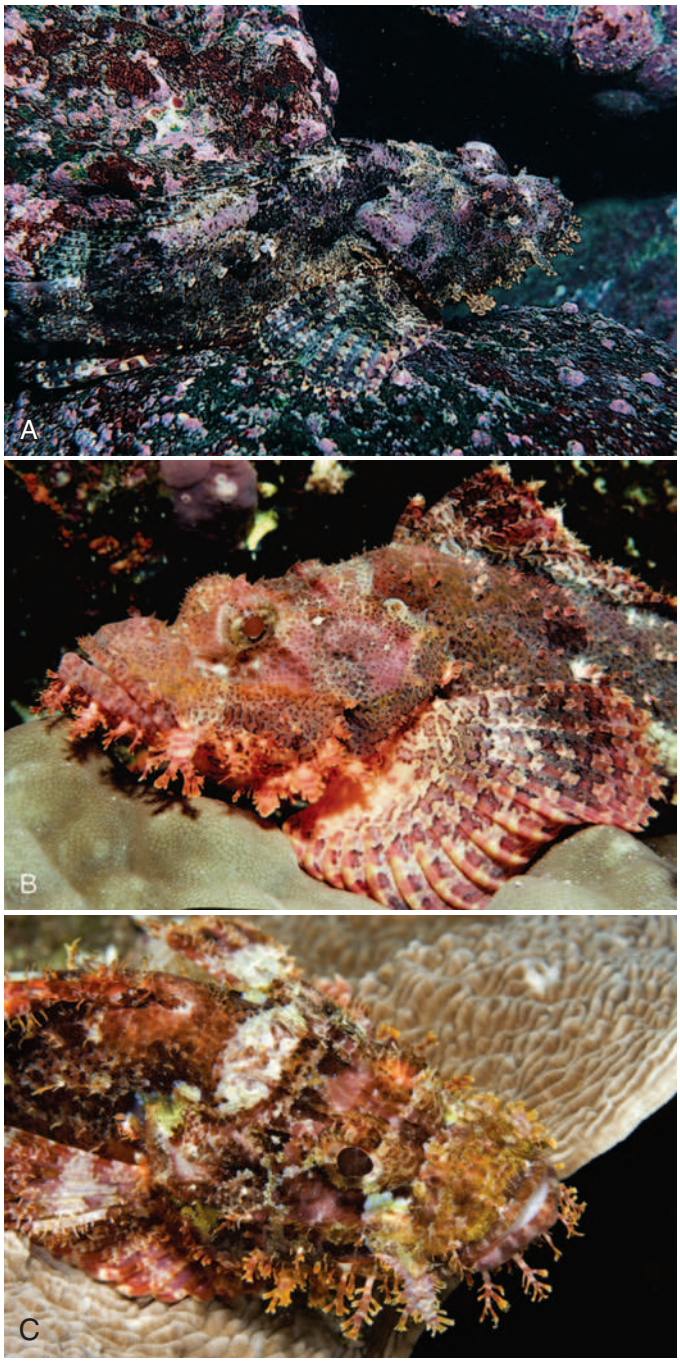

FIGURE 75-29 Three examples of scorpionfish. **A,** Scorpionfish assuming the coloration of its surroundings. **B,** Scorpionfish in the Red Sea. **C,** Scorpionfish. *(**A** courtesy Paul S. Auerbach, MD; **B** copyright Carl Roessler; **C** copyright Stephen Frink.)*

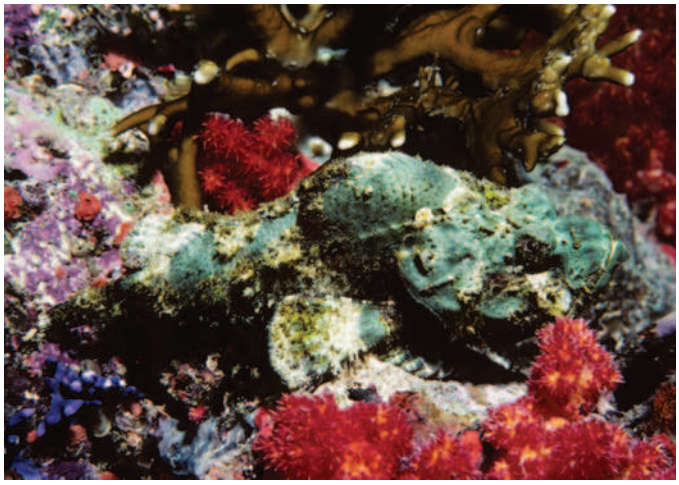

FIGURE 75-30 Scorpionfish camouflaged like debris in Fiji. *(Copyright Carl Roessler.)*

FIGURE 75-33 Raggy scorpionfish. *(Copyright 2011 Norbert Wu: norbertwu.com.)*

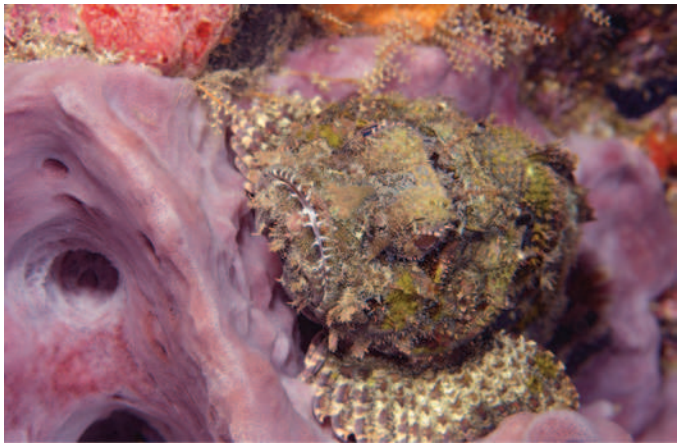

FIGURE 75-31 Scorpionfish nestled on a sponge. *(Copyright Stephen Frink.)*

75-40). However, the skin over the venom gland is loosely attached, so when a human treads on the fish, the skin is pushed down the spine and the venom gland is compressed by the crumpled sheath. The pressure forces the venom gland to empty up the paired narrow ducts so that venom and glandular tissue spurt into the wound.[47]

When any of these fish is removed from the water, handled, stepped on, or otherwise threatened, it reflexively erects the spiny dorsal fin and flares out the armed gill covers and pectoral and anal fins. If provoked while still in the water, it actually attacks. The venom is injected by a direct puncture wound through the skin, which tears the sheath and may fracture the spine, in a manner analogous to that of a stingray envenomation. Fishermen are commonly injured, particularly when emptying nets or extracting hooks from captured fishes.[50]

CLINICAL ASPECTS

Native residents of the Indo-Pacific islands have great fear of a sting from the dreaded venomous stonefish, such as the "ikan hantu" (devil fish), Tahitian "nohu" ("nofu" or "no'u," the waiting one) or the Australian "warty ghoul." The presentation of the injury is similar to that of stingray envenomation in that the unwary diver or fisherman steps on or handles the fish. In the United States, marine aquarists and beneficiaries of illegal importation of tropical animals are increasingly envenomed as they unknowledgeably handle *P. volitans, Pterois radiata,* or *Scorpaena guttata.* In Indo-Pacific waters, envenomations of the foot and lower extremity are more commonly caused by the stonefish, such as *S. horrida, S. trachynis,* or *S. verrucosa.* Scorpionfish stings vary according to the species, with a progression in severity from the lionfish (mild) through the scorpionfish (moderate to severe) to the stonefish (severe to life threatening). The severity of envenomation depends on the number and type of stings, species, amount of venom released, and age and underlying health of the victim. Pain is immediate and intense, with

FIGURE 75-32 Scorpionfish. *(Copyright Stephen Frink.)*

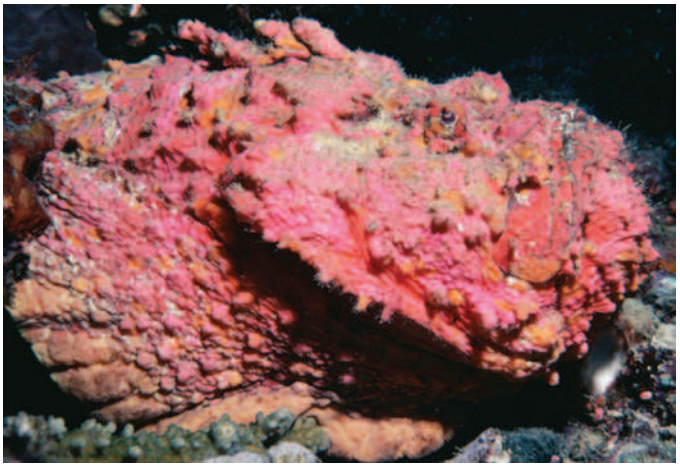

FIGURE 75-34 Stonefish in Papua New Guinea. *(Copyright Carl Roessler.)*

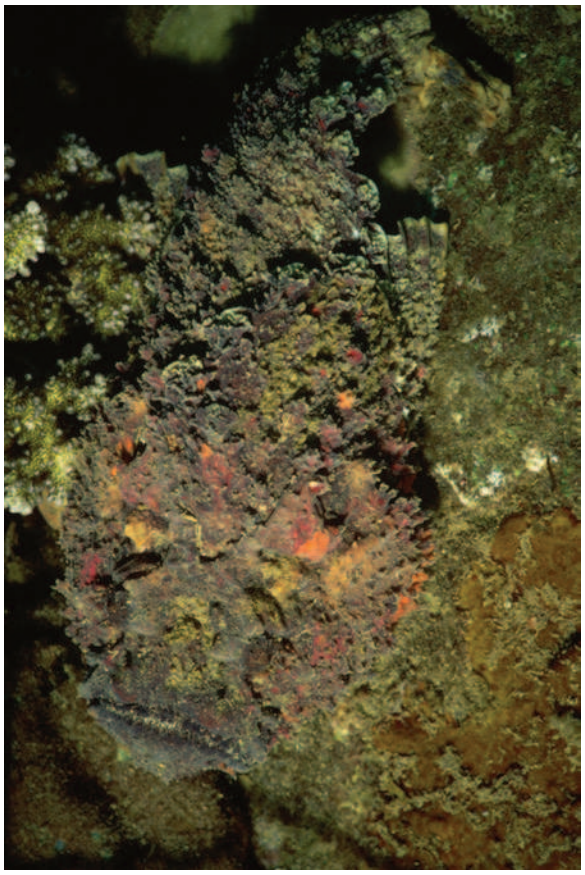

FIGURE 75-35 Stonefish. *(Copyright Lynn Funkhouser.)*

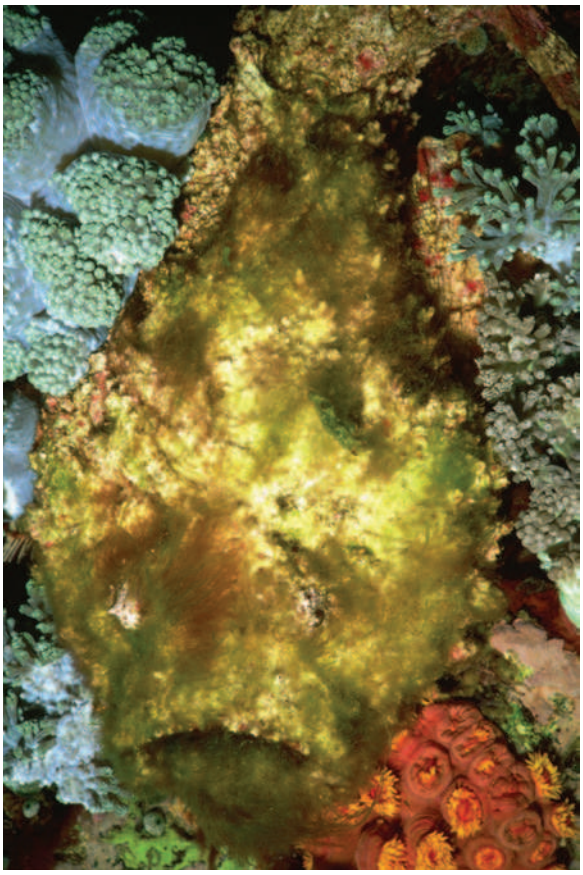

FIGURE 75-37 Stonefish. *(Copyright Lynn Funkhouser.)*

FIGURE 75-36 Some stonefish are so sedentary that algae grow on their skin. *(Courtesy Paul S. Auerbach, MD.)*

radiation centrally. Untreated, pain peaks at 60 to 90 minutes and persists for 6 to 12 hours. With a scorpionfish or stonefish envenomation, pain may be severe enough to cause hallucinations or delirium and may persist at high levels for hours (scorpionfish) or days (stonefish).[50] The wound and surrounding area are initially ischemic and then cyanotic (Figure 75-41), with more broadly surrounding areas of erythema, edema, and warmth. Vesicles may form (Figure 75-42). Human (hand) vesicle fluid after the sting of the lionfish *P. volitans* was analyzed for mediators of inflammation and demonstrated an appreciable quantity of prostaglandin $F_{2\alpha}$; thromboxane B_2, prostaglandin E_2, and 6-keto-prostaglandin $F_{1\alpha}$ were present in negligible quantities. Whether or not residual venom is present in blister fluid is a matter of conjecture. Rapid tissue sloughing and close surrounding areas of cellulitis, with anesthesia adjacent to peripheral hyperesthesia, may be present within 48 hours. Necrotic

FIGURE 75-38 Scorpionfish spines. *(Courtesy Kenneth Kizer, MD.)*

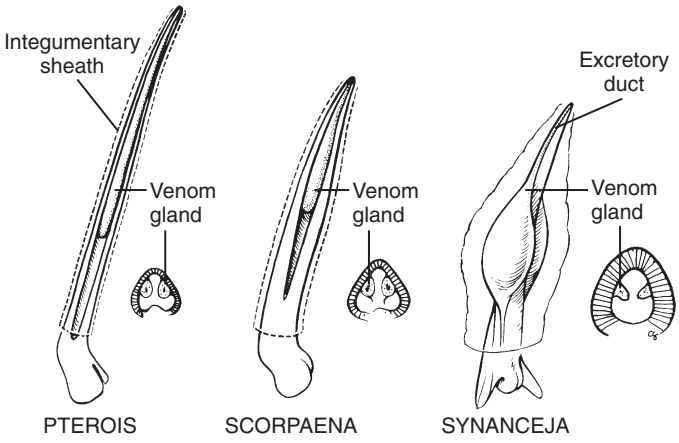

FIGURE 75-39 Lionfish *(Pterois)*, scorpionfish *(Scorpaena)*, and stonefish *(Synanceja)* spines with associated venom glands.

FIGURE 75-40 Spines of the venomous stonefish, demonstrating venom glands. *(Courtesy John Williamson, MD.)*

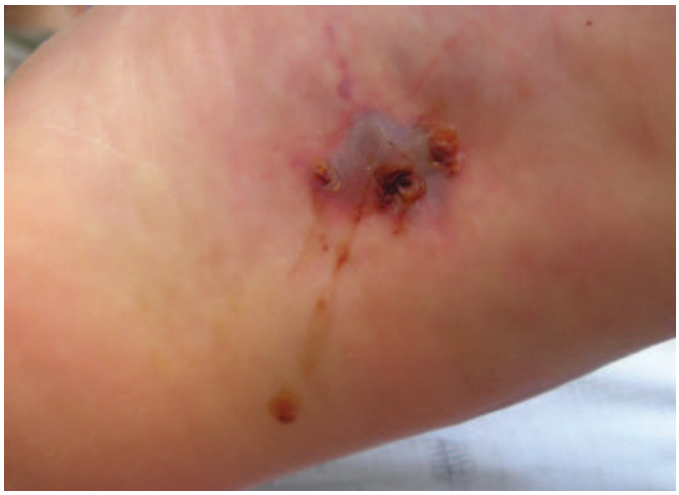

FIGURE 75-41 Stonefish puncture wound. *(Courtesy Richard Lyon, MD.)*

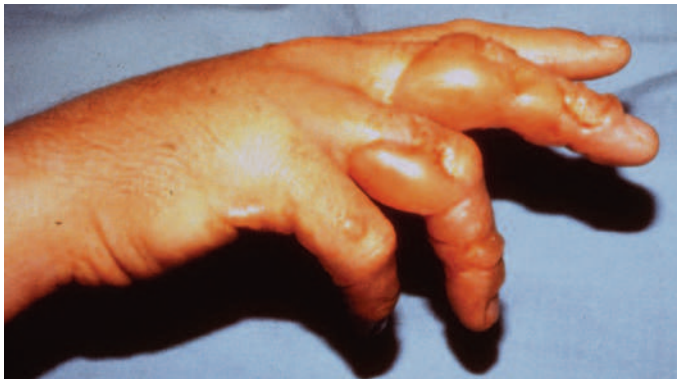

FIGURE 75-42 Vesiculation of the hand 48 hours after the sting of a lionfish. *(Courtesy Howard McKinney.)*

ulceration is rare but may occur after a lionfish envenomation (Figure 75-43).[85] Severe local tissue reaction is more common after the sting of a scorpionfish or stonefish.

Systemic effects include anxiety, headache, tremors, maculopapular skin rash, nausea, vomiting, diarrhea, abdominal pain, diaphoresis, pallor, restlessness, delirium, seizures, limb paralysis, peripheral neuritis or neuropathy, lymphangitis, eosinophilia, arthritis, fever, hypertension, respiratory distress, bradycardia, tachycardia, atrioventricular block, ventricular fibrillation, congestive heart failure, pulmonary edema, pericarditis, hypotension, syncope, and death.[16,72] Pulmonary edema is a bona fide sequela.[72] Death in humans, which is extremely rare, usually occurs within the first 6 to 8 hours. The wound is indolent and may require months to heal, only to leave a cutaneous granuloma or marked tissue defect, particularly after a secondary infection or deep abscess. Mild pain may persist for days to weeks. Lionfish envenomation has been used as a fabricated chief complaint to seek a prescription for narcotic drugs.[98] After successful therapy, paresthesias or numbness in the affected extremity may persist for a few weeks.

TREATMENT

As soon as possible, the wound or wounds should be immersed in nonscalding hot (upper limit 45° C [113° F]) water to tolerance. This may inactivate at least one of the thermolabile components of the protein venom that might otherwise induce a severe

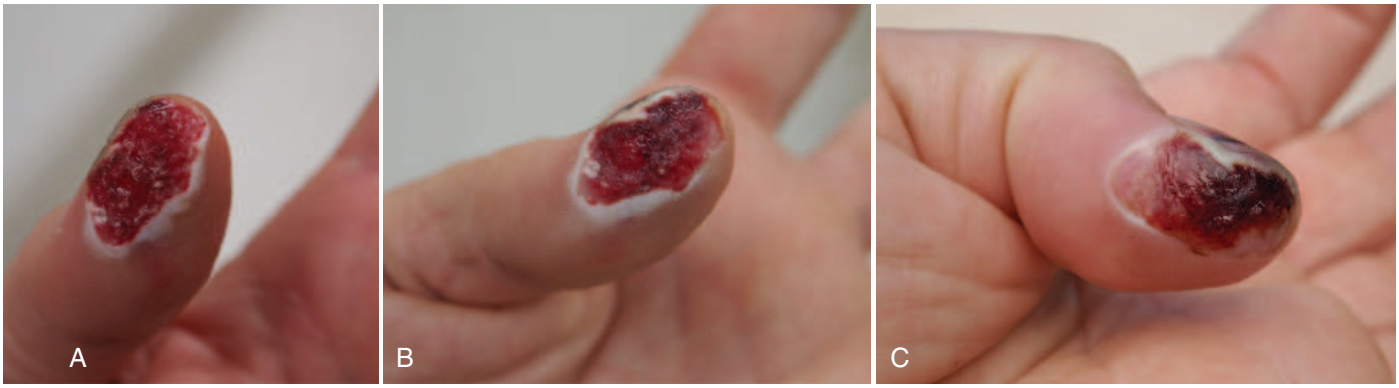

FIGURE 75-43 Necrotic ulceration following a lionfish sting at 5 (**A**), 7 (**B**), and 11 (**C**) days. *(Photos courtesy Elly Wray.)*

systemic reaction. Platelet aggregation in blister fluid is inhibited by heat treatment, which suggests that the venom or some other active component may be neutralized. The soak should be maintained for a minimum of 30 minutes and may continue for up to 90 minutes. Recurrent pain that develops after an interval of 1 to 2 hours may respond to a repeat hot water treatment. As soon as is practical, all obvious pieces of spine and sheath fragments should be gently removed from the wound. Vigorous irrigation should be performed with warmed sterile saline to remove any integument or slime. If pain is severe or inadequately controlled (in terms of degree or rapidity of relief) by hot water immersion, local tissue infiltration with 1% to 2% lidocaine without epinephrine or regional nerve block with an anesthetic, such as 0.25% bupivacaine, may be necessary. After injection with a local or regional anesthetic, the hot water immersion should be discontinued or closely observed, to avoid inadvertent creation of a burn wound in the now insensate body part. Infiltration with emetine hydrochloride, potassium permanganate, or Congo red has been abandoned, despite reports of favorable experiences with acidic emetine. The biochemical bases for the success of folk remedies, such as application of meat tenderizer, mangrove sap, or green papaya (papain), have yet to be confirmed. The effectiveness of alternative remedies may be related to the protein behavior of the venom, which is inactivated by heat, extremes of pH (it is partially inactivated at pH of greater than 8.6 and completely at a pH of less than 4), hydrogen peroxide, iodine, and potassium permanganate (which is, unfortunately, tissue toxic). One health care provider has recommended using vitreous humor from the black rock cod *Epinephelus daemelii* as a topical pain relief preparation for a sting from this species. Currently, no data are available to support topical administration of empirical remedies, such as mineral spirits, organic dye, ground liver, or formalin. Cryotherapy is absolutely contraindicated, to avoid an iatrogenous cold-induced injury.

Although the spine rarely breaks off into the skin, the wound should be explored to remove any spine fragments, which will otherwise continue to envenom and act as foreign bodies, perpetuating an infection risk and poorly healing wound. If the spine has penetrated deeply into the sole of the foot, surgical exploration should be performed in the operating room with magnification. Vigorous warmed saline irrigation should be performed. Wide excision and debridement are unnecessary. Because of the nature of the puncture wound, tight suture or surgical tape closure should not be undertaken; rather, the wound should be allowed to heal open with provision for adequate drainage. If the puncture wound is high risk (deep, into the hand or foot, or both), prophylactic antibiotic(s) should be administered. It is wise to remove blister fluid using aseptic technique.

Stonefish envenomation may cause profound tissue necrosis. This may be of a severity to require debridement, including amputations of soft tissues and bone.

A stonefish antivenom is manufactured by the Commonwealth Serum Laboratories (CSL Limited, Parkville, Victoria, Australia) (Figure 75-44). In cases of severe systemic reactions from stings of *Synanceja* species, perhaps from soldierfish *(G. marmoratus)* or bullrout *(N. robusta),* and rarely from other scorpionfish, it is administered intramuscularly or diluted for intravenous administration.[24,32] The antivenom is supplied in vials containing 1.5 to 3 mL of liquid containing 2000 units of hyperimmune $F(ab')_2$ horse serum active against *S. trachynis,* with 1000 units (one-half a vial) capable of neutralizing 10 mg of dried venom.[30] $F(ab')_2$ preparations are obtained by pepsin treatment of IgG at pH 2, whereas Fab fragments are produced by papain treatment at pH 7 to 8.[100] The former product is believed to be easier to standardize than the latter, and better in its plasma distribution and venom neutralization. After skin testing to estimate the risk for an anaphylactic reaction to equine sera, the antivenom should be given. If skin testing is omitted, anticipate and be prepared to treat an allergic reaction. As a rough estimate, one vial of antivenom should neutralize one or two significant stings (punctures). For one or two puncture wounds, administer one vial; for three or four puncture wounds, two vials; for more than four puncture wounds, administer three vials. One or more additional vials may be necessary if there is recurrent severe pain. When not in use, the antivenom should be protected from light and stored at 2° to 8°C (35.6° to 46.4°F), and never frozen. Unused portions should be discarded.

FIGURE 75-44 Stonefish antivenom. *(Courtesy John Williamson, MD.)*

The fact that stonefish antivenom cross-reacts with most piscine venoms suggests that piscine venoms may possess structural similarities in addition to their functional similarities, which include induction of profound cardiovascular changes, release of nitric oxide from endothelial cells, smooth muscle contraction, depolarizing action on nerve and muscle cells, and potent cytolytic activity.[26]

PREVENTION

The most effective way to prevent envenomation is to avoid handling or setting down upon a scorpionfish. A diver should make a careful inspection before contacting the ocean floor or a rocky ledge. Amateur aquarists should be exceedingly cautious when handling exotic tropical fish. Seemingly dead fish may yield an unpleasant surprise for the unwary.

CATFISH

LIFE AND HABITS

Approximately 1000 species of catfish inhabit both freshwaters and saltwaters; many of these are capable of inflicting serious stings. Marine animals include the Oriental catfish *(Plotosus lineatus),* which lurks in tall seaweed and can inflict extremely painful stings, the larger sailcat *(Bagre marinus),* and the common sea catfish *(Galeichthys felis),* which hovers along the sandy bottom. The coral catfish *(Plotatus lineatus)* has also been reported to sting humans.[95] Ocean catfish, particularly juveniles, "swarm" and feed along the bottom (Figure 75-45). There are 39 species of catfishes native to the North American continent. Freshwater catfish of North America include the brown bullhead *(Ameiurus nebulosus),* Carolina madtom *(Noturus furiosus),* channel *(Ictalurus punctatus),* blue *(Ictalurus furcatus),* and white *(Ameiurus catus)* catfish. Some of the catfish of South America can grow to a very large size (Figures 75-46 and 75-47).

The catfish derives its name from the well-developed sensory barbels ("whiskers") surrounding the mouth. The barbels of catfish carry well-developed sensory organs that are used to transmit both touch and taste. All catfishes are adapted to foraging in muddy and dark waters, where feeding by senses is essential.

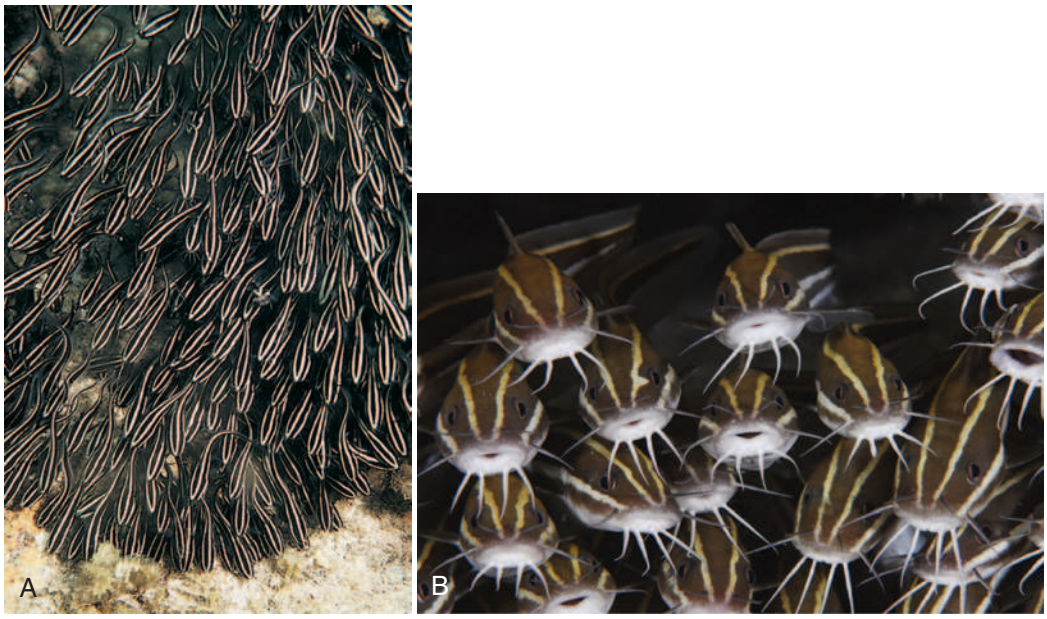

FIGURE 75-45 Marine catfish. **A,** Juvenile ocean catfish. **B,** Marine catfish. *(**A** copyright 2006 Norbert Wu: norbertwu.com; **B** copyright Lynn Funkhouser.)*

Catfish possess a slimy skin without any true scales. Marine catfish, unlike freshwater catfish, frequently travel in large schools. Most freshwater catfish are bottom feeders noted for their junkyard diet. They are poor swimmers and not very evasive.

The South American astroblepids have flattened suctorial lips that allow them to scale cliffs. Tiny South American (Amazonian) catfish of the genus *Vandellia* (species *cirrhosa, balzanii, plazaii, sanguinea,* and *beccarii*) are known as "urethra fish" in English, *candirú* by Brazilians, and *canero* by Spanish speakers.[15]

FIGURE 75-46 Amazonian catfish with pectoral fin spines. *(Courtesy George Hertner, MD.)*

FIGURE 75-47 Amazonian catfish pectoral spine. *(Courtesy George Hertner, MD.)*

Approximately 2.5 to 7.5 cm (1 to 3 inches) long, they carry short spines on their gill covers (Figure 75-48). This "vampire fish" is predominately a bottom-feeding "junkfish" found in murky or muddy waters in the Amazon and Orinoco Rivers and perhaps select tributaries and is putatively attracted to urine (water motion, warmth). It can swim into the gills of a larger fish, or reputedly up the human urethra or other urogenital apertures, where it extends the spiny gill covers and thus becomes embedded, preventing removal by pulling on the fish's tail. Within the gills of a fish, it anchors itself with its spines and rasps with teeth to obtain a blood meal. Within the human urethra, it causes extreme pain and inflammation. Because the animal normally seeks the outflow stream from a larger fish's gills (where it may enter and parasitize the host fish), perhaps it is not urinophilic, but merely swimming into a stream. Others theorize that it is attracted to ammonia. Natives wear pudendal shields when urinating in natural bodies of water. A tight-fitting bathing suit is certainly prudent.

At best, extraction is painful (Figure 75-49). Amputation of the penis by natives has been described in the older literature. Ingestion of the green fruit of the jagua (xagua or xaqua) tree or buitach apple *(Genipa americana)* as a concoction (tea) apparently works to dispel the urethra-lodged candirú by the action of a large quantity of citric acid (megadose vitamin C), which softens calcium spines. Other references cite placement of either or both plants (or their extracts) within the urethra (or other invaded body orifice) in order to dispatch and dissolve the fish. Typically, removal is performed mechanically while the victim is anesthetized. The veracity of the threat of the candirú to humans has been called into question.[11a]

FIGURE 75-48 Amazonian catfish (candirú), which can enter the human urethra. *(Courtesy Vidal Haddad, Jr.)*

FIGURE 75-49 Candirú extracted from human urethra. *(Courtesy George Hertner, MD.)*

VENOM AND VENOM APPARATUS

The venom apparatus of the catfish consists of the single dorsal and two pectoral fin spines ("stings") and the axillary venom glands. Both the dorsal and pectoral spines are exquisitely sharp and can be locked into an extended position by the fish when it is handled or becomes excited. The spines are enveloped by glandular tissue within an integumentary sheath; some spines are barbed or have sharp retrorse teeth. Scattered reports note envenomation in persons who handled only the tail of the fish, such as the Arabian Gulf catfish *(Arius thalassinus),* which suggests the presence of a toxic skin secretion (crinotoxin). Other observers note that toxin released from epidermal skin cells can cause throbbing pain, tissue necrosis, and perhaps muscle fasciculations.[42] Oriental catfish toxin, which is poorly antigenic, contains vasoconstrictive, hemolytic, edema-forming, dermatonecrotic, and other biogenic fractions.[96] It behaves in vivo much like a milder version of stingray venom. In contrast, the crinotoxin of the Arabian Gulf catfish contracts smooth muscle and stimulates release of prostaglandins; pretreatment with atropine and indomethacin attenuates the response.[3,95] Furthermore, wound healing responses are accelerated by repeated local application of preparations from the epidermal secretions of another Arabian gulf catfish (*Arius bilineatus,* Valenciennes).[2]

Clinical Aspects

Most stings are incurred when a fish is handled, which creates an injury out of proportion to the mechanical laceration. Other injuries occur when the animal is accidentally or intentionally stepped upon or kicked (Figure 75-50). When the spine penetrates the skin, the integumentary sheath is damaged, and the venom gland exposed. Catfish stings are described as instantaneously stinging, throbbing, or scalding, with central radiation up the affected limb. Normally the pain subsides within 30 to 60 minutes, but in severe cases it can last for 48 hours. The area around the wound quickly appears ischemic, with central pallor that gradually becomes cyanotic before the onset of erythema and edema. Swelling can be severe, and secondary infections are frequent; gangrenous complications have been reported. Common side effects include local muscle spasm, diaphoresis, and fasciculations. Bleeding from the puncture wounds may be more severe than expected. Less common sequelae are peripheral neuropathy, lymphedema, adenopathy, lymphangitis, weakness, syncope, hypotension, and respiratory distress. Death is extremely rare. A marine catfish *(Genidens genidens)* sting caused a fatal heart perforation in a fisherman, who fell upon a net carrying several catfish.[53] "Finning" occurs when a person is punctured by a fin while handling a fin. This often occurs when removing a hook from a fish or a fish from a net. In one instance of catfish finning, in addition to the immediate typical immediate toxic reaction, the victim suffered recurrent episodes of pain and swelling on the dorsum of the hand over the course of 6 months, which eventually led to spontaneous skin rupture and blood-tinged fluid drainage.[1] Plain radiography revealed two catfish spines embedded in the soft tissues between the third and fourth metacarpal bones. Thirteen months after the initial injury, one spine was removed easily with local exploration; more extensive surgery did not lead to successful localization of the second spine, but revealed extensive edematous tenosynovitis. Because of the clinical course, the patient was treated presumptively for *Mycobacterium marinum* infection. Development of a necrotizing fasciitis-like reaction of the hand requiring extensive debridement was noted in a case report describing catfish spine envenomation.[20] In another case, the radial artery was lacerated by a spine that became embedded in the volar-radial aspect of the nondominant wrist (Figure 75-51).[40] This was repaired by lateral arteriorrhaphy rather than segmental resection and reanastomosis (Figure 75-52).

The sting of the marine catfish is usually more severe than that of its freshwater counterparts and may have a propensity to more local hemorrhage.[79] Infection risk is similar to that for any aquatic-acquired wound, in that *Vibrio* and *Aeromonas* species may be pathogens and the infection may be polymicrobial.[81,82] Other organisms that have been reported to be associated with marine or freshwater catfish-related injuries include *Edwardsiella tarda, Citrobacter freundii, Fusobacterium mortiferum, Morganella morganii, Providencia rettgeri, Enterococcus faecalis, Pseudomonas aeruginosa, Mycobacterium terrae,* and *Enterobacter cloacae.*[82] *E. tarda* is a gram-negative bacillus of the family Enterobacteriaceae that is mainly associated with aquatic environments and the animals that inhabit them, particularly catfish and other cold-blooded animals.[5,8] It may be a pathogen for eels and catfish. If *E. tarda* infection is determined, it is sensitive in vitro to ampicillin, aminoglycosides, β-lactamase stable

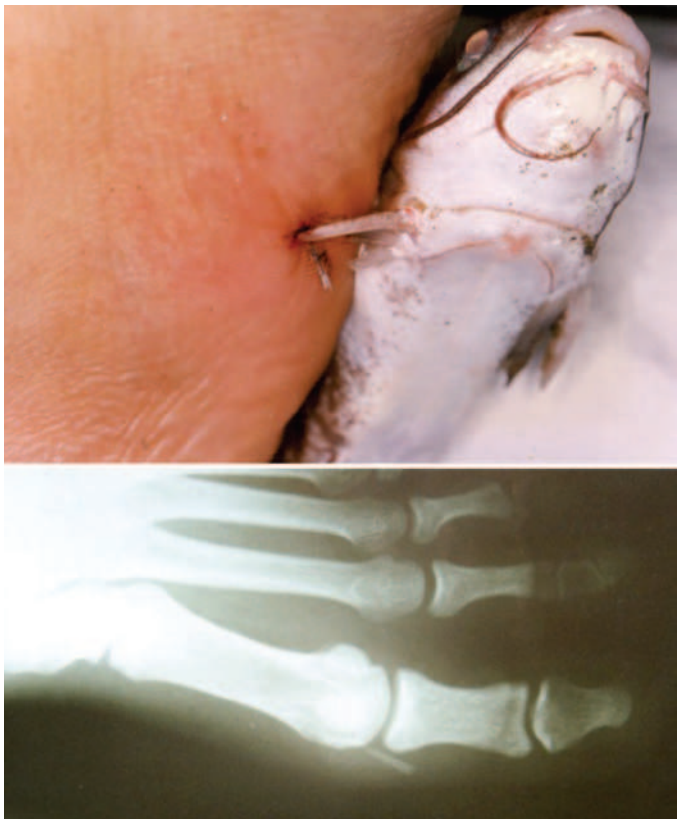

FIGURE 75-50 Catfish spine broken off into foot. *(Courtesy Vidal Haddad, Jr.)*

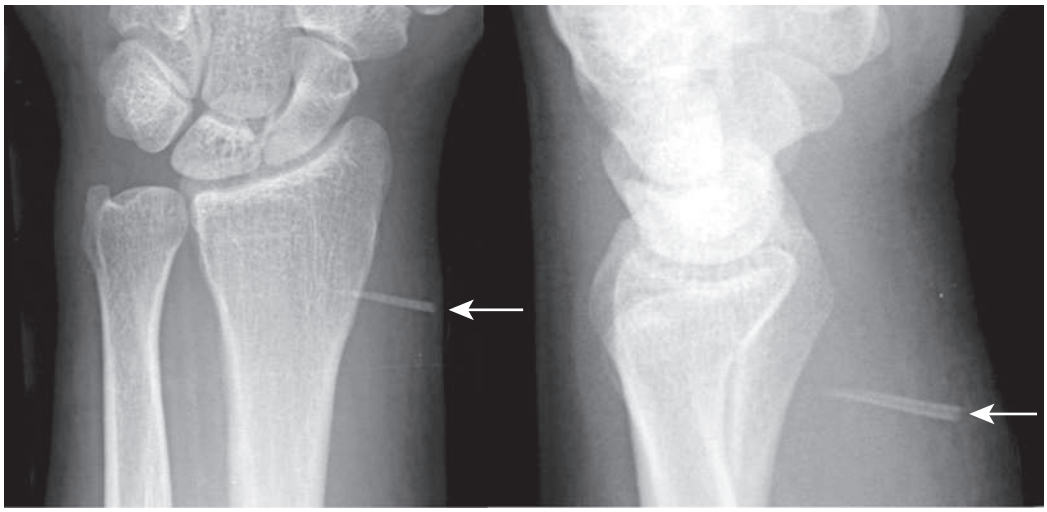

FIGURE 75-51 Plain films with a catfish fin in the volar wrist. *(Courtesy Ekkehard Bonatz.)*

cephalosporins, quinolones, tetracycline, and trimethoprim-sulfamethoxazole.[8]

TREATMENT

There are no specific antidotes. As with stingray and scorpionfish envenomations, the success of therapy is related to the rapidity with which it is undertaken. With catfish envenomations, in contrast to those of stingrays, constriction bandages have never been recommended for first aid. The wound should be immediately immersed in nonscalding hot water to tolerance (upper limit 45°C [113°F]) for 30 to 90 minutes or until there is significant pain relief. This may inactivate heat-labile components of the venom and perhaps helps to reverse local toxin-induced vasospasm. There is no evidence that adding mineral salts, solvents, antiseptics, or other chemicals to the water is of additional benefit. Cryotherapy is not efficacious. A popular and unstudied local (U.S. rural) remedy is to rub the sting with skin mucus (slime) from the catfish. If the hot water soak is not sufficient to control pain, local infiltration of the wound with buffered (alkalinized) bupivacaine or lidocaine without epinephrine or a regional nerve block may be necessary. It has been theorized that the pH alteration offered by the alkalinized local anesthetic may neutralize venom.[75] The wound should be explored surgically to remove all spine and sheath fragments. Standard radiographs or soft tissue exposures may locate a radiopaque foreign body (Figure 75-53). Advanced imaging may be necessary. The wound should be left unsutured to heal, to allow adequate drainage and minimize the risk of infection. All wounds must be carefully observed for infection until healed. If the puncture wound is of high infection risk (i.e., deep or into the hand or foot), a prophylactic antibiotic(s) should be administered.

PREVENTION

Catfish should be handled without grabbing the dorsal or pectoral fins, preferably by using a mechanical instrument or gaff. If possible, *Plotosus lineatus* should not be handled at all.

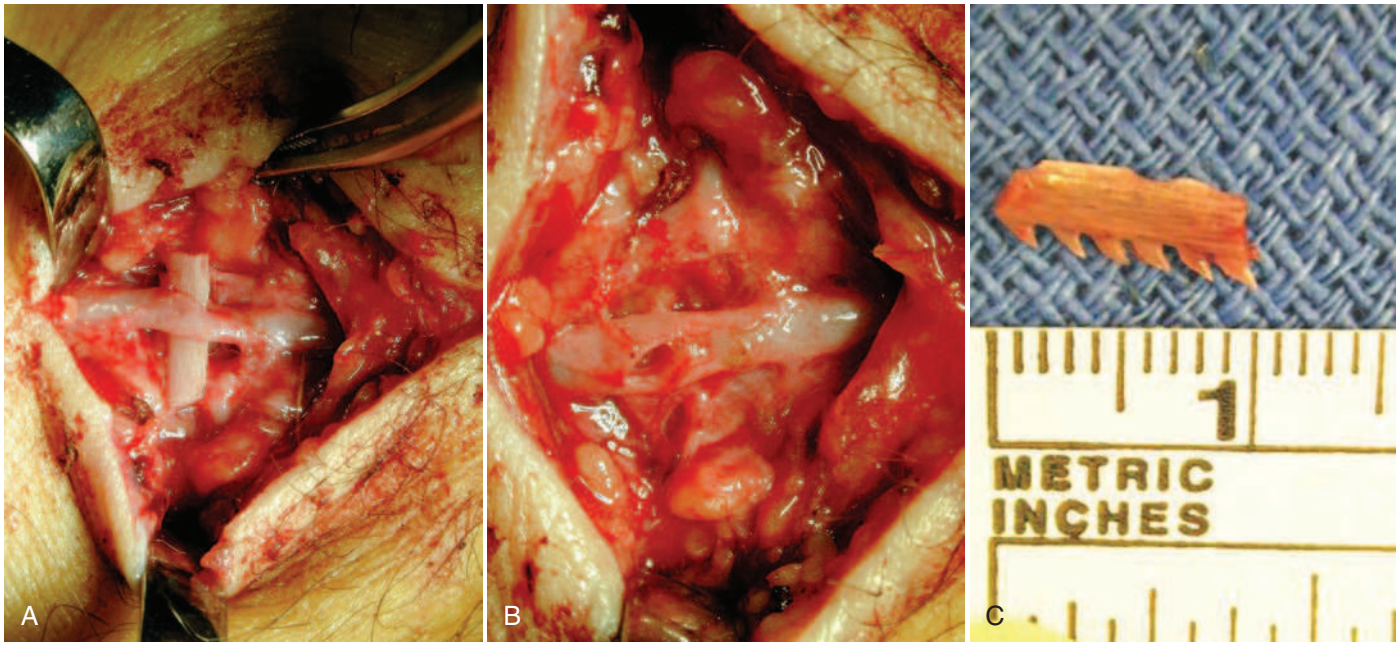

FIGURE 75-52 **A,** Catfish spine piercing the radial artery. **B,** Radial artery with residual holes from catfish spine, which has been removed. **C,** The retrobarbed structure of the catfish spine is apparent. *(Courtesy Ekkehard Bonatz.)*

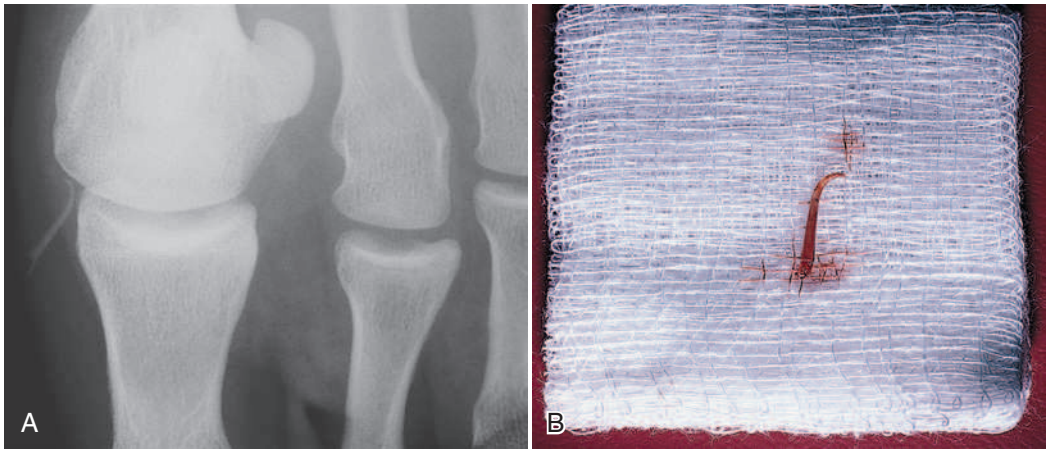

FIGURE 75-53 Catfish spine lodged in the foot. **A,** Radiograph shows a foreign body. **B,** The spine removed. *(Courtesy Paul S. Auerbach, MD.)*

WEEVERFISH

LIFE AND HABITS

The weeverfish *(Echiichthys* species, formerly named *Trachinus)* (Figure 75-54) is the most venomous fish of the temperate zone. It is found in the Black Sea, Mediterranean Sea, eastern Atlantic Ocean, North Sea, and European coastal areas. Common names for the weeverfish include adder-pike, sea dragon, sea cat, and stang. Weeverfish are small (10 to 53 cm [4 to 21 inches]) marine creatures that inhabit flat sandy or muddy bays, usually burying themselves in the soft bottom with only the head partially exposed. They lead sedentary lives but when provoked can strike out with unerring accuracy. "Weevers" are terrors to fishermen working in shallow sandy areas.

VENOM AND VENOM APPARATUS

The venom apparatus consists of four to eight elongate (up to 4.5 cm [1.75 inches] in length) and needle-sharp dorsal and two opercular and dagger-like dentinal spines, associated holocrine glandular tissue, and a thin, enveloping stratified squamous epithelium integumentary sheath. When excited, the fish extends the dorsal fin and expands the operculum, projecting the opercular spine out at a 35- to 40-degree angle from the longitudinal axis of the body. Weeverfish survive for hours out of the water, and the toxin remains potent for hours in dead animals, particularly when they are well refrigerated. Although incompletely characterized, the unstable (heat-labile) protein venom (ichthyoacanthotoxin) contains several peptides, at least one protein of high molecular weight (324,000), and possibly 5-hydroxytryptamine, epinephrine, norepinephrine, histamine, and mucopolysaccharide components. To date, serotonin has not been identified in weeverfish venom. The greater weeverfish *(Echiichthys draco)* releases a protein venom, dracotoxin, which has membrane-depolarizing and hemolytic activities. It appears to be a single polypeptide of molecular weight 105,000.[21] Other weeverfish of significance include *Echiichthys vipera, Echiichthys radiatus,* and *Echiichthys lineolatus.*

Clinical Aspects

Weeverfish stings usually afflict professional fishermen or vacationers who wade or swim along sandy coastal areas. The thrust of the spine is sufficient to penetrate a leather boot and creates a substantial puncture wound. The integumentary sheath is torn, and venom is injected into the wound. The onset of pain is instantaneous, described as intensely burning or crushing, and spreads rapidly to involve the entire limb. The pain usually peaks at 30 minutes and subsides within 24 hours, but can last for days. Its intensity can induce irrational behavior and syncope; even narcotics are poorly effective. An account dating from 1782 informs that a fisherman amputated his own finger to alleviate the pain caused by a weeverfish sting.[17] If an upper extremity is envenomed, the pain may radiate into the thorax and mimic the symptoms of myocardial ischemia.[56] The puncture wound bleeds little and often appears pale and edematous initially. The sting of *E. vipera* may bleed freely. Over the course of 6 to 12 hours, the wound becomes erythematous, ecchymotic, and warm. The edema may increase for 7 to 10 days, causing the entire limb to become markedly swollen. Secondary bacterial infections are common, and gangrene has been reported. The indolent wound may require months to heal, depending on the nature of the sting and underlying health of the victim. Raynaud's phenomenon in an envenomed digit occurring a few weeks after a weeverfish sting has been reported.[19] This may develop in a delayed fashion and persist for months after envenomation.[78] Persistent edema has been noted to last for more than 1 year.

Systemic symptoms associated with weeverfish envenomation include headache, delirium, aphonia, fever, chills, dyspnea, diaphoresis, cyanosis, nausea, vomiting, seizures, syncope, hypotension, and cardiac arrhythmias. Death has been reported, perhaps attributable to direct intravascular injection of venom.[14]

TREATMENT

The wound should be immersed immediately in nonscalding hot water to tolerance (upper limit 45° C [113° F]) for 30 to 90 minutes or until there is significant pain relief. This may inactivate heat-labile components of the venom and perhaps helps reverse local vasospasm that might contribute to local sequestration of venom and inhibition of free bleeding. Addition of mineral salts, ammonia, vinegar, urine, or other substances to the water is of no proved value. Immersion in hot water is often a less successful therapy for a weeverfish sting than for that of a scorpionfish. When the heat inactivation method is inadequate to control pain,

FIGURE 75-54 Greater weeverfish *(Echiichthys draco),* Mediterranean Sea. *(Courtesy H. Göthel.)*

it is necessary to infiltrate the wound with a local anesthetic (1% to 2% lidocaine without epinephrine) or perform a regional nerve block. The liberal use of narcotics is often required. Prolonged immersion cryotherapy is contraindicated. However, a practice known as "thermic shock" has been touted by practitioners along the French Mediterranean coast. This consists of application of intense local temperature variation (heat for 2 to 10 minutes, followed by application for 10 to 30 minutes of an ice cube insulated within a tissue or thin cloth).

Rarely, a spine breaks off into the skin. The wound should be explored gently, all fragments of sheath should be removed, and the wound should be irrigated vigorously with warmed saline. Wide excision and debridement are unnecessary. Because of the nature of the puncture wound, tight suture or surgical tape closure should not be undertaken; rather, the wound should be allowed to heal open with provision for adequate drainage. If the puncture wound is high risk (i.e., deep or into the hand or foot), prophylactic antibiotic(s) should be administered. No commercial antivenom is currently available.

PREVENTION

Weeverfish hide in bottom sand and mud; thus, people must shuffle along with adequate footwear. These fish are easily provoked and should be avoided by scuba divers. They should never be handled alive and must be treated with extreme caution even when dead. Weeverfish survive for hours out of the water, and careless handling of a seemingly dead fish may result in an envenomation.

VENOMOUS (HORNED) SHARKS

LIFE AND HABITS

Horned sharks are species that possess dorsal fin spines. In the United States, the group is essentially limited to the spiny dogfish *(Squalus acanthias)* (Figure 75-55). These and similar animals are distributed throughout sub-Arctic, temperate, tropical, and sub-Antarctic seas. The Port Jackson shark *Heterodontus portusjacksoni* (Figure 75-56) is particularly dangerous.

The fish are sluggish and prefer cooler water and shallow protected bays. They are erratic in their migration and may be found singly or in schools. Voracious feeders, they eat other fish, coelenterates, mollusks, crustaceans, and worms.

The venom apparatus consists of a spine anterior to each of two dorsal fins and the associated venom glands.

CLINICAL ASPECTS

As with other vertebrate stings, there is immediate intense stabbing pain that may last for hours and is accompanied by erythema and edema. Although systemic side effects are rare, fatalities are possible.

TREATMENT

Treatment is the same as for stingray envenomation.

FIGURE 75-55 Spiny dogfish *(Squalus acanthias). (Copyright 2006 Norbert Wu:* norbertwu.com.*)*

FIGURE 75-56 Port Jackson shark. *(Courtesy Marty Snyderman.)*

SURGEONFISH

LIFE AND HABITS

The surgeonfish (doctorfish or tang) is a tropical reef fish of the family Acanthuridae that carries one or more retractable jackknife-like epidermal appendages ("blades") on either side of the tail (Figure 75-57). When the fish is threatened, the blade may be extended out at a forward angle, where it serves to inflict a laceration. There does not appear to be any associated envenomation.

CLINICAL ASPECTS

A victim cut by a surgeonfish notes a laceration or deep puncture wound that is immediately painful; it usually bleeds freely. The pain is moderate to severe and of a burning nature. Systemic reactions are infrequent and consist of nausea, local muscle aching, and apprehension.

TREATMENT

The wound should be irrigated and then soaked in nonscalding hot water to tolerance (upper limit 45°C [113°F]) for 30 to 90 minutes or until pain is relieved, although this may be of variable efficacy. It should be scrubbed vigorously to remove all foreign material and watched closely for development of a secondary infection. Unless absolutely necessary for hemostasis, sutures should not be used to close the wound.

FIGURE 75-57 Surgeonfish "blades." *(Courtesy Paul S. Auerbach, MD.)*

FIGURE 75-58 The poison-delivering spur (*arrow*) is found only on the male platypus's hind limbs. *Ornithorhynchus anatinus. (Used with permission via the GNU Free Documentation License; copyright 1995 E. Lonnon.)*

PLATYPUS

VENOM AND VENOM APPARATUS

The platypus *Ornithorhynchus anatinus* (Figure 75-58) is a furry venomous mammal that inhabits riverine systems of eastern Australia between northern Queensland and southern Tasmania.[34] These strange, fat animals have bills like a duck, webbed feet, a paddlelike tail, and claws on the feet. The male animal has an erectile keratinous spur on each hind limb linked via a distensible duct to a venom gland. There is a duct on each side that connects the spur to a venom gland situated under the thigh muscles. The venom appears to have components that mediate a type I hypersensitivity reaction with mast cell degranulation, which is consistent with the clinical presentation of soft tissue edema. Other venom fractions include a natriuretic peptide, proteases, and hyaluronidase. Venom-induced local edema in laboratory rats is attenuated by ketanserin and, to a lesser degree, by cimetidine, which may indicate a role of 5-hydroxytryptamine and histamine in the pathogenesis of the envenomation.

CLINICAL ASPECTS

Normally, the platypus is a shy creature; however, when provoked, it grasps its opponent with the hind legs and thrusts a spur or spurs into the victim, when 2 to 4 mL of venom may be released. When a human is envenomed, symptoms include immediate severe pain, tissue edema, and prolonged local sensitivity to painful stimuli. Movement, even remote (such as coughing), worsens the pain. The pain and hyperesthesia may generalize for several days before the pain recedes back to the envenomed limb. The pain may last for weeks, and in a severe case, muscle mass may be lost.

TREATMENT

Therapy is supportive and includes pain medication, wound care, and physical therapy after the acute episode. Hot water immersion does not appear to be of benefit acutely. Short-term corticosteroid therapy has been suggested to diminish pain and mitigate swelling, but there is no proof that antiinflammatory agents are definitively useful.

SEA SNAKES

LIFE AND HABITS

Sea snakes (Figures 75-59 to 75-62) of the family Hydrophiidae (subfamilies Hydrophiinae [genera *Hydrophis, Hydrelaps, Kerilia, Thalasophina, Enhydrina, Acalyptophis, Thalassophis, Kolpophis, Lapemis, Astrotia, Pelamis,* and *Microcephalophis*] and Laticaudinae [genera *Laticauda, Aipysurus,* and *Emydocephalus*]) are probably the most abundant reptiles on Earth. There are at least

FIGURE 75-59 Olive sea snake. *(Courtesy Michele Hall.)*

FIGURE 75-60 Sea snake. *(Copyright Lynn Funkhouser.)*

52 species, all venomous. Species implicated in serious envenomations or human fatalities include *Astrotia stokesii, Enhydrina schistosa, Hydrophis ornatus, Hydrophis cyanocinctus, Lapemis hardwickii, Pelamis platura,* and *Thalassophis viperina.*

The snakes are distributed in the tropical and warm temperate Pacific and Indian Oceans, with the highest number of

FIGURE 75-61 Sea snake. *(Copyright Lynn Funkhouser.)*

FIGURE 75-62 Olive sea snake in the Coral Sea. *(Copyright Carl Roessler.)*

envenomations occurring along the coast of Southeast Asia, in the Persian Gulf, and in the Malay Archipelago. No sea snakes live in the Atlantic Ocean or in the Caribbean Sea. Hawaii is the only U.S. state that has sea snakes (predominantly *P. platura*). The Pacific snakes usually inhabit sheltered coastal or coral reef waters and congregate about river mouths, and only on rare occasion do they venture into the open ocean. *P. platura,* the most widely distributed sea snake, is pelagic and may be found in the Pacific coastal waters of Central and South America. It does not migrate to the Caribbean, because of the freshwater barrier of Gatun Lake in the center of the Panama Canal.

Although sea snakes have the general appearance of land snakes, true sea snakes and sea kraits have valve-like nostril flaps and rudimentary ventral plates, without gills, limbs, ear openings, sternum, or urinary bladder. Most species of sea snakes are 0.9 to 1.2 m (3 to 4 feet) long, but some attain lengths of up to 2.7 m (9 feet). They are sinuous scaled creatures whose bodies are compressed posteriorly into a flat, paddle-shaped tail designed for marine locomotion (Figure 75-63). They swim in an undulating fashion and can move backward or forward in the water with equal speed. On land, however, they are awkward and do not survive readily. They may be brightly colored, such as the yellow-bellied sea snake, *P. platura*. With a single lung, the sea snake is capable of diving to 100 m (328 feet) and remaining submerged for 2 hours. The sea snake is an air breather and must surface periodically. The sea snake can be distinguished from a sea eel (Figure 75-64) by the presence of scales and absence of gills and fins.

Sea snakes use an air retention mechanism in the lungs to control buoyancy. Their food, small fish swallowed whole, is captured underwater, usually around bottom rocks and coral.

FIGURE 75-63 Sea snake in the Coral Sea. *(Courtesy Carl Roessler.)*

FIGURE 75-64 Harmless snake eel **(A)** mimics venous sea snake **(B)**, Sulawesi Island, Indonesia. *(***A** *copyright 2006 Norbert Wu:* norbertwu.com*;* **B** *copyright Lynn Funkhouser.)*

In general, sea snakes are docile creatures and flee when approached. However, when cornered or handled, they may become aggressive and strike out. During the reproductive season, some males adopt more irritable attitudes. The banded sea snake (sea krait) *Laticauda semifasciata* is served as a food (raw, smoked, or cooked) in certain Asian countries, notably Japan and the Philippines.

VENOM AND VENOM APPARATUS

The well-developed venom apparatus consists of two to four hollow maxillary fangs and a pair of associated venom glands. Fortunately, because the fangs are short and easily dislodged from their sockets, most bites (≈80%) do not result in significant systemic envenomation. Most fangs, except for those of *A. stokesii* and *Aipysurus laevis,* are not long enough to penetrate a wetsuit. The venom yield of sea snakes varies with species and is largely related to the size of the venom glands. An average-sized snake can produce 10 to 15 mg of venom, which is approximately 10 times the lethal dose in humans.

The protein venom is highly toxic and includes stable peripheral neurotoxins more potent than those of terrestrial snakes. Neuromuscular transmission is blocked predominantly at the postsynaptic membrane and caused by attachment of toxin to the alpha subunit of the acetylcholine receptor. Presynaptic toxin in sea snake venom has been less well studied but appears to be related to inhibition of transmitter release by blocking resynthesis of acetylcholine from choline. It seems probable that the action of *L. semifasciata* venom on excitable membranes is to alter ionic permeability, particularly that of sodium and chloride, without effect on Na^+,K^+-dependent adenosine triphosphatase activity. Calcium transport abnormalities are currently under investigation. Among other fractions of the venom are phospholipases, nerve growth factors, capillary permeability factor, anticomplement-active factor, enzymes (including acetylcholinesterase, hyaluronidase, leucine aminopeptidase, 5′-nucleotidase, phosphomonoesterase, and phosphodiesterase), and hemolytic and myotoxic compounds, which result in skeletal muscle necrosis, intravascular hemolysis, and renal tubular damage. Myonecrosis is related to phospholipase A, which may inhibit calcium

FIGURE 75-65 Beaked sea snake *(Enhydrina schistosa)*. A common sea snake of Southeast Asia, the average length is about 1 m (3 feet). This creature inflicts a high proportion of the sea snake bites recorded in Asian coastal waters. *(Courtesy Sherman Minton, MD.)*

uptake into the sarcoplasmic reticulum. Neurotoxins are believed to exert their toxicity by binding in a nondepolarizing fashion to the nicotinic acetylcholine receptor and blocking neuromuscular transmission.[83]

The venoms of sea snakes are similar, as reflected in positive reactions during immunodiffusion, immunoelectrophoresis, and cross-neutralization by antivenom against heterologous venoms, and amino acid composition and sequences of neurotoxins. This is a reflection of phylogenetic relationships and is a logistic aid in preparation of effective antivenom.

Although large venom yields have been obtained from *A. stokesii, E. schistosa* is considered the most dangerous sea snake (Figure 75-65). *E. schistosa* is the most widely distributed sea snake in the Arabian sea. *Aipysurus duboisii* and *Acalyptophis peronii* from the Coral Sea have recently be shown to carry venoms of high human lethality potential. In an evaluation of poisonous land and sea snakes representative of those encountered in Saudi Arabia, sea snakes were noted to have an average lethal dose in dogs of 0.05 mg/kg, in comparison with the average lethal dose of vipers (1.13 mg/kg) and elapids (0.69 mg/kg).[102] Deaths were attributed to respiratory paralysis and failure.

CLINICAL ASPECTS

Bites are usually the result of accidental handling of snakes snared in the nets of fishermen or of accidentally stepping on a snake while wading. Most sea snake poisonings occur in remote fishing villages and in boats engaged in fishing. Nearly all bites involve the extremities.

The diagnosis of sea snake bite is based on the following:

Location. A person usually must have been in the water or handling a fishing net containing a sea snake to have been bitten. Some snakes may foray briefly onto land, particularly in areas of heavy mangrove growth, but it is quite unusual for a bite to occur out of the water. Because snakes may inhabit sheltered coastal waters and frequently congregate near river mouths, a bite can occur in an estuarine setting, up to 5 km (3 miles) inland.

Absence of pain. Initially, a sea snake bite does not cause great pain and may resemble no more than a pinprick.

Fang marks. These are multiple pinhead-sized, hypodermic-like puncture wounds, usually 1 to 4, but potentially up to 20. If the skin is not broken, envenomation cannot occur. In some cases, particularly with a superficial injury through the arm or leg of a neoprene wetsuit, the fang marks may be difficult to visualize because of lack of a localized reaction.

Identification of the snake. If excellent digital photographs of the snake can be taken, these should be used for identification by an expert. If the decision is made to capture or kill the snake, this should be done very carefully. The snake may be killed with a nonmacerating blow behind the head.

Development of characteristic symptoms. These include painful muscle movement, lower extremity paralysis, arthralgias, trismus, blurred vision, dysphagia, drowsiness, vomiting, and ptosis. Neurotoxic symptoms are rapid in onset and usually appear within 2 to 3 hours. If symptoms do not develop within 6 to 8 hours, there has almost certainly not been a clinically significant envenomation.

Envenomation by a sea snake characteristically shows an evolution of symptoms over a period of hours, with the latent period being a function of venom volume and victim sensitivity. The onset of symptoms can be as rapid as 5 minutes or as long as 8 hours. There is no appreciable local reaction to a sea snake bite other than the initial pricking sensation. The first complaint may be euphoria, malaise, or anxiety. Over 30 to 60 minutes, classic muscle aching and stiffness (particularly of the bitten extremity and neck muscles) develop, along with a "thick tongue" and sialorrhea, indicative of speech and swallowing dysfunction. Within 3 to 6 hours, moderate to severe pain is noted with passive movements of the neck, trunk, and limbs. There may be a brief period of spastic muscular and neurologic reflex hyperreactivity. Ascending flaccid or spastic paralysis follows shortly, beginning in the lower extremities, and deep tendon reflexes diminish and may disappear. Nausea, vomiting, myoclonus, muscle spasm, ophthalmoplegia, ptosis, dilated and poorly reactive pupils, facial paralysis, trismus, and pulmonary aspiration of gastric contents are frequent complications. Occasionally, bilateral painless swelling of the parotid glands develops.

Severe envenomations are marked by progressively intense symptoms within the first 2 hours of symptoms. Victims become cool and cyanotic, begin to lose vision, and may lapse into coma. Failing vision is reported to be a preterminal symptom. If peripheral paralysis predominates, the victim may remain conscious if hypoxia is avoided. Leukocytosis may exceed 20,000 white blood cells per milliliter; elevated plasma creatine kinase is variable. Elevated glutamic oxaloacetic transaminase reflects hepatic injury. Pathognomonic myoglobinuria becomes evident about 3 to 6 hours after the bite and may be accompanied by albuminuria and hemoglobinuria. Cerebrospinal fluid is normal. Respiratory distress and bulbar paralysis, pulmonary aspiration–related hypoxia, electrolyte disturbances (predominantly hyperkalemia), and acute renal failure (attributed in part to myonecrosis and pigment load) all contribute to the ultimate demise, which can occur hours to days after the untreated bite. Preterminal hypertension may occur. The mortality rate is 25% in victims who do not receive antivenom and 3% overall.

It is interesting to note the effects of sea snake *(A. laevis)* venom on prey fish.[107] The prey are subdued in six stages, which correlate roughly to certain aspects of a human envenomation: stage 1, increased ventilatory rate; stage 2, loss of mouth control, fin control, coordination, and buoyancy; stage 3, depressed ventilation, weakness, and ineffective swimming; stage 4, apnea; stage 5, near paralysis and body color darkening; and stage 6, death.

TREATMENT

If possible, the offending snake should be identified (see above), taking care not to increase the number of victims. The therapy for bites by snakes of the family Hydrophiidae is similar to that for terrestrial snakes of the family Elapidae. The affected limb should be immobilized and maintained in a dependent position while the victim is kept as quiet as possible. The pressure-immobilization technique for venom sequestration (see Figure 35-30) should be applied. If the bite is on a digit where a compression bandage cannot be applied, a loose constriction bandage that constricts only the superficial venous and lymphatic flow may be applied proximal to the wound. This should be released for 90 seconds every 10 minutes and should be completely removed after 4 to 6 hours. If the bite is older than 30 minutes, neither technique may be very effective.

There is no clinical enthusiasm for incision and suction therapy, which has been universally relegated to therapeutic history.

The victim must be kept warm and as still as possible. As with terrestrial snakebite, cryotherapy (immersion into ice water) is inefficacious and potentially harmful.

With any evidence of envenomation, sea snake antivenom (an equine pepsin-digested immunoglobulin from CSL Limited) prepared against the venoms of *E. schistosa* and the Australian tiger snake *Notechis scutatus* should be administered intravenously after appropriate skin testing for equine serum hypersensitivity. If skin testing is omitted, anticipate and be prepared to treat an allergic reaction. Tiger snake *(N. scutatus)* antivenom was formerly recommended for use if sea snake antivenom is unavailable, but this is no longer recommended, because tiger snake antivenom does not appear to be efficacious against sea snake bites in humans.[105] However, it is still commented in product literature that one vial of CSL sea snake antivenom is equivalent to 2 to 4 vials of CSL tiger snake antivenom. Sea snake antivenom is specific and absolutely indicated in cases of envenomation. Supportive measures, although critical in management, are no substitute. Administration of antivenom should begin as soon as possible and is most effective if initiated within 8 hours of the bite. Each vial of sea snake antivenom contains 1000 units of antivenom in 15 to 35 mL of liquid. The minimum effective adult dosage is one vial (1000 units), which neutralizes 10 mg of *E. schistosa* venom. The victim may require 3000 to 10,000 units (3 to 10 vials), depending on the severity of the envenomation. The proper administration of antivenom is clearly described on the antivenom package insert. Antivenom should be protected from light and stored refrigerated at 2° to 8°C (35.6° to 46.4°F). It must not be frozen.

Commercial Thai cobra *(Naja kaouthia)* antivenom was found to be effective in neutralizing sea snake *(L. hardwickii)* venom in mice. The application of this finding to humans is as yet undetermined.[66]

Sea snake envenomation may induce severe physiologic derangements that require intensive medical management. Urine output and measured renal function should be closely monitored, because hemolysis and rhabdomyolysis release hemoglobin and myoglobin pigments into the circulation, which precipitates acute renal failure. If hemoglobinuria or myoglobinuria is detected, urine should be alkalinized with sodium bicarbonate and diuresis promoted with a loop diuretic (furosemide or bumetanide) or mannitol, to avoid progressive nephropathy. Acute renal failure may necessitate a period of peritoneal dialysis or hemodialysis. Hemodialysis offers an alternative therapy that may be successful if antivenom is not available.

Respiratory failure should be anticipated as paralysis overwhelms the victim. Endotracheal intubation and mechanical ventilation may be required until antivenom adequately neutralizes the venom effects. Serum electrolytes should be measured regularly to guide administration of fluids and electrolyte supplements. Hyperkalemia related to rhabdomyolysis and renal dysfunction must be promptly recognized and treated.

As previously mentioned, symptoms usually occur within 2 to 3 hours after envenomation. If there is no early evidence of envenomation, the victim should be observed for 8 hours before discharge from the hospital.

SUMMARY

A summary algorithmic approach to marine envenomation can be followed when the causative agent cannot be positively identified (see Figure 74-113).[6] Once the physician has made a commitment to a course of treatment based on a presumption of what creature has caused the injury, the subtleties of therapy can be deployed.

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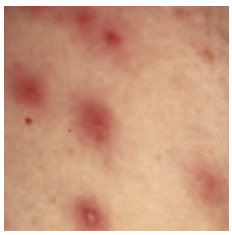

CHAPTER 76
Aquatic Skin Disorders

EDGAR MAEYENS JR AND SARAH A. WOLFE

Human interaction with marine and freshwater aquatic environments is becoming more frequent. People travel to remote and exotic areas to participate in aquatic activities. When in these areas, be they for vacation or adventure, contact with aquatic animals, plants, and microbes is responsible for allergic reactions, trauma, infections, and envenomations. The dermatologic manifestations of many of these disorders are presented in this chapter.

PHYTOPLANKTON DERMATOSES

This category of aquatic dermatoses includes diseases caused by algae, cyanobacteria, and dinoflagellates. Each of these organisms produces predictable disorders in aquatic life forms and humans. When phytoplanktons are "blooming," they are able to cause a variety of dermatoses. Terminology defining these disorders can be ambiguous and misleading. Current taxonomy and genetic techniques are redefining and clarifying the exact nature and origins of these organisms, thus allowing more accuracy, less ambiguity, and better comprehension of disease states produced by phytoplankton.

The following vignettes attempt to differentiate organisms. Absolute separation of species is not possible, because chimerism is prevalent and gene sharing occurs.

CYANOBACTERIA

Cyanobacteria are true gram-negative bacteria, although they are often erroneously referred to as "blue-green algae." Their habitats include almost every conceivable environment, from soil to freshwater lakes and oceans. Some are endosymbionts in plants, sponges, slime molds, and protozoans, for whom they provide energy. Cyanobacteria do not possess a nucleus (prokaryotic) or membrane-bound organelles. Most species are autotrophic.

Aquatic cyanobacteria can form "blooms" (massive reproduction in an area) in both marine and freshwater environments, giving the appearance of blue-green paint or scum on the water

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surface. If these blooms are created by toxin-producing cyanobacteria, they can be harmful to both animals and humans and thus become "harmful blooms." These toxins can be hepatotoxins, cytotoxins, neurotoxins, and endotoxins. Because of the ability to produce harmful blooms, cyanobacteria are confused with dinoflagellates, which also produce harmful blooms. Examples of cyanobacteria toxin–related diseases are paralytic shellfish poisoning, neurotoxic shellfish poisoning, diarrheic shellfish poisoning, amnestic shellfish poisoning, and ciguatera fish poisoning. Common to all blooms are lipopolysaccharides, which are a cause of skin irritation. Cyanobacteria toxins are not absorbed through the skin but only via ingestion or inhalation. All of these toxins are resistant to boiling.

DINOFLAGELLATES

Dinoflagellates are organisms common to all types of aquatic ecosystems. Approximately one-half of the species are photosynthetic[63]; the remainder are heterotrophic and feed by phagotrophy and osmotrophy. Dinoflagellates are prominent members of the zooplankton and phytoplankton marine and freshwater ecosystems. Of the 2000 living species, more than 1700 are found in oceans and 220 in freshwater.[171] These organisms are frequently and erroneously referred to as "algae," because most are eukaryotic and derive energy by photosynthesis. Dinoflagellates exist as biflagellate unicells, plasmodia (i.e., multinucleated organisms), and coccoid stages.

Dinoflagellates are at their greatest concentration in temperate coastal waters, where they bloom in middle to late summer when sunshine and vertical stability allow aggregations to develop.[171] In tropical waters and nutrient-poor temperate regions, all types of phytoplankton are generally scant. In polar waters, diatoms predominate over dinoflagellates.

About 75% to 80% of toxic phytoplankton species are dinoflagellates.[33] When dinoflagellates bloom, *red tides* are produced and frequently kill fish and/or shellfish, either directly via toxin production or by clogging fish gills, depleting oxygen, or other means.[165] Colors of red tides vary from red to red-brown to brown. Anthropogenic and natural factors contribute to their development. Dinoflagellate toxins are some of the most potent biotoxins known. Accumulation in fish or shellfish produces diseases in humans like neurotoxic shellfish poisoning, paralytic shellfish poisoning, diarrheic shellfish poisoning, and ciguatera fish poisoning. Blooms, when aerosolized, produce cutaneous disorders in humans, such as dermatitis and urticaria (Figure 76-1).

ALGAE

The derivation of the term *alga* is from the Latin word for "seaweed." Algae are a very large and diverse group of autotrophic, unicellular (microscopic), or multicellular (macroscopic) organisms. They are eukaryotic and therefore possess a nucleus enclosed within a membrane and membrane-bound chloroplasts (photosynthetic machinery derived from cyanobacteria).[4] Phylogenetically, chloroplasts are membrane-bound organelles containing DNA similar to that of cyanobacteria. It is presumed that chloroplasts represent reduced cyanobacteria endosymbionts.[4] Traditional terminology has used the terms *algae* and *cyanobacteria* synonymously and is currently regarded as outdated.[4]

The exact number of algae species is estimated to be 1 to 10 million and most are microalgae.[14] They are found in all waters (both fresh and marine), the atmosphere, and soil. Microscopic forms suspended in the water column are designated phytoplankton. When conditions are present that facilitate proliferation, overgrowth occurs, resulting in "algal blooms." Waters containing algal blooms become discolored, asphyxiate or poison surrounding aquatic life forms, and threaten the health of humans. Algae have been compared with plants but differ in many ways. For instance, algae are devoid of certain structures found in land plants, such as roots, leaves, stems, and vascular tissues.[13] Plants and algae are photosynthetic. Algal photosynthetic pathways vary among different groups, some deriving energy from photosynthesis and uptake of organic carbon and others utilizing photoautotrophism.

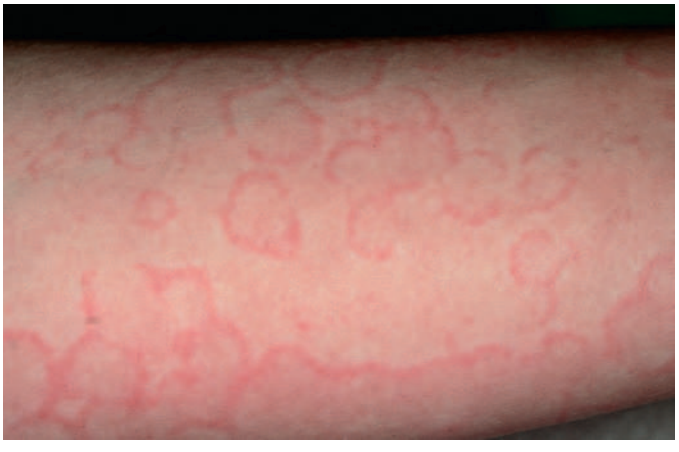

FIGURE 76-1 Red tide dermatitis. Petaloid pattern of urticaria following swimming in red tide–contaminated water. *(Courtesy Edgar Maeyens, Jr., MD.)*

TABLE 76-1 Potency Ranking of Topical Steroids*

Potency	Generic	Sizes
High potency (not for use on face, groin, or axillae)	Clobetasol propionate 0.05% cream/ointment	15, 30, 45, 60 g
	Fluocinonide 0.05% cream/ointment	15, 30, 60 g
Medium potency (not for use on face, groin, or axillae)	Triamcinolone 0.1% cream/ointment	15, 80, 454 g
	Betamethasone valerate 0.1% cream/ointment	15, 45 g
Low potency (safe for face, groin, or axillae)	Hydrocortisone 2.5% cream/ointment	30 g
	Desonide 0.05% cream/ointment	15, 60 g

*These topical steroids must be applied once or twice daily. Larger volumes or multiple tubes may be needed for greater surface area involvement.

Sargassum algae Dermatitis

Definition. *Sargassum* is a brown macroalgae distributed throughout tropical and temperate oceans. The name is derived from the Sargasso Sea, which is home to several species of *Sargassum*. Their habitat is coral reefs and shallow water. Although these species are normally benthic, they can exist in planktonic and pelagic forms.

Physiology. Certain species of these algae grow to lengths of several meters. They are brown or deep green in color. To keep afloat, the algae possess air vesicles or bulb-like gas-filled bladders. When detached from their moorings, *Sargassum* become beach drift. *Sargassum* in quantity usually appear as a large, tangled mass. Many fishes use these algae as habitat.

Clinical Presentation. Contact with skin can result in an exuberant erythematous, urticarial-like dermatitis (Figure 76-2).[28]

Treatment. Symptomatic treatment with oral antihistamines and topical corticosteroids is usually adequate (Tables 76-1 and 76-2).

Prevention. Avoid contact with these algae, not only when they are part of beach drift, but also when they are floating mats.

Lyngbya Dermatitis

Lyngbya majuscula is an alga that produces tissue-damaging toxins. Direct contact with *Lyngbya* can result in serious skin reactions and tissue necrosis.

Definition. *L. majuscula* (also known as *Microcoleus lyngbyaceus*) is finely filamentous and dark green or olive in color. It grows in hairlike masses in clumps at depths of up to 30 m

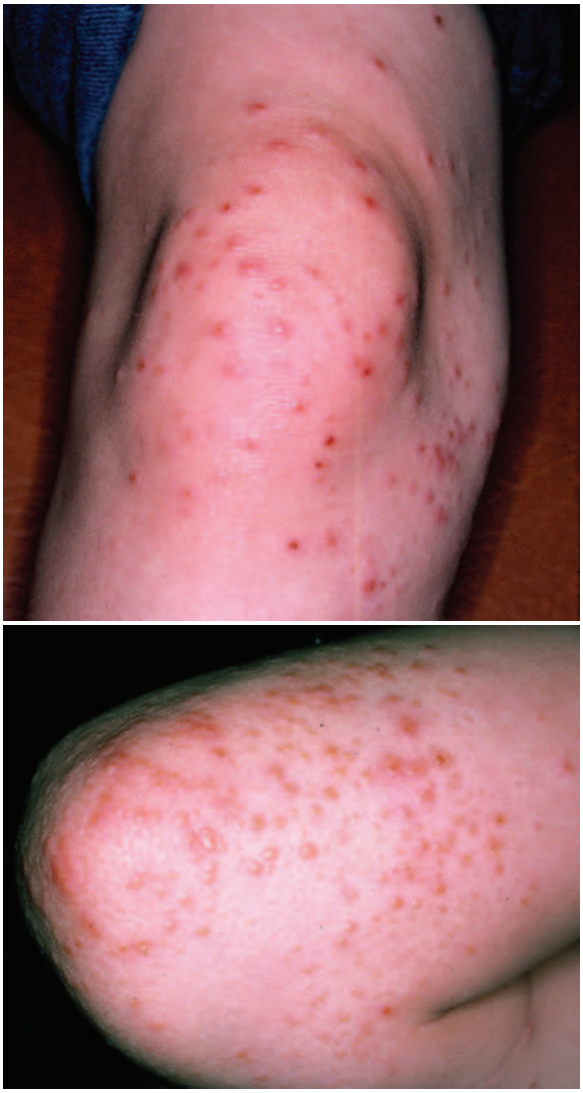

FIGURE 76-2 An urticaria-like papular eczematous dermatitis from contact with *Sargassum algae.*

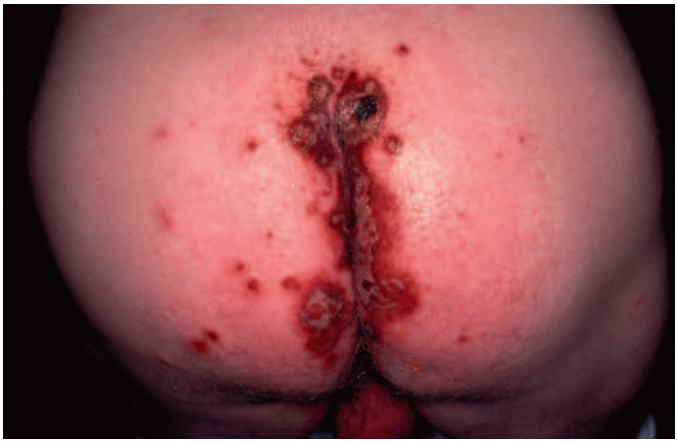

FIGURE 76-3 Rare and extreme example of superficial necrosis and inflammation secondary to dermonecrotic toxins of *Microcoleus lyngbyaceus. (Courtesy Edgar Maeyens, Jr., MD.)*

(100 feet) and is often found entangled with other algae in tide pools and reef flats.[162]

Epidemiology and Risk Factors. *Lyngbya* is found throughout the Pacific and Indian Oceans and the Caribbean Sea. Strong currents and winds dislodge the alga from its normal habitat, fragment it, and carry it to the surf line. Dermatitis occurs only when the alga or its fragmented components are trapped beneath swimwear. On exiting the water, algae fragments are either washed off or dry out, rendering them harmless.

Pathophysiology. *L. majuscula* produces the dermatonecrotic toxins lyngbyatoxin A and debromoaplysiatoxin. Toxicity varies depending on season, type, and location of the algae.[153] Not every strain of *Lyngbya* is toxic. It is the potency and/or concentration of these toxins against the skin that determines the degree of cutaneous damage.

Clinical Presentation. Within minutes to hours of contact, pruritus, burning sensations, and erythematous dermatitis develop in a swimsuit-patterned distribution. This is followed by varying degrees of blister formation, which ultimately may progress to epidermal and dermal necrosis (Figures 76-3 and 76-4). Additional symptoms can include periorbital edema, irritation of nasal mucosa, conjunctivitis, headache, and fatigue.[81] Symptoms last a few hours to days. Skin necrosis takes weeks to resolve. Anatomic locations typically are the genital, perineal, and perianal regions.

Differential Diagnosis. Differentiating *Lyngbya* dermatitis from "seabather's eruption" and "swimmer's itch" can be difficult when there is limited contact with the algae.

Treatment. Treatment consists of prompt cleansing with copious amounts of soapy water to remove residual algal fragments. This is followed with two to three sequential isopropyl alcohol rinses and then application of a topical corticosteroid ointment (Table 76-1). Severe dermatitis may require oral corticosteroids. If necrosis is present, any of a variety of agents and techniques may be used to facilitate wound healing and prevent

TABLE 76-2 Topical Antipruritics and Oral Antihistamines

Product (Brand Name)	Chemical Name	Adult Doses [Children <12 Years Doses]
Topical Antipruritics		
Camphor/menthol (Sarna)	Camphor 0.5%/menthol 0.5%	Apply up to 4 times a day
Pramoxine (Sarna Sensitive, Gold Bond Anti-Itch)	Pramoxine HCl 1%	Apply up to 4 times a day
Neutrogena Norwegian Formula Soothing Relief Anti-Itch Moisturizer	Camphor 0.1%/lidocaine HCl 2%	Apply up to 4 times a day
Pramosone cream, ointment, lotion	Hydrocortisone acetate 1% or 2.5% with pramoxine HCl 1%	Apply up to 4 times a day
Aveeno Oatmeal Bath	Colloidal oatmeal	Daily as needed
Oral Antihistamines		
Allegra	Fexofenadine	180 mg daily [30 mg twice a day; minimum age 2 years]
Claritin	Loratidine	10 mg daily [2.5-10 mg daily; minimum age 6 months]
Zyrtec	Cetirizine	10 mg daily [2.5-10 mg daily; minimum age 6 months]
Benadryl	Diphenhydramine	25-50 mg every 6 hours [12.5-25 mg every 6 hours; minimum age 2 years]

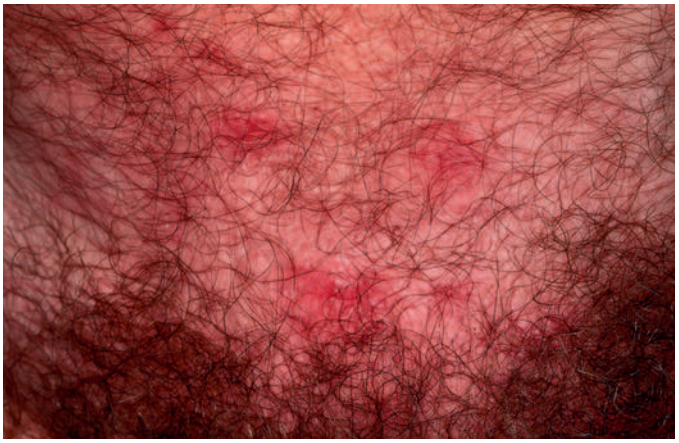

FIGURE 76-4 Folliculitis in the bathing trunk area caused by *Microcoleus lyngbyaceus. (Courtesy Edgar Maeyens, Jr., MD.)*

infection. Choices are predicated upon the severity of the process and the care provider's preferences. Methods range from sterile saline cleanses followed by white petroleum jelly to Hydrofera Blue bacteriostatic wound dressings (Hydrofera LLC, Willimantic, Connecticut). Difficulty with breathing may indicate a systemic allergic response causing bronchospasm or early signs of anaphylaxis, requiring epinephrine and antihistamines.

Sequelae. If the condition is diagnosed and treated promptly, no adverse sequelae occur. If diagnosis and therapy are delayed, skin necrosis will occur, resulting in possible secondary infection with severe scarring.

Prevention. Remove swimsuits and shower with soap on exiting the water. Avoid waters where algae densities are high or algae blooms exist. Swimsuits and swim gear must be machine washed to remove any residual algae fragments.

Ciguatera Dermatitis

Definition. Ciguatera fish poisoning is the name given to a food-borne illness caused by consumption of fish contaminated with ciguatoxins (see Chapter 77). Dermatoses can occasionally be a feature of the illness. Ciguatera dermatitis is not diagnostic of ciguatera fish poisoning, because it is nonspecific and manifests with a wide range of clinical presentations.

Epidemiology and Risk Factors. Ciguatoxin accumulates in predator fish, such as grouper, snappers, amberjacks, and barracudas. Ciguatoxin is produced by dinoflagellates, such as *Gambierdiscus toxicus.*[188] The toxin is heat resistant, so it cannot be destroyed by cooking. Ciguatoxin-producing dinoflagellates are localized to tropical waters of the Caribbean and Pacific. Ciguatoxin is found in hundreds of species of reef fish.

Pathophysiology. The precise pathophysiology of ciguatoxin dermatitis is unknown.

Clinical Presentation. Dermatologic manifestations of ciguatera fish poisoning include intense generalized pruritus associated with a diffuse, maculopapular eruption that can progress to bullae or desquamation (Figure 76-5). Other manifestations that have been reported include hair and nail loss, intense diaphoresis leading to dehydration, cyanosis, and urticaria.

Diagnostic Tests. No routine test exists to diagnose ciguatera dermatitis.

Treatment. There is neither a specific therapy nor an antidote for ciguatera fish poisoning. Treatment of cutaneous manifestations, as well as systemic ciguatera fish poisoning, is symptomatic and supportive.

Sequelae. No long-term cutaneous adverse effects have been reported.

Prevention. Avoid ingestion of fish likely to be ciguatoxic.

Prototheca Dermatitis

Prototheca spp. are unicellular algae lacking chlorophyll. *Prototheca* spp. are often preliminarily misidentified as fungi in tissue and cultures. They are infrequent causes of cutaneous and systemic infections.

Definition. The genus *Prototheca* consists of nonpigmented algae from the family Chlorellaceae. Human and animal infections have been caused by an achlorophyllic mutant of the green algae *Chlorella pyrenoidosa*. Three species of *Prototheca* are recognized: *Prototheca stagnora, P. wickerhamii,* and *P. zopfii*. *P. wickerhamii* and *P. zopfii* are the pathogens most commonly implicated in human protothecosis.[24,53,95,181]

Epidemiology and Risk Factors. *Prototheca* spp. occur globally on every continent except Antarctica.[101] *Prototheca* have been isolated from fresh and marine water, streams, lakes, sewage treatment systems, tree slime, and soil. Infections usually occur after inoculation into skin following exposure to contaminated water or soil. The incubation period for the onset of symptoms is not well known.[190] Periods of weeks to months have been reported.[38,173] Most people do not recall the moment of trauma and thus the duration of incubation. Preexisting skin wounds facilitate entry of *Prototheca*. Person-to-person transmission has not been reported. The organism is of low virulence. Immunosuppressed persons or persons taking immunosuppressive medications are at increased risk of acquiring protothecosis.[91,101,181] The infection is usually localized in healthy individuals, but can disseminate in the immunocompromised.

Pathophysiology. *Prototheca* species are unicellular, aerobic, and spherical organisms without chlorophyll that have hyalin sporangia that reproduce asexually. They are unable to produce energy from photosynthesis and therefore exist as saprophytes.[24] *Prototheca* species are distinct from fungi and bacteria in size, morphology, and method of reproduction.

Histologically, organisms can be found within giant cells or lying freely in the dermis. *Prototheca* cells are round; each cell, or sporangium, contains two to eight tightly packed endospores (Figure 76-6). Sporangia are described as being frambesiform (raspberry-like). The organism stains well with Grocott-Gomori methenamine silver nitrate, colloidal iron, and periodic acid–Schiff.[18,70]

Clinical Presentation. Clinical features of human protothecosis include:

1. Superficial Cutaneous Lesions. These manifest as papulonodules or verrucous plaques with or without ulcerations[47] (Figure 76-7). Bullous lesions may occur, with subsequent rupture, drainage, and crusting.[18,70] Rarely, eczematous and cellulitis-like lesions occur.

2. Olecranon Bursitis. The elbow is swollen and erythematous and, on occasion, drains spontaneously. This is not accompanied by fever or chills. The presentation is similar to other causes of bursal inflammation. A history of preceding trauma should suggest protothecosis.[18,47,70]

3. Systemic Infection. Immunosuppressed patients, such as those undergoing chemotherapy or infected with human immunodeficiency virus (HIV), are more predisposed to disseminated infection than are immunocompetent persons. At least

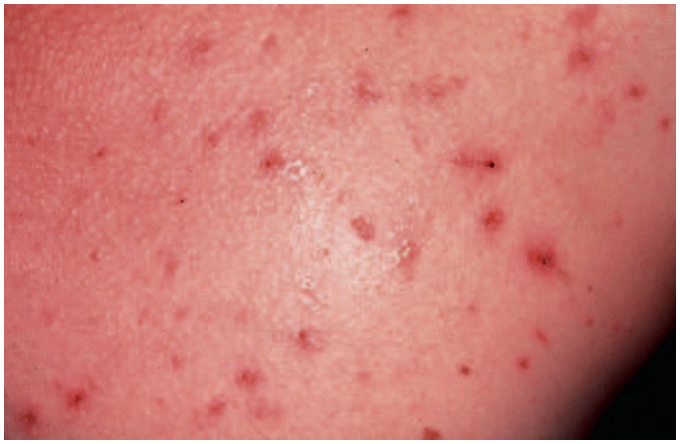

FIGURE 76-5 Ciguatera dermatitis. Thirty-year-old man's posterior hemithorax showing papules and rare blisters as a cutaneous manifestation of his ciguatera intoxication. *(Courtesy Edgar Maeyens, Jr., MD.)*

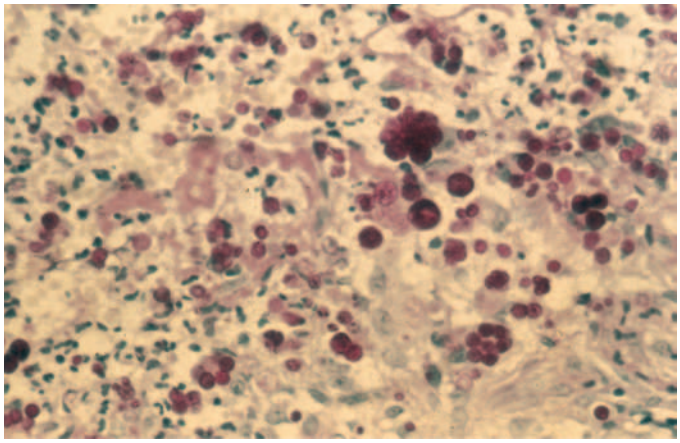

FIGURE 76-6 Protothecosis histology. *(Courtesy Edgar Maeyens, Jr., MD.)*

50% of reported individuals with cutaneous protothecosis are immunosuppressed.[31,136]

Mucosal Protothecosis. Lacoviello and colleagues reported a case of protothecosis of the esophagus complicating prolonged endotracheal intubation.[100]

In cases associated with a traumatic episode, the initial lesion is a tender, red papule or an asymptomatic nodule that enlarges, becomes pustular, and ulcerates. Purulent, malodorous, and blood-tinged discharge may be present. Satellite lesions surrounding the primary lesion develop and frequently become confluent. Lesions can become verrucous and resemble chromomycosis. Regional lymph nodes may develop metastatic granulomas. Lesions extend centrifugally and occasionally disseminate. In the olecranon bursitis form, infection develops several weeks after an elbow injury and is localized to the bursa. Overlying sinus tracts may develop.[129]

Differential Diagnosis. The differential diagnosis includes the following diseases: atypical *Mycobacterium* infection, chromoblastomycosis, pyoderma gangrenosum, deep fungal infection, blastomycosis-like pyoderma, and Majocchi's granuloma.

Diagnostic Tests. Diagnosis of protothecosis can be made either by tissue biopsy or tissue culture. If uncertainty exists as to the exact nature of the organism, electron microscopy reveals a double-layered cell wall and no chloroplasts. These are features differentiating *Prototheca* from other algae.

Treatment. There is no defined pharmacologic protocol for eradication of *Prototheca*. Protothecosis shows no tendency to self-heal. It is a chronic and progressive disease.[85] Cutaneous lesions are cured with surgical excision. Amphotericin B has been used successfully.[31] Prolonged treatments with the algaecidal agents ketoconazole, itraconazole, fluconazole, and voriconazole[60] have been reported effective.[92,118,170]

Human Pythiosis Dermatitis

The aquatic fungus-like organism *Pythium insidiosum* is a zoosporic plant pathogen and newly emerging human pathogen. It is phylogenetically more closely related to algae than to true fungi.[62] *P. insidiosum* is a long-recognized plant pathogen causing seed decay and root rot of seedlings.[58] The disease in humans and animals is called *pythiosis*.

Definition. Pythiosis is a cutaneous/subcutaneous disease of humans and animals. Although primarily a cutaneous and intestinal disease of animals (horses, cats, dogs, and cattle), it is now an emerging human pathogen that presents as a localized or systemic/vascular form.[58]

Epidemiology and Risk Factors. The organism is found in tropical, subtropical, and temperate areas of the world. Preferential ecologic niches are swampy environments, where the organism produces mobile biflagellate zoospores that are attracted chemotactically to traumatized human and animal tissues.[86] The disease has been identified in the United States, Australia, Asia, South and Central America, and New Zealand. Individuals with hemoglobinopathies are especially susceptible to developing systemic disease.[182]

Pathophysiology. The chemoattractants keratin and collagen from wounded skin attract *P. insidiosum* sporangia, which release biflagellated, mobile zoospores. Zoospores are attracted to hair and lacerated skin, where they encyst on contact. At the time of encystment in tissue, the flagellae detach and the zoospores become globose, forming germ tubes in 24 hours. Once attached, encysted zoospores secrete an amorphous material that acts as an adhesive substance.[122] *Pythium* species produce pectic and cellulolytic enzymes, macerating enzymes, and phytotic fungal products.[58] The role of these enzymes in production of the granulomatous response seen in human tissue is unknown.

Clinical Presentation. Cutaneous pythiosis typically begins as a pustule at the site of inoculation. The inflammatory response to the organism mimics cellulitis and eventuates in suppurative necrosis. Prototypically, the lower extremities are most frequently involved, but any cutaneous surface is vulnerable (Figures 76-8 and 76-9). Pythiosis can also progress to a systemic disease involving the vascular system, where it causes arterial occlusion.[21]

Differential Diagnosis. Although not a true fungus, *P. insidiosum* has some morphologic characteristics in common with the order Zygomycetes. These similarities are best appreciated histologically by their resemblance to the Zygomycetes *Aspergillus* and *Mucor*. Zygomycetes fungi are ubiquitous in nature, found in soil and decaying vegetation.

Hyphae of *P. insidiosum* species are broad, branched at right angles, usually nonseptate, and irregularly shaped. They are

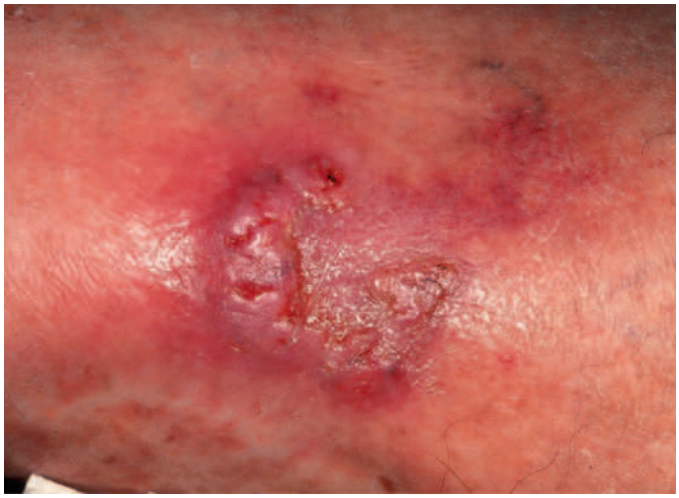

FIGURE 76-7 Protothecosis of anterior leg. *(Courtesy Edgar Maeyens, Jr., MD.)*

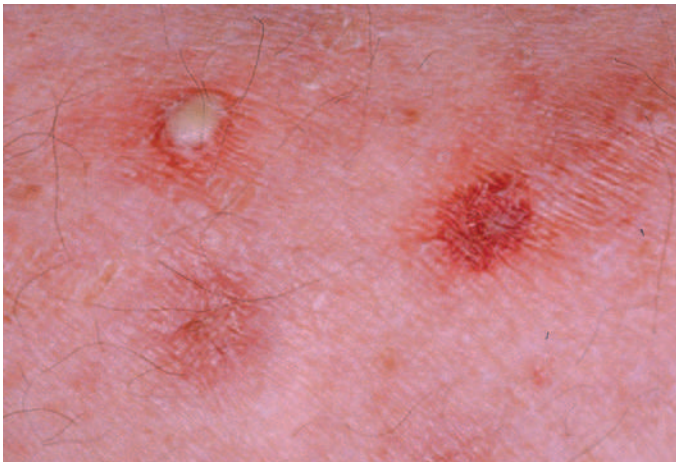

FIGURE 76-8 Human pythiosis. A pustule at the site of inoculation of *Pythium insidiosum*.

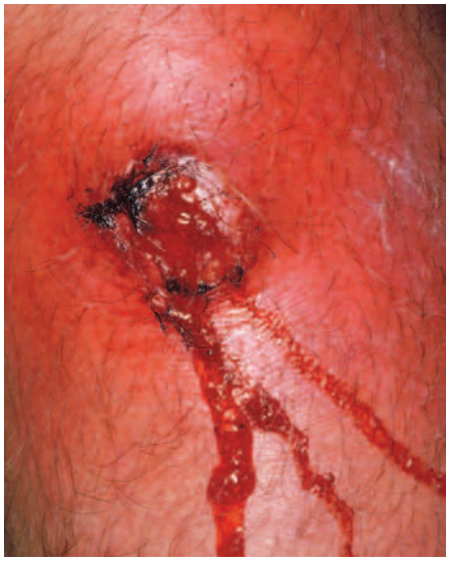

FIGURE 76-9 Human pythiosis. Suppurative necrotizing cellulitis of *Pythium insidiosum* infection.

described as ribbon-like (Figure 76-10).[7] Fungi of the class Zygomycetes (e.g., *Mucor, Rhizopus,* and *Absidia*) are etiologic agents of a variety of infections in humans. Diseases caused by this group of fungi were formerly termed mucormycoses but are now called zygomycoses.

The spectrum of zygomycoses includes cutaneous, gastrointestinal, renal, central nervous system, pulmonary, and rhinocerebral infections.[7] Cutaneous zygomycosis has been associated with burns, traumatic wounds, surgical wound infections, contaminated dressings, and intramuscular injections.[7] Cutaneous zygomycosis begins with erythema and induration, gradually evolving into a necrotic ulcer virtually identical to pythiosis. It is believed that many cases of pythiosis have been misdiagnosed as therapeutically nonresponsive zygomycosis.

Diagnostic Tests. It is possible to culture pus, lesion exudate, or biopsy material on Sabouraud glucose or brain heart infusion agar. In 24 to 48 hours at 28° to 37°C (82.4° to 98.6°F), there appears a flat or submerged, colorless or white growth with short or no apparent aerial hyphae.[86] Cotton blue dye–assisted microscopic examination shows broad, nonseptate, and/or sparsely septate hyaline hyphae.

Histopathologic examination of lesional tissue reveals broad, branched, and nonseptate or sparsely septate hyphae. The organism is best visualized with Gomori methenamine silver (GMS) or periodic acid–Schiff (PAS) stains. Microscopically, *P. insidiosum* resembles the hyphae of Zygomycetes (Figure 76-11).[86]

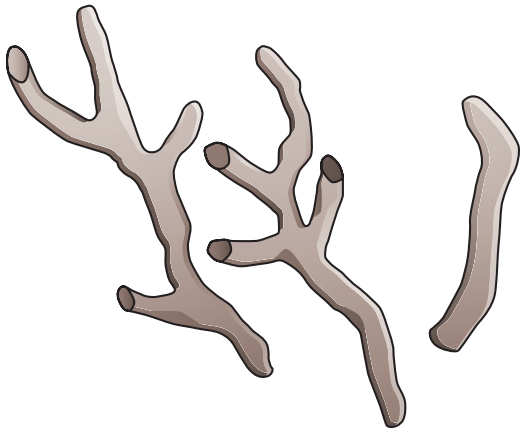

FIGURE 76-10 *Pythium insidiosum.* Illustrations of *Pythium insidiosum* with right-angled branching, broad, nonseptate hyphae. These are microscopically similar to the Zygomycetes. *(Courtesy Jan Mucklestone.)*

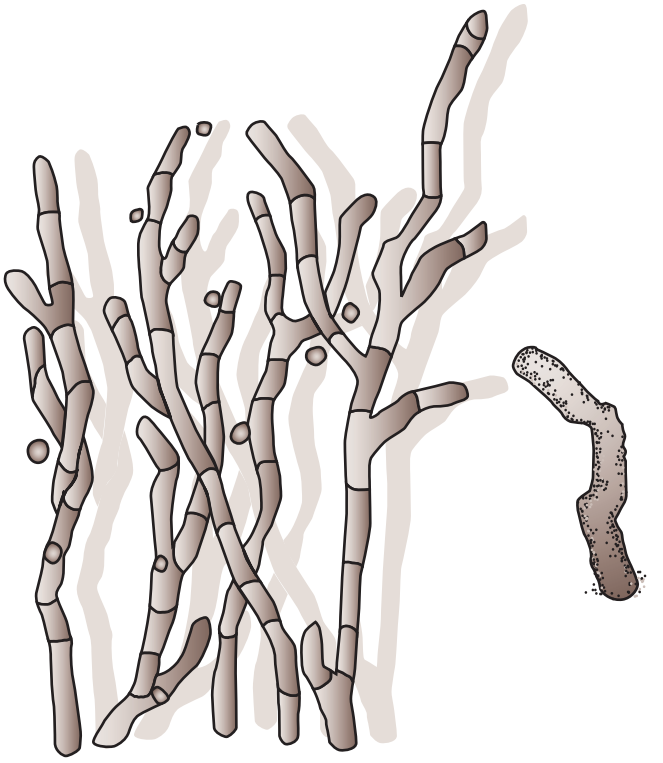

FIGURE 76-11 *Pythium insidiosum.* Illustration of *Aspergillus niger* showing its septated branching hyphae contrasted with the nonseptated hyphal elements of *Pythium insidiosum. (Courtesy Jan Mucklestone.)*

Fluorescein-labeled *P. insidiosum* antiglobulin and immunoperoxide procedures are specific for the organism in tissues.

Serologic tests, such as enzyme-linked immunosorbent assay (ELISA) or immunodiffusion, are also diagnostic.[20] In the absence of a positive culture, polymerase chain reaction and a species-specific DNA probe from ribosomal DNA complex have proven useful in identifying *P. insidiosum.*

Treatment. Little information exists on the efficacy of therapy. Whether a single agent or combination of antimycotic agents can be curative has not been clearly established. Medical treatment alone for vascular and systemic involvement is ineffective.[89] Most patients require both extensive surgical treatment and medical treatment. Treatment results with conventional antimycotic medications, such as amphotericin B, have been contradictory. *Pythium sp.* do not possess ergosterol in their cytoplasmic membranes, so do not respond to medications directed against ergosterol. In vitro studies have recently identified minocycline and tigecycline as potentially effective therapies.[108,113] There are isolated case reports of successful treatment with itraconazole and terbinafine for 1 year.[158] Immunotherapy with *P. insidiosum*–antigen injection has been effective for complete or partial remission[182] following uncleared systemic infection treated with surgery or antimycotics.

Prevention. Given that pythiosis occurs in animals and humans that frequent aquatic habitats harboring *P. insidiosum,* awareness of the potential for infection should prompt avoidance of aquatic environs such as ponds, marshes, and bodies of water rich in plants or decaying organic material. Cleansing of lacerations or abrasions acquired in such environments should be prompt and thorough. If a cutaneous wound exists prior to entry into a body of water, protective covering is recommended.

BACTERIAL INFECTIONS

AEROMONAS HYDROPHILA INFECTIONS

The Aeromonads are inhabitants of brackish and freshwater. Currently, the four main species of *Aeromonas* are *A. hydrophila,*

A. caviae, A. salmonicida, and A. sobria. The spectrum of disease ranges from soft tissue infection to sepsis, and increasingly, diarrheal disease.

Definition

Aeromonas organisms are gram-negative, nonsporulating, facultative anaerobic bacilli. Formerly of the family Vibrionaceae, they have been reclassified as members of their own family, Aeromonadaceae. *A. hydrophila* have polar flagella.

Epidemiology and Risk Factors

These Aeromonads have a ubiquitous presence and can be found in a wide variety of aquatic environs, including brackish, fresh, bottled, chlorinated, well, and polluted waters. Entrance into soft tissue is gained through open wounds. Immunocompromised people more commonly develop serious complications, such as septicemia, meningitis, gastroenteritis, and pneumonia.[3]

Pathophysiology

A. hydrophila is the cause of most *Aeromonas* soft tissue infections. Pathogenicity results from production of the virulence factors cytotoxic enterotoxin (Act), heat-stable cytotoxic enterotoxin (Ast), and heat-labile cytotoxic enterotoxin (Alt). Hemolysins, aerolysins, and serine proteases are also present.[46]

Clinical Presentation

Cellulitis develops within 8 to 48 hours and may progress to focal, superficial, and cutaneous necrosis with purulent discharge (Figure 76-12), ecthyma gangrenosum–like cutaneous necrosis, fasciitis, myonecrosis, and osteomyelitis. On occasion, infections may be associated with gas production. Ecthyma gangrenosum and myonecrosis are uncommon and tend to occur in immunocompromised individuals.

Differential Diagnosis

A. hydrophila cutaneous infections must be differentiated from streptococcal or *Pseudomonas aeruginosa* cellulitis, abscesses, and septicemia with ecthyma gangrenosum. *Vibrio* and *Serratia* species mimic both environmental exposures and cutaneous manifestations of *Aeromonas* infections. Presented with an individual who has cellulitis secondary to a water-related injury, one must consider *Aeromonas* and *Vibrio* species infections. In the rare gas-producing infections, evaluate for other gas-producing organisms, such as *Clostridium* species.

Diagnostic Tests

Culture exudates and purulent material from wounds. Surgical samples of myonecrotic tissue should be cultured. Differentiation of *Aeromonas* from other gram-negative rods can be readily facilitated by culturing on blood agar containing ampicillin 10 or 30 μg/mL in a selective growth media or in cefsulodin-Irgasan-novobiocin agar.[82]

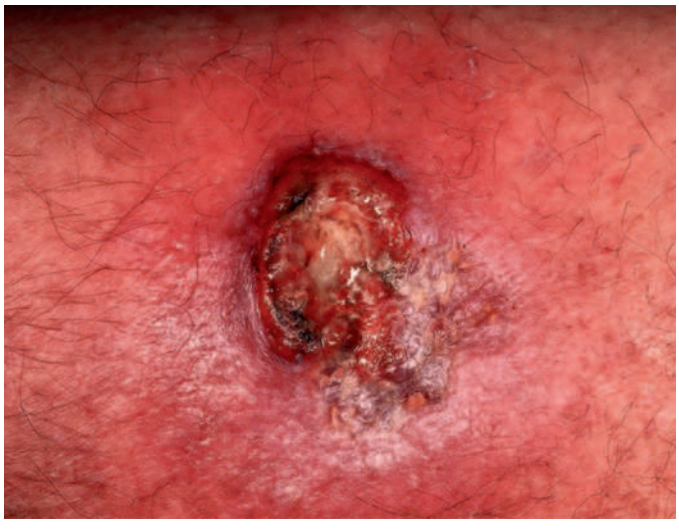

FIGURE 76-12 Trauma-induced necrotic ulcer of the anterior leg of a fisherman caused by *Aeromonas hydrophila*. *(Courtesy Edgar Maeyens, Jr., MD.)*

Treatment

Wounds should be drained and debrided as needed. *Aeromonas* species are all usually sensitive to third-generation cephalosporins, carbapenems, and aztreonam. Fluoroquinolones are highly active against *Aeromonas*.[179] Pertinent disease-producing *Aeromonas* species are resistant to early-generation penicillins and cephalosporins, such as amoxicillin-clavulanate and cephalexin, but are typically sensitive to piperacillin-tazobactam.[5] Resistance to trimethoprim-sulfamethoxazole, aminoglycosides, and tetracycline are increasingly being reported.[96]

Prevention

Do not enter any body of water with an open wound or abrasion. If skin trauma occurs while in fresh or brackish water, perform meticulous wound cleansing upon exiting. A prophylactic course of fluoroquinolones should be considered if there appear early signs of infection, such as erythema, purulence, or increasing pain.

CHROMOBACTERIUM VIOLACEUM INFECTIONS

The bacterium *Chromobacterium violaceum* rarely causes human disease, but can result in life-threatening sepsis with multiple metastatic abscesses. *C. violaceum* septicemia is clinically similar to melioidosis, the causative agent of which is *Burkholderia pseudomallei*.[80] Microscopically, *C. violaceum* can be confused with vibrios.

Definition

C. violaceum is found in water and soil. It is capable of producing skin abscesses, sepsis, and metastatic abscesses, and carries a mortality rate of greater than 50%. The mortality rate increases up to 75% to 80% for persons with septicemia or sepsis.[111,156,164]

Epidemiology and Risk Factors

C. violaceum is found in water and soil. It is abundantly present in the tropics and subtropics. More than three dozen cases have been reported in the United States, almost all from the southeast, primarily Florida.[137,164] Infections occur primarily in the summer months. Cases have been reported from Africa, India, South America, and Australia.[55,116] *C. violaceum* infects humans through exposure of nonintact skin to contaminated water and soil or after ingesting contaminated food or water.

Physiology

C. violaceum is a facultative, anaerobic, elongated, gram-negative bacillus that is slightly curved and therefore resembles the vibrios. It produces purple pigment (violacein), from which it derives its name. Violacein protects the microorganism's cell membrane from oxidation and peroxidation.[125] *C. violaceum* adapts well to either aerobic or anaerobic conditions because it has an efficient and flexible energy-generating metabolism. *C. violaceum* is also a reporter strain in quorum sensing.[110]

Clinical Presentation

The initial symptom is inflammation of soft tissue with or without adenopathy. Clinically, this manifests as cellulitis. As the infection progresses, there is focal abscess formation. Untreated, cellulitis rapidly progresses to sepsis and metastatic abscesses (Figures 76-13 and 76-14). The entire infectious process can occur suddenly, leading to a life-threatening situation. It is not unusual for *C. violaceum* infection to present as sepsis with fever, pneumonia, and spleen, liver, and lung abscesses.[116]

Differential Diagnosis

The initial stages of infection may resemble staphylococcal or streptococcal cellulitis. Cutaneous ulcerations are similar to those found in the diseases of leishmaniasis, melioidosis, and ulceroglandular tularemia and superficial infections caused by

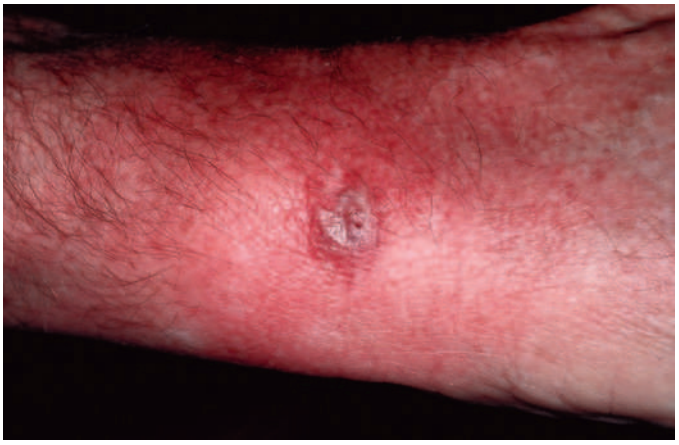

FIGURE 76-13 A minor abrasion while snorkeling led to this forearm infection with *Chromobacterium violaceum*. *(Courtesy Edgar Maeyens, Jr., MD.)*

Aeromonas and *Pseudomonas*. Systemic infection with *C. violaceum* must be differentiated from melioidosis.

Treatment

Although the optimal antibiotic therapy is not known, *C. violaceum* is typically susceptible to fluoroquinolones, tetracycline, imipenem, and trimethoprim-sulfamethoxazole.[102,157,195] It is resistant to penicillin and first-generation cephalosporins, and its susceptibility to third-generation cephalosporins is variable. Aztreonam (Azactam), a product of *C. violaceum,* is a monobactam antibiotic active against gram-negative bacteria and most strains of chromobacterium.[56]

Prevention

Avoid exposure to soil and/or stagnant or potentially contaminated water if there has been even a minor injury to the skin. If this is the situation, seek prompt medical attention at the first sign of cutaneous inflammation or purulence.

PSEUDOMONAS AERUGINOSA INFECTIONS

In 1850, Sèdillot noted blue-green discharges on infected surgical dressings. In 1925, Osler defined the organism as an opportunistic or secondary invader of damaged tissue. The name *aeruginosa* derived from cultured organisms having the color of verdigris, that is, the rust of copper or brass. *Pseudomonas aeruginosa* is one of the most serious sources of nosocomial bacterial infections.

Definition

P. aeruginosa is a ubiquitous, motile, nonfermentative, primarily aerobic, gram-negative rod.[1,77] Ultrastructurally, *P. aeruginosa* possesses a polar flagellum and many surface pili. Virtually all

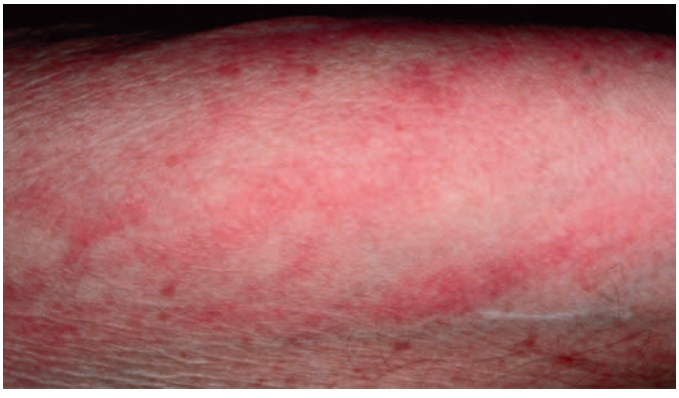

FIGURE 76-14 *Chromobacterium violaceum*. Lymphangitis of the forearm. *(Courtesy Edgar Maeyens, Jr., MD.)*

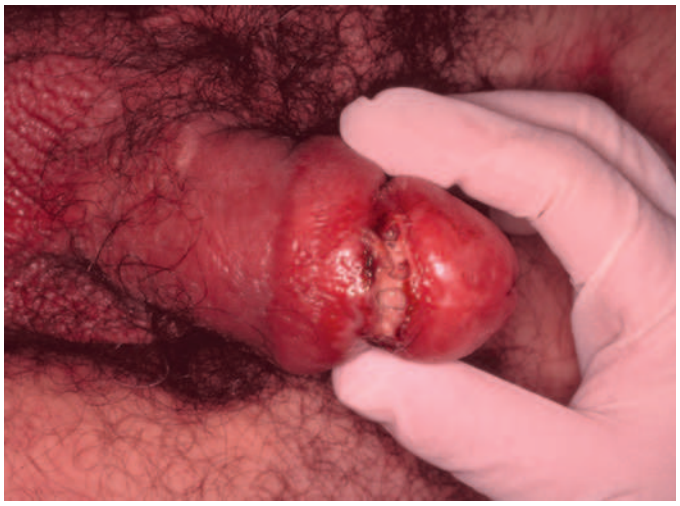

FIGURE 76-15 *Pseudomonas aeruginosa*. Primary infection of the penis in a young man with atopic dermatitis following hot tubbing. *(Courtesy Edgar Maeyens, Jr., MD.)*

strains produce an extracellular polysaccharide matrix necessary for biofilm formation.[149,172] It is a fastidious organism that survives extremes of temperature, under hostile conditions and with minimal nutritional support. It infects humans, other vertebrates, animals, and plants. The infection is often associated with moist conditions or environs. *Pseudomonas* skin infections can follow exposure to hot tubs, swimming pools, and whirlpools (Figures 76-15 and 76-16). *P. aeruginosa* is the most common cause of skin disorders in occupational saturation divers and can occur after recreational use of diving suits. Skin infection manifestations in these divers include folliculitis, abscesses (primarily of the head and neck), and otitis externa[1,99]

Epidemiology

P. aeruginosa, although primarily a nosocomial pathogen, grows in a wide variety of environments with minimal nutritional components.[127] It is commonly found in soil, water, and plants, but healthy humans and animals can be colonized. Up to 7% of healthy humans carry *P. aeruginosa* on their skin and in their nasal mucosa and throat. A rate of fecal carriage as high as 24% has been reported.[127]

Pathogenesis

Healthy humans are resistant to *Pseudomonas* skin infection. It is only when barrier functions of the skin are disrupted that *P. aeruginosa* organisms become invasive. *Pseudomonas* contains

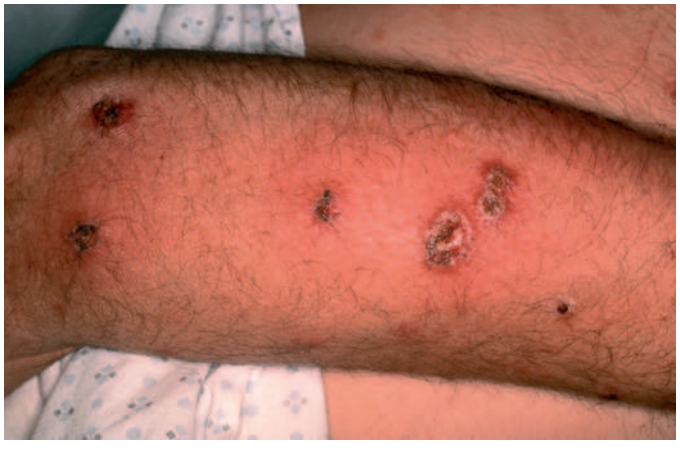

FIGURE 76-16 *Pseudomonas aeruginosa*. Primary infection of the forearm of a young man with atopic dermatitis following hot tubbing. *(Courtesy Edgar Maeyens, Jr., MD.)*

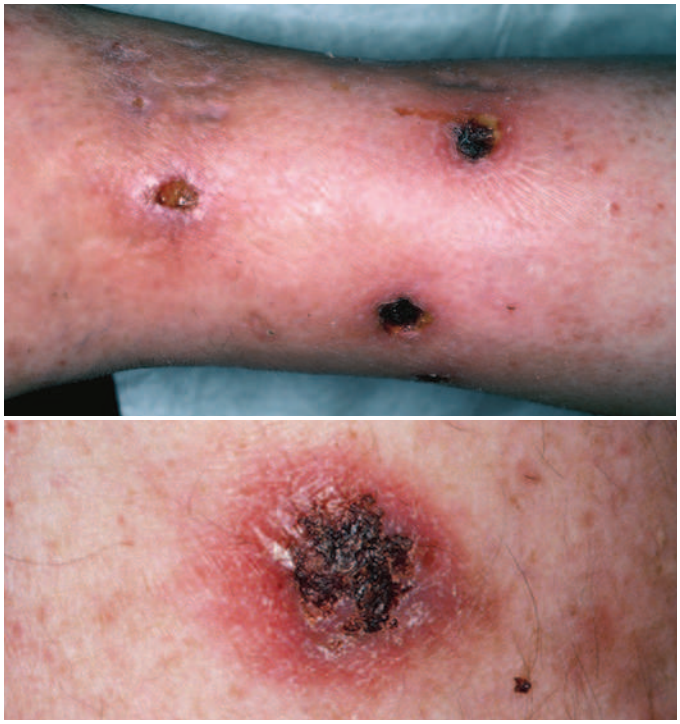

FIGURE 76-17 *Pseudomonas aeruginosa.* Discrete foci of necrotizing vasculitis (ecthyma gangrenosum) caused by *P. aeruginosa.*

virtually all major classes of bacterial virulence systems and can potentially infect any site in the body. The virulence is in part determined by the status of the host resistance, such as the site of infection, comorbid conditions, and immune function. An example is ecthyma gangrenosum, which is cutaneous necrotizing vasculitis seen in persons with *P. aeruginosa* bacteremia (Figure 76-17).

Hot Tub Folliculitis

Definition. One of the more common types of cutaneous *Pseudomonas* infections is hot tub folliculitis, which is infection of the infundibuli of hair follicles by *P. aeruginosa*.

Epidemiology. This infection is seen most often following immersion in inadequately chlorinated whirlpools or hot tubs, but can occur following swimming or scuba diving, both of which produce hyperhydration and maceration of the epidermis that predispose to *Pseudomonas* colonization and invasion. Numerous cases of "hot tub" or "whirlpool" dermatitis have been described.[34,150,184] Eruptions can also occur after use of heated recreational water sources, such as swimming pools, water slides, and communal bathtubs. Contaminated bath toys, loofah sponges, moisturizing creams, and diving suits have been implicated as fomites in cases of *Pseudomonas* folliculitis.[23,59,61,77]

Pathophysiology. Histologically, an inflammatory response, primarily composed of polymorphonuclear leukocytes, surrounds and infiltrates the follicular epithelium. Clinically, this manifests as a pustule surmounting an erythematous papulonodule. Depending on the stage of evolution of this infection, purulence may or may not be present, and only inflammatory papulonodules may be evident (Figures 76-18 and 76-19). Histopathologically and microbiologically, this folliculitis rarely demonstrates the bacterium.

Clinical Presentation. The eruption is perifollicular in distribution and appears within 48 hours of exposure. It is most pronounced in the skin folds, trunk, buttocks, and proximal extremities, whereas the head and neck are typically spared.[154,198] The extent and severity of the eruption depend on the concentration of bacteria in the water source, duration of exposure time, presence or absence of preexisting skin disease, water temperature, and individual susceptibility. Pruritus and mild pain are common associated symptoms. Other symptoms include external

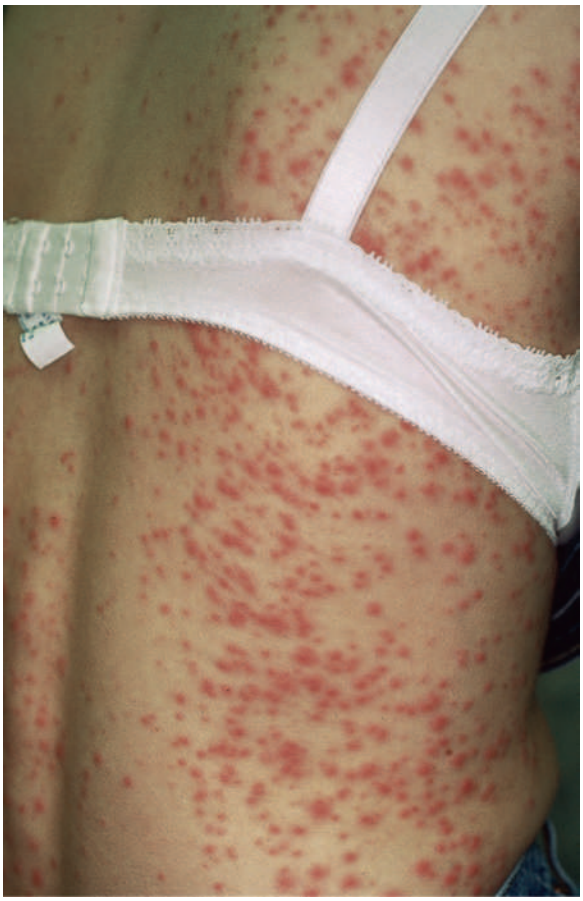

FIGURE 76-18 Hot tub folliculitis. *(Courtesy Edgar Maeyens, Jr., MD.)*

otitis, conjunctivitis, tender breasts, enlarged and tender lymph nodes, fever, and malaise.[77,151] Serious infections arise in immunocompromised and debilitated individuals. Rapid progression to severe systemic disease, as manifested by hemorrhagic bullae, pneumonia, or septicemia, suggests immunosuppression.[57,66,148]

Diagnostic Tests. Bacterial culture from a pustule helps to confirm the diagnosis, although clinical presentation is often sufficient.

Treatment. Hot tub folliculitis usually resolves spontaneously without therapy in 7 to 14 days. Keeping the skin dry and cool expedites resolution without formal therapy. Systemic infection may be treated with a fluoroquinolone (ciprofloxacin or levofloxacin), an antipseudomonal penicillin, antipseudomonal cephalosporin, carbapenems, or monobactams (e.g., aztreonam)

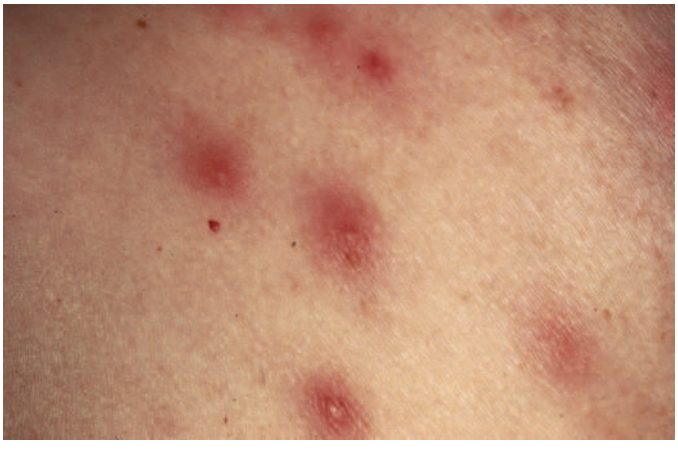

FIGURE 76-19 Hot tub folliculitis. *(Courtesy Edgar Maeyens, Jr., MD.)*

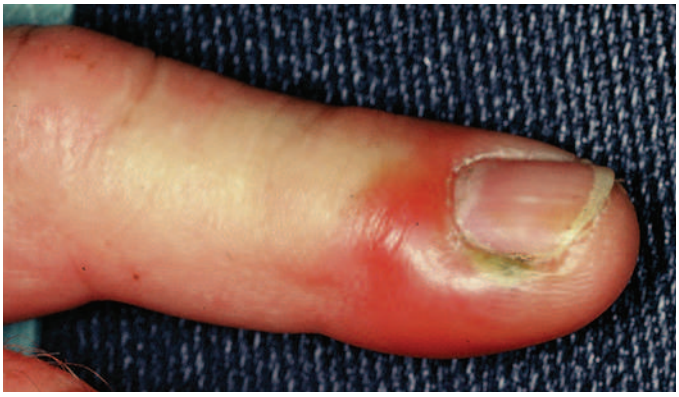

FIGURE 76-20 Green nail syndrome. Acute purulent *Pseudomonas aeruginosa* paronychia with early pigment formation.

as single agents. Aminoglycosides must be given in combination with another antibacterial agent for systemic infection.

Prevention. Prevention of *P. aeruginosa* infection requires either use of adequate disinfectant or avoidance of recreational closed-water systems and disinfection of reservoirs that are vehicles of transmission. Prompt drying of skin when exposed to wet, environmental conditions can prevent or at least minimize the degree of infection. Once colonization occurs, showering does not appear to prevent the disorder.[151]

Green Nail Syndrome

Definition. Green nail syndrome is defined as greenish-black discoloration of the nail plate secondary to the combination of pigments, pyocyanin, and pyoverdin synthesized by the bacterium *P. aeruginosa*.

Pathophysiology. Hydration of paronychial skin, usually with entry into the epidermal barrier, predisposes to colonization with *P. aeruginosa*. Infection follows, producing erythema, edema, pain, and discoloration of the adjoining nail plate. If the course of infection is prolonged, the infection extends into the hyponychium, at which point onycholysis occurs.

Among the many virulent factors of *P. aeruginosa* are pyocyanin. Pyocyanin damages cells by producing hydrogen peroxide and superoxide. These substances impart pigment to the nail plate and hyponychium. The typical discoloration of the nail plate seen in green nail syndrome is bluish-green and is the end point of the combination of two different pyocyanins (Figures 76-20 and 76-21). With loss of the epidermal barrier function in onycholysis, a polymicrobial infection may ensue.

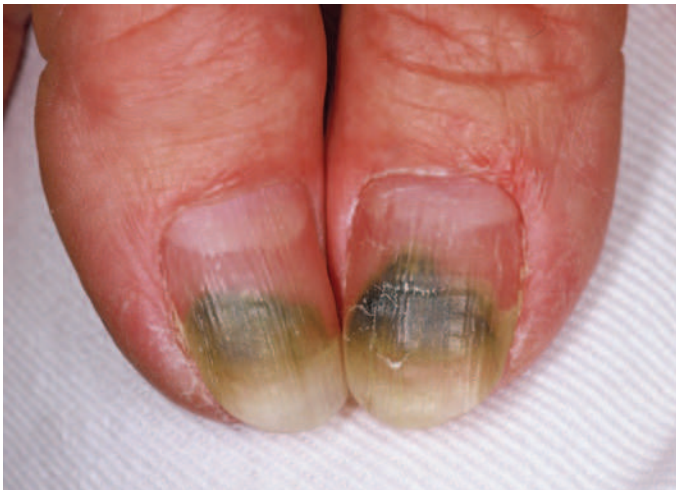

FIGURE 76-21 Green nail syndrome. Greenish-black discoloration of *Pseudomonas onychia*.

Risk Factors. Prolonged or frequent exposure to water, such as water sports, tending bar, and housecleaning, predisposes individuals to *Pseudomonas* paronychia, especially if the nails and the cuticles are poorly manicured.

Clinical Presentation. Infection is characterized by onycholysis and bluish-green discoloration of the nail plate with or without paronychia.[9] With paronychia, pain and swelling of nail fold tissue is the initial presentation. Occasionally, foci of purulence develop. If infection is not promptly treated, pigmentary changes within the nail plate appear and infection of the nail bed and matrix follow.

Differential Diagnosis. Without the pigmentary changes of the nail plate, diagnosis of *P. aeruginosa* as an etiologic agent is not clinically possible. Pseudomonal infection should be suspected if the patient has a history of abundant water exposure. Otherwise, consider *Staphylococcus* species, nonpseudomonal gram-negative organisms, or polymicrobial species as causes.

Diagnostic Tests. Culture purulence if present. No additional tests are needed once the pigmentary changes occur.

Treatment. Cessation of water exposure, debridement of the affected nail plate and subungual debris, and topical antibiosis effect resolution. Twice-a-day topical application of the antibiotics tobramycin ophthalmic solution or nadifloxacin cream, or soaks with antiseptics such as diluted acetic acid solution or 0.1% octenidine dihydrochloride solution are therapeutic options. To reduce swelling and erythema of the paronychium, application of a topical corticosteroid cream or ointment, such as clobetasol, is beneficial[10,140,146] (see Table 76-1).

Otitis Externa

Definition. Otitis externa is a general term that includes more than one inflammatory or infectious disease process of the external auditory canal or ear itself. Etiologically, it is rarely unifactorial. Contributing causes include inflammatory dermatoses such as seborrheic dermatitis and psoriasis; physical factors of trauma, heat, humidity, and moisture; and microbial exposure.[119] *Pseudomonas* is the most common causative microorganism.[183] Malignant otitis externa is an infection involving the external ear and skull base that can be life-threatening.

Epidemiology and Risk Factors. Any of the common causes of otitis externa are potentially worsened in an aquatic environment. For example, moisture, humidity, and heat are important predisposing factors for "swimmer's ear," which is characterized by erythema, edema, and pronounced dermatitis. Water encourages epidermal maceration, predisposing to secondary bacterial or fungal infection. According to Springer, freshwater is particularly prone to producing swimmer's ear.[168] Otitis externa does not appear to be associated with bacterial indicators of recreational water quality, such as fecal coliform bacteria or *Enterococcus* or *Pseudomonas* organisms.[30]

Diabetes mellitus and immunosuppression facilitate development of malignant otitis externa.[71]

Pathophysiology. The epidermis of the adult pinna and ear canal is normally as resistant to infection as is skin elsewhere. The adult ear canal is a cul-de-sac approximately 5 mm (0.2 inches) in diameter and 25 mm (1 inch) in length lined by stratified squamous epithelium.[183] The outer one-third of the canal produces cerumen, an acidic-waxy mantle mixed with sloughed epithelial cells. Cerumen is a physiologic barrier to infection. However, this barrier is not present to the same degree in the more delicate epithelium of the inner two-thirds of the ear canal. In addition, darkness and inaccessibility to air flow create an excellent milieu for certain microbial growth.

Interaction of moisture retention, moderate to high temperatures, and bacterial colonization predispose an individual to otitis externa (Figure 76-22). Other predisposing factors include canal occlusion by exostoses, cerumen plugs, ear plugs, and entrapped particles of sand; trauma related to mechanical attempts to clean the canal; intrinsic dermatoses; cerumen degradation; and pH variation above the normal pH of 4 to 5. Bacterial otitis externa is most often caused by *P. aeruginosa,* other gram-negative bacteria, and *Staphylococcus* species.

Clinical Presentation. Initial symptoms of otitis externa are pruritus of the ear canal, a sense of pressure or fullness within

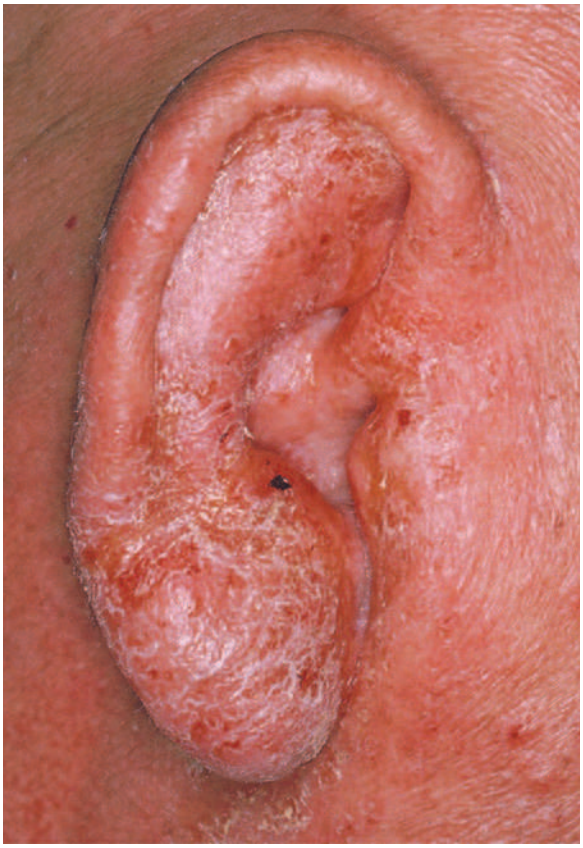

FIGURE 76-22 Otitis externa. The entire pinna is erythematous, edematous, scaly, and colonized by *Staphylococcus aureus.*

the canal, and diminished hearing. As inflammation progresses, the pain intensifies. Pain is elicited by applying pressure to the external auditory meatus or the tragus or by pulling on the lobule. Initially, there is a dermatitis, which if left untreated, is followed by progressive inflammation, edema, superficial fissures, serous exudate, and microbial overgrowth. Secondarily infected otitis externa may be associated with or progress to otitis media, canal occlusion, cervical lymphadenopathy, headache, nausea, fever, cellulitis, associated purulent discharge, and toxemia. Infection can extend to periauricular soft tissues, the parotid gland, and the temporomandibular joint. A condition called infectious eczematous dermatitis occurs when exudate from the infected ear canal discharges onto the surrounding skin of the neck or face, producing secondary infection or dermatitis of those areas.

Malignant otitis externa (Figure 76-23) usually manifests with severe pain and purulent discharge. Otologic examination reveals excessive granulation tissue at the junction of the cartilaginous and osseous components of the external auditory canal.[71] Infection penetrates the cartilage surrounding the external auditory canal and extends into the middle ear, mastoid air cells, and temporal bone. This is a severe and dangerous infection that could extend into the brain, producing thromboses of the venous sinuses and carotid artery, resulting in cerebral infarction.

Differential Diagnosis. Cholesteatomas are able to produce a thick, malodorous discharge that can be confused with infected otitis externa. Although *P. aeruginosa* and *S. aureus* are the predominant organisms producing infection, other bacteria and fungi can produce identical clinical presentations. These organisms include *Proteus mirabilis, Enterococcus faecalis, Bacteroides fragilis, Acinetobacter calcoaceticus, Aspergillus,* and *Candida.*[49,73,191,194]

Diagnostic Tests. Bacterial swab culture can help to identify causative bacteria; however, tissue biopsy culture may be indicated if swab culture–directed therapy is not diagnostic.

Treatment. The guiding principal of treatment of uncomplicated otitis externa is to treat with a topical anti-septic or antibiotic formulation and to combine this with a topical steroid to hasten reduction of associated itch or pain. Although numerous effective antimicrobial combinations will result in resolution in 1 to 2 weeks, common options include acetic acid (vinegar) in a 1:1 mixture with rubbing alcohol, Cortisporin Otic (generic form: neomycin/polymyxin B/hydrocortisone 1%) or 0.3% ofloxacin otic.[87,152] Note that patients should apply enough medicine to coat the ear canal and remain with their head in side tilt for 3 to 5 minutes. If the canal is edematous to the point of occlusion, a gauze wick soaked with the topical antibiotic ofloxacin otic should be inserted and kept in place for 24 to 72 hours. Systemic antibiotic use with a quinolone antibiotic, such as ciprofloxacin or ofloxacin, is only indicated when complications of cellulitis, adenopathy, fever, or profuse, purulent discharge are present. Antibiotics should be continued for at least 7 to 10 days in addition to topical therapy. Intravenous antibiotics are indicated when the infection worsens or does not respond to therapy within 48 hours.

For symptomatic control, analgesics are required for pain control, and short courses of systemic corticosteroids can reduce edema and any associated dermatitis. Before institution of corticosteroids, antibiotics must be started. For example, prednisone 40 mg daily for 4 days may be given simultaneously with the antibiotic.

Treatment of malignant otitis externa consists of debridement of all necrotic tissue, including cartilage and bone, plus administration of antipseudomonal antibiotics. The treatment of choice is IV ciprofloxacin, switched to oral ciprofloxacin, for 2 to 8 months once clinical markers improve.

An antipseudomonal beta-lactam antibiotic (piperacillin, piperacillin-tazobactam, ceftazidime, cefepime) may be indicated if ciprofloxacin resistance is present.[17]

Sequelae. Acquired atresia of the external auditory canal may rarely be a consequence of chronic otitis externa.

Prevention. Resolution of all existing dermatoses prior to water activities is recommended. One must thoroughly dry both the pinnae and ear canals after completion of aquatic activities. Seeking low-humidity environs will allow for continued epidermal water evaporation and drying. Rubbing alcohol applied directly to the ear canal facilitates water evaporation. Dilute acetic acid (vinegar 1 part to 3 parts water) ear rinses lower the pH of the auditory canal and discourage bacterial proliferation. When

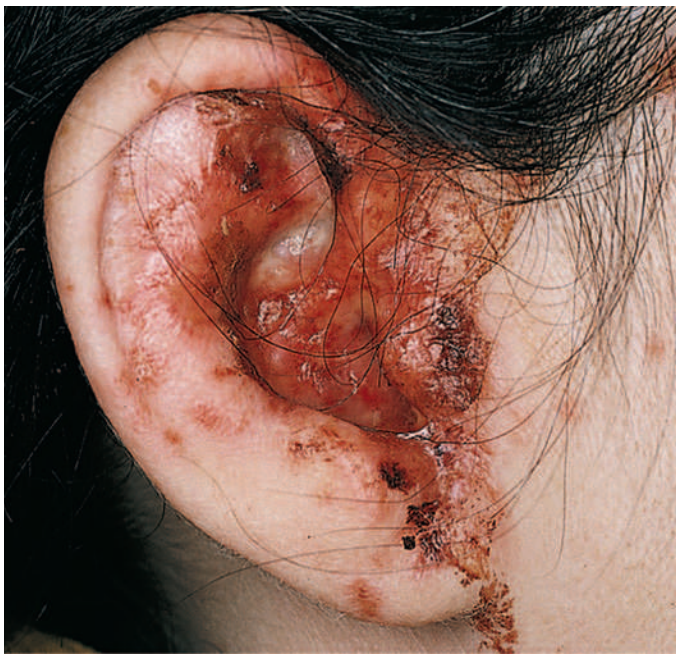

FIGURE 76-23 Malignant otitis externa. *(Courtesy Edgar Maeyens, Jr., MD.)*

available, blow-drying the canals with a hair dryer is very effective.

VIBRIO VULNIFICUS INFECTIONS

The bacteria *Vibrio vulnificus* is a part of normal marine flora and a recognized virulent pathogen. The organism has been isolated in warm (20° C [68° F] or warmer) coastal waters and in waters with salinity of 0.7% to 1.6%.[131] It is also found in brackish inland waters. *V. vulnificus* is detectable at high concentrations in filter-feeding sea life, such as aquatic animals, oysters, mussels, clams, scallops, and crabs, and also fish inhabiting coral reefs.[169]

Definition

V. vulnificus is a curved, flagellated, and gram-negative rod. The genus *Vibrio* is classified in the family Vibrionaceae, along with the genera *Photobacterium, Aeromonas,* and *Plesiomonas*. Infection with *V. vulnificus* can be localized to skin or be systemic.

Epidemiology and Risk Factors

Individuals develop cutaneous infection following contamination of a preexisting wound or as a result of an injury acquired while a person is exposed to warm, coastal waters. Primary bacteremia occurs following ingestion of raw or undercooked seafood, particularly oysters, without direct skin injury. Individuals who are especially at risk include those with liver disease and hemochromatosis, or chronic diseases, including diabetes mellitus and persons who are immunocompromised.[106]

Clinical Presentation

The course of the initial wound infection is erythema, edema, and pain that rapidly progresses to cellulitis with characteristic hemorrhagic bullae.[18] Primary bacteremia can result in metastatic cutaneous lesions that evolve into hemorrhagic bullae and necrotic ulcers.[48] Septicemia is virtually inevitable in the presence of fasciitis.

Pathophysiology and Histology

Skin lesions caused by *V. vulnificus* may, in part, be attributed to the destructive capabilities of enzymes released during infection. These enzymes are proteolytic, collagenolytic, and elastolytic. In the latter stages of cutaneous infection, there is intercellular edema and necrosis of the epidermis, dermis, and subcutaneous fat (Figure 76-24). The histopathologic features are infiltration of the dermis and subcutaneous tissues by a mixed inflammatory cell infiltrate composed of neutrophils, lymphocytes, and histiocytes, with areas of necrosis.

Differential Diagnosis

Staphylococcal and streptococcal infections induce identical patterns of cellulitis. Skin infections with *P. aeruginosa* and *Aeromonas* species mimic the hemorrhagic and necrotic lesions occurring in the later stages of *Vibrio* infection.

Diagnostic Tests

Culturing wound or bulla fluid is recommended. One should obtain blood cultures if the patient is febrile, has hemorrhagic bullae, or is septic.

Treatment

Because of the severity and rapid progression of *V. vulnificus* wound infections, prompt diagnosis plus antimicrobial therapy and early surgical debridement of necrotic tissue are recommended.[84] Fasciotomies are necessary to control infection in the presence of necrotizing fasciitis.[81] Despite prompt diagnosis and treatment, the mortality rate remains high, especially in people who are chronically ill, are immunologically compromised, or have liver disease. Favored treatment for serious skin infections or septicemia includes the use of a tetracycline analog and a third-generation cephalosporin antibiotic. Specific treatment options include combining doxycycline or minocycline (both 100 mg orally twice daily) with either IV ceftriaxone (1 g a day) or IV cefotaxime (2 g three times a day).[106] Alternately, levofloxacin 500 mg daily, intravenously or orally, may be given.[42] For minor, localized wound infections, oral treatment with a tetracycline or fluoroquinolone is sufficient.

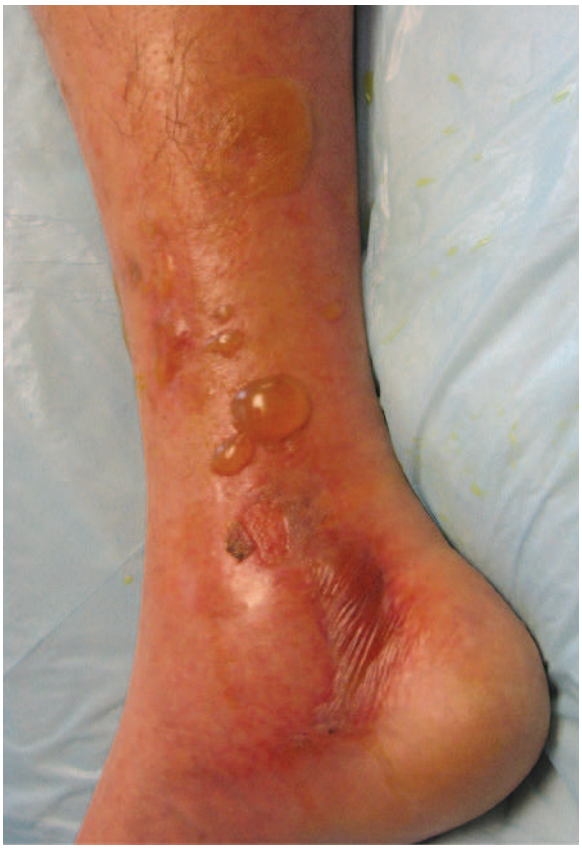

FIGURE 76-24 *Vibrio vulnificus* infection. Cellulitis with bullae and hemorrhage. *(Courtesy Sarah A. Wolfe, MD.)*

Prevention

Avoid entering warm coastal waters with a preexisting skin wound. Promptly attend to any injury acquired in an aquatic environment with meticulous wound care. Persons with known risk factors should avoid eating undercooked seafood, especially oysters.

SHEWANELLA PUTREFACIENS INFECTIONS

The taxon *Shewanella* species contains, among others, two bacteria known to be human pathogens. These are *Shewanella algae* and *Shewanella putrefaciens*. Key characteristics of these gram-negative, mobile rods are production of hydrogen sulfide gas on triple sugar iron (TSI) slants, positive catalase and oxidase reactions, and release of trimethylamine as it participates in the decay of rotting fish.[90]

Definition

S. putrefaciens is a member of the family Vibrionaceae. It is most frequently recovered from aquatic reservoirs (freshwater, marine water, and sewage), fish, and aquatic animals, but can also be found in poultry, beef, dairy products, soil, oil emulsions, natural gas, and oil fields.[155] *S. algae* is a tetrodotoxin-producing isolate recovered from red algae.[160] This group of bacteria infrequently is the cause of cutaneous and systemic disease in humans.

Pathophysiology

S. putrefaciens produces the extracellular enzymes DNAase, lipase, and lecithinase.[160] Other enzymatic activities detected among select *Shewanella* isolates include tyrosine alkyl sulfatase, elastase, and chitinase.[90] The exact role of these enzymes in human disease can at best be inferred. Chen suggests possible exotoxin involvement in *S. putrefaciens* cellulitis.[41] *S. putrefaciens*

is frequently found in association with other bacterial pathogens, rendering its pathogenic role unclear.[43,90] This bacterium produces trimethylamine as it participates in the decay of rotting fish; hence, the name putrefaciens, meaning putrid.[121]

Clinical Presentation

Skin and soft tissue manifestations include wound infections, cellulitis, dacryocystitis, and otitis externa.

Risk Factors

Persons with underlying diseases, such as hepatobiliary disease, malignancy, or renal failure, or those who are immunocompromised are at risk for bacteremia and fulminant illness. The course of localized skin infections is believed to proceed from colonization to invasion, especially in individuals with open wounds.[197] Tissues with compromised circulation are predisposed to infection with *Shewanella* species.

Differential Diagnosis

Clinically, there is nothing unique about cutaneous infections with *S. putrefaciens* or *S. algae*. They often manifest as necrotic areas with marked inflammation and necrosis not dissimilar to other gram-negative soft tissue infections. Therefore, deciphering these organisms from other gram-negative infections is necessary for proper treatment. *Vibrio vulnificus* and *Aeromonas* species should be considered with a rapidly progressive soft tissue infection. *Pseudomonas* species are the organisms most frequently mistaken for *Shewanella* using routine bacterial culture techniques.

Diagnostic Tests

Obtain routine specimens for Gram's stain, culture, and sensitivity. Colonies in culture have a pink water-soluble pigment or reddish-tan color. However, specific microbiologic laboratory testing is necessary for differentiation of *Shewanella* species. Automated identification systems are unable to differentiate between *S. putrefaciens* and *S. algae,* because *S. algae* is not included in these systems' databases. Retrospectively, it has become apparent that most *Shewanella* infections that had been previously attributed to *S. putrefaciens* were actually caused by *S. algae*. Species differentiation of *S. algae* and *S. putrefaciens* can be obtained with extensive phenotypic characterization.[78] Use of 16S rRNA gene sequence analysis correctly identifies the species.[22]

Treatment

Shewanella species are usually susceptible to levofloxacin, aminoglycosides, most third- and fourth-generation cephalosporins, and piperacillin.[174]

Prevention

If a person is immunocompromised, exposure to aquatic environments presents a potential for infection. Open wounds should be protected from exposure to freshwater lakes and oceans.

MYCOBACTERIUM MARINUM INFECTIONS

Mycobacterium marinum is a nontuberculous mycobacterium commonly recognized as the etiologic agent of "fish tank" or "swimming pool granuloma."[26] Most infections manifest 2 to 3 weeks after contact with contaminated water. Infections are localized primarily to skin.

Definition

M. marinum is found in freshwater and saltwater environs. It is an acid-fast, rod-shaped bacillus of Runyon group 1 and is a photochromogen producing yellow pigment when cultured and exposed to light. In contradistinction to *Mycobacterium tuberculosis,* which cannot multiply outside of the host, *M. marinum* is a free-living soil and water saprophyte. It is an infrequent human pathogen.

Epidemiology and Risk Factors

Persons at risk for infection with *M. marinum* are those who incur trauma while in contact with fresh or marine water, marine animals, or aquariums. Tap water is considered to be a reservoir for most nontuberculous mycobacteria, where they may be present as a biofilm.[64] Immunosuppression predisposes an individual to a more aggressive cutaneous infection and systemic dissemination.

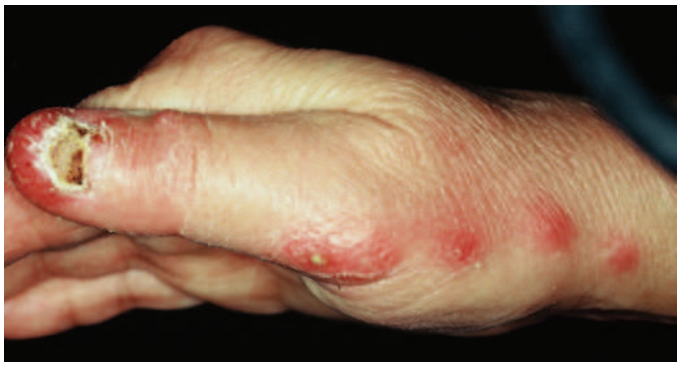

FIGURE 76-25 *Mycobacterium marinum* nodular lymphangitis.

Pathophysiology

Because the optimal temperature range for growth in tissues is 31° to 32°C (87.8° to 89.6°F), cooler extremities are infected more often than are warmer body sites. *M. marinum* is capable of growing at temperatures as high as 37°C. An example of this is their ability to cause systemic infection in persons who are immunocompromised.[88] At the time of inoculation, *Mycobacteria* are phagocytized by macrophages. The organisms are either destroyed by macrophages or escape extracellularly to spread cell to cell. Cytokines, such as tumor necrosis factor (TNF), facilitate destruction of the bacterium. In the absence of TNF, *Mycobacteria* are engulfed by macrophages but not destroyed.[50]

Clinical Presentation

Within 2 to 3 weeks of inoculation into skin, a papule, nodule, or shallow ulceration develops. The upper extremities are the most commonly involved sites. Lesional pain and induration are common. As the inflammatory process progresses, nodules predominate over ulcerations. There may be progression of nodules along lymphatics in up to 50% of infections. Lymphatic distribution of nodules is called "sporotrichoid" because of the resemblance to sporotrichosis (Figures 76-25 to 76-29). Lymphadenopathy is inconsistent in its occurrence. Extracutaneous infections include septic arthritis, bursitis, osteomyelitis, and tenosynovitis. Dissemination to viscera or bone marrow is rare. Immunocompromised individuals are those most at risk for development of disseminated infection with fever and lymphadenopathy.

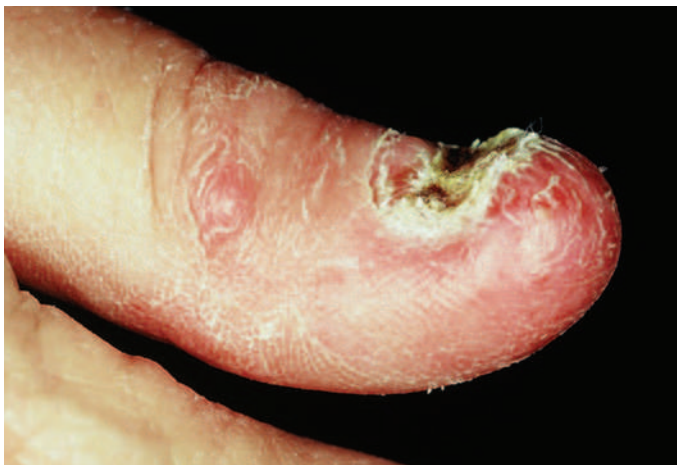

FIGURE 76-26 Dermatitis-like initial infection with *M. marinum*.

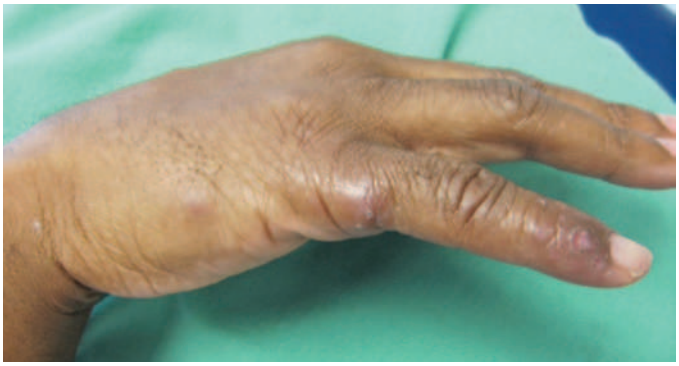

FIGURE 76-27 The granulomatous nodules of *M. marinum* lymphangitis following infection of the fingertip. *(Courtesy Sarah A. Wolfe, MD.)*

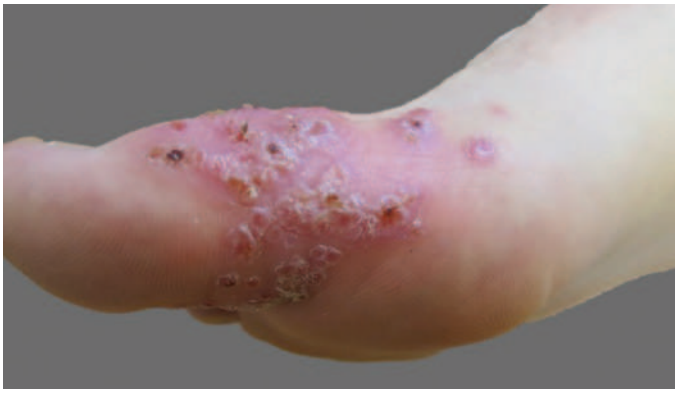

FIGURE 76-28 Vesicular eruption at site of inoculation with *Mycobacterium marinum. (Courtesy Jessica Kim So, MD.)*

Differential Diagnosis

The following diseases share morphologic similarities to cutaneous *M. marinum* infections: sporotrichosis, sarcoidosis, nocardiosis, tularemia, cutaneous protothecosis, leprosy, leishmaniasis, cowpox, verrucae vulgaris, iododerma, bromoderma, chronic pyogenic infections, and other cutaneous mycobacterioses.

Diagnostic Tests

Diagnosis of *M. marinum* infection is confirmed by tissue biopsy culture grown on standard *Mycobacterium* culture medium (Lowenstein-Jensen) at 30° to 32°C (86° to 89.6°F), or more rapidly by polymerase chain reaction where testing is available.[52,139] Histopathologically, acid-fast bacilli are visualized in only 10% to 13% of biopsies. Approximately 70% to 80% of tissue cultures are positive (Figure 76-30). Skin tests show cross-reactivity between *M. marinum* and *M. tuberculosis.*

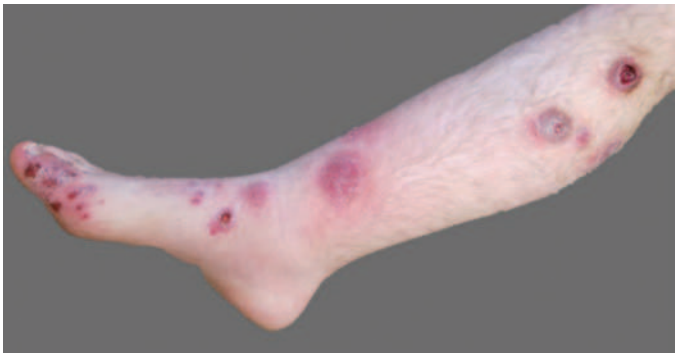

FIGURE 76-29 Lymphocutaneous (sporotrichoid) spread of *Mycobacterium marinum. (Courtesy Jessica Kim So, MD.)*

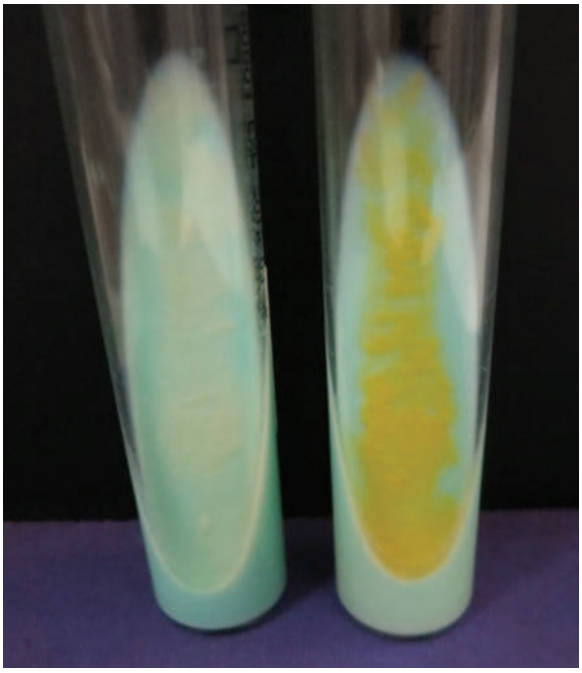

FIGURE 76-30 Tissue cultures grew smooth photochromogenic colonies supportive of a diagnosis of *Mycobacterium marinum.* **A,** photoprotected cultures grew buff-colored colonies. **B,** cultures exposed to light grew colonies producing yellow pigment. *(Courtesy Jessica Kim So, MD.)*

Treatment

There is no consensus on treatment, and *M. marinum* has a natural pattern of multidrug resistance.[6] Most cases of *M. marinum* are treated empirically because routine antibiotic susceptibility testing is not available in most laboratories. Testing may be necessary, however, following months of treatment failures. Successful monotherapy for focal soft tissue infections includes clarithromycin, minocycline, doxycycline, amikacin, and sulfamethoxazole.[6,192] For treatment failure or more extensive infection, combination treatment may be warranted.[139] Options include clarithromycin plus ethambutol, ethambutol plus rifampin, or a combination that includes a tetracycline. High resistance to doxycycline has been reported in Taiwan.[192] Treatment is recommended for 1 to 2 months beyond clinical clearance; for most, this equates to 3 to 4 months total. Involvement of deeper structures, such as joints, tendons, or bone, may require months longer. Surgical debridement may be beneficial in cases of treatment failure or when closed spaces of the hand are involved, although appropriateness of this modality has not been well studied.

Prevention

Cognizance of the potential for *M. marinum* infection in aquatic environments, avoidance of entry into such environments when skin wounds are present, and prompt attention/hygiene to wounds sustained while in an aquatic environment will help avoid infection.

MELIOIDOSIS

Melioidosis, also called Whitmore's disease, was first described by the pathologist Alfred Whitmore as a "glander-like" disease among drug addicts in Rangoon, Burma.[140] This name is derived from the Greek *Melis* (distemper of asses) and *Eidos* (resemblance).[130] Once solely perceived as an esoteric tropical disease, melioidosis is now increasingly recognized as an important public health problem worldwide. *Burkholderia pseudomallei* is the causative agent.

Definition

B. pseudomallei are small, gram-negative, oxidase-positive, aerobic, and mobile bacilli that reside in soil and water. The entry

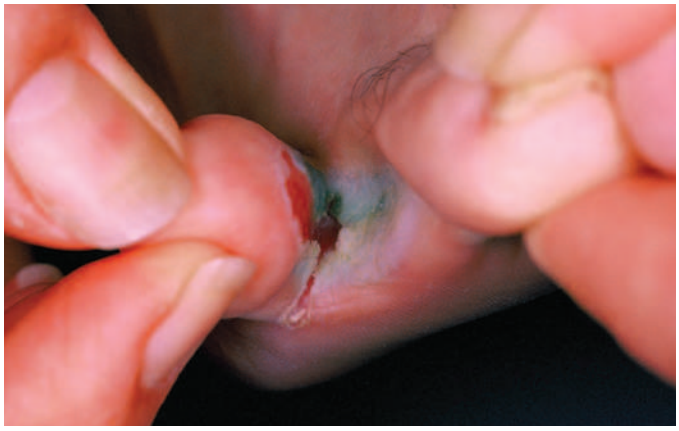

FIGURE 76-31 Melioidosis. Foot web space infection with *Burkholderia pseudomallei.*

sites for infection are primarily percutaneous and via inhalation. Common disease manifestations include pneumonia and cutaneous disease, but infection may extend to multiple organs, including the central nervous system. The mortality rate is as high as 40% in endemic areas.[186] This section focuses on cutaneous disease.

Epidemiology and Risk Factors

Although northern Australia and Southeast Asia are recognized as highly endemic, cases have also been reported in the Indian subcontinent, China and Taiwan, the Indian Ocean islands, the Americas, and Africa.[104,186] Risk factors for infection include diabetes, heavy alcohol use, chronic lung disease, chronic kidney disease, and, less frequently, thalassemia, glucocorticoid therapy, and cancer.[52,105] Infection is more common in adults than children; however, children are more likely than adults to develop primary cutaneous melioidosis.[120]

Localized Form. *B. pseudomallei* enter the skin through any type of breach in the epidermal barrier or via a laceration. Mucous membranes may occasionally be a site of entry. After entry into the skin, acute inflammation is followed by cellulitis and then abscess formation, ulceration, and lymphadenitis (Figure 76-31). Rarely, superficial soft tissue infection can progress to necrotizing fasciitis or a cutaneous granulomatous reaction mimicking mucormycosis[189] (Figure 76-32).

Chronic Form. Chronic melioidosis characteristically presents as multiple abscesses widely disseminated to organ systems that include the spleen, liver, muscles, or skin (Figure 76-33). This form of the disease can reactivate many years after the primary infection. Draining sinuses from lymph nodes or bones may develop.

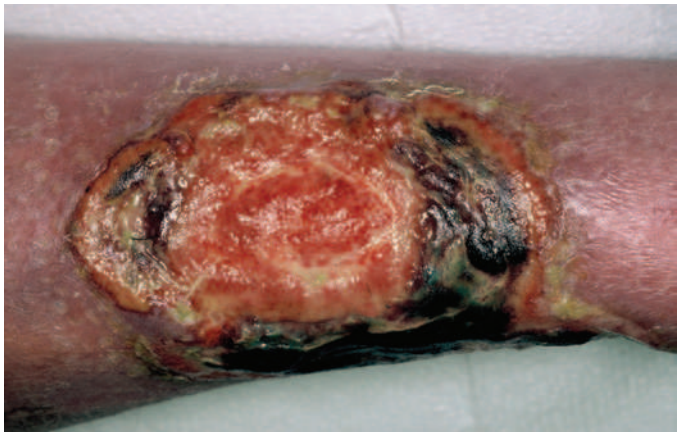

FIGURE 76-32 Melioidosis. An exuberant granulomatous infection caused by *Burkholderia pseudomallei* clinically mimicking mucormycosis.

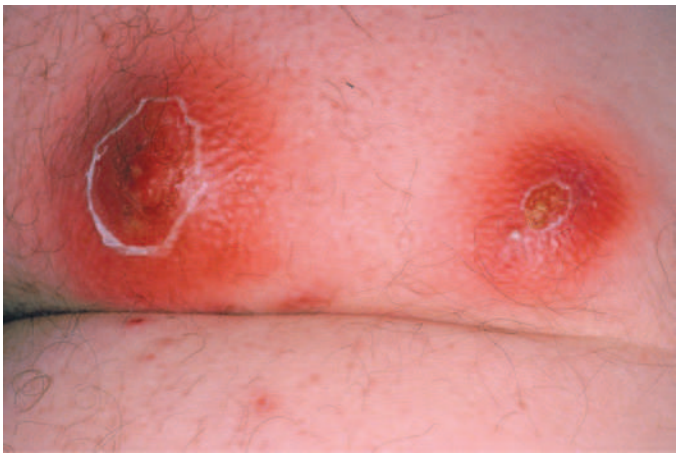

FIGURE 76-33 Melioidosis. Cutaneous abscesses in an individual with chronic melioidosis.

Differential Diagnosis

Cutaneous lesions must be differentiated from those of *Staphylococcus* species, *Streptococcus* species, *Pseudomonas* species, varicella-zoster virus, *Bacillus anthracis* bacteria (the cause of anthrax), and variola virus.

Diagnostic Tests

Gram's staining of skin abscesses and sputum show small, gram-negative bacilli; the bacilli look like bipolar safety pins when stained with Wright or methylene blue stains. Culture is the gold standard for diagnosis. The medium used for culture is Ashdown agar, but *B. cepacia* selective agar is an effective substitute if the Ashdown agar is not available.[135] Other tests include polymerase chain reaction assays, direct immunofluorescence microscopy, and enzyme immunoassays, but each is less sensitive than culture.[79,123,193]

Treatment

Treatment requires an initial intensive therapy with IV antibiotics for at least 10 days followed by oral eradication therapy for 3 months at a minimum. The intensive therapies of choice are ceftazidime, meropenem, or imipenem.[39,44,161] The addition of trimethoprim-sulfamethoxazole during treatment with ceftazidime may be beneficial for severe disease.[167] Trimethoprim-sulfamethoxazole is the best antibiotic for eradication therapy.[51] In pediatric cases verified to have localized skin infection, oral treatment alone with high-dose trimethoprim-sulfamethoxazole plus folic acid for 3 months has resulted in clearance.[120]

Prevention

There is no vaccine for melioidosis. Individuals with skin lesions, diabetes mellitus, renal failure, immune deficiencies, and chronic lung disease should avoid contact with soil or standing water, especially in endemic disease areas. In health care settings, use blood and body fluid precautions.

ERYSIPELOTHRIX RHUSIOPATHIAE (ERYSIPELOID)

Erysipelothrix rhusiopathiae, formerly known as *Erysipelothrix insidiosa,* is a gram-positive bacterium that causes an infection of skin known as erysipeloid. In 1909, Rosenbach isolated the organism from a patient with a cutaneous lesion.[143] Rosenbach labeled the infection erysipeloid to differentiate it from erysipelas, a cellulitis caused by group A streptococci.[142]

Definition

E. rhusiopathiae is an aerobic or facultatively anaerobic, nonmobile, non–spore-forming, and gram-positive bacillus. It is found worldwide as a commensal or pathogen in many invertebrate and vertebrate species.[143] The primary terrestrial reservoir is domestic swine.[143]

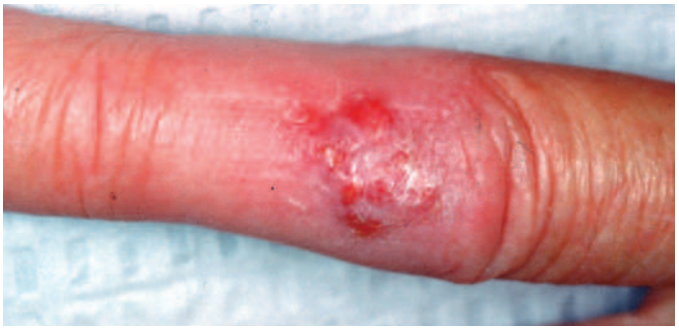

FIGURE 76-34 *Erysipelothrix rhusiopathiae*. Early skin lesion of *E. rhusiopathiae* with central pallor and raised, marginated, erythematous borders.

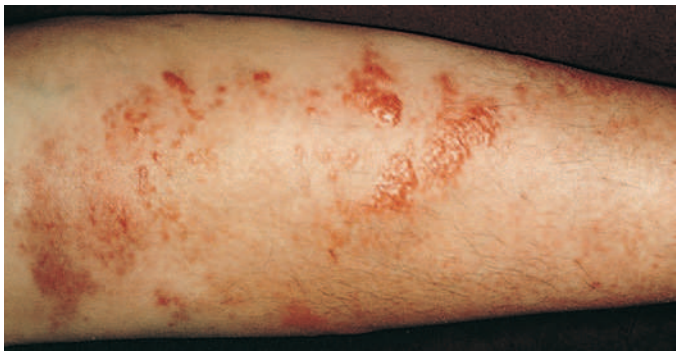

FIGURE 76-36 *Erysipelothrix rhusiopathiae* infection. *(Courtesy Edgar Maeyens, Jr., MD.)*

Epidemiology

In the aquatic environment, *E. rhusiopathiae* inhabits the exterior mucoid slime of fish and can be cultured from the skin of mammals, such as whales. Direct contact with marine animals is one source of infection. Persons at greatest risk are fisherman, fish handlers, butchers, slaughterhouse workers, and so forth.[142] *E. rhusiopathiae* can survive 12 days in sunlight, 4 months in putrefied flesh, and 9 months in buried carcasses.

Pathophysiology

E. rhusiopathiae gains entrance into the skin via abrasions or puncture wounds. Hyaluronidase, neuraminidase, and surface proteins are its virulence factors.[159] Having an ability to evade phagocytosis and to replicate intracellularly facilitates *E. rhusiopathiae* pathogenicity.[67]

Clinical Presentation

Erysipeloid has three clinical presentations in humans: localized cutaneous, diffuse cutaneous, and generalized or systemic.

In the localized cutaneous (erysipeloid) form, *E. rhusiopathiae* enters the skin through a puncture wound or abrasion, usually of the finger or hand. One to 7 days later, the lesion begins as a minor, purple-red irritation or infected paronychia with edema and a small amount of purulent discharge. Characteristically, the peripheral edge of the lesion spreads slowly with central fading (clearing), resulting in a well-demarcated, erythematous or violaceous ring[93] (Figure 76-34). The infected site is typically warm and edematous with associated pruritus and pain. There is often proximal progression along the dorsal edge of the finger into the web space and then distally along the adjoining finger. Suppuration is absent. Infection seldom occurs on the palm. Although the infection is generally limited to the hand (Figure 76-35), it may spread to the wrist and forearm.[94] Regional, painful lymphadenopathy is present in a third of patients; low-grade fever and arthralgias are less common.[130]

In the diffuse cutaneous form, the infection progresses proximally from the initial site to involve remote areas of the body or multiple areas regionally[69] (Figure 76-36). Fever and adenopathy are common, blood cultures are negative, and the course is more protracted than the localized form.

Systemic involvement with *E. rhusiopathiae* infection is rare. Endocarditis is the most common sequela of systemic erysipeloid and carries a mortality risk approaching 40%.[67] In systemic *E. rhusiopathiae* infection, characteristic skin lesions may be present in 40% of patients.

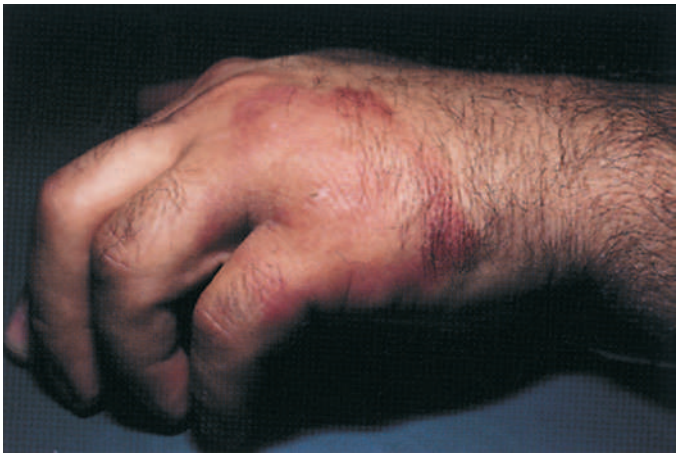

FIGURE 76-35 Typical appearance of *Erysipelothrix* skin infection. *(Courtesy Paul S. Auerbach, MD.)*

Differential Diagnosis

Staphylococcal or streptococcal cellulitis is the most frequent simulator. Vibrios and *Shewanella putrefaciens* also cause cellulitis.

Diagnostic Tests

For a definitive diagnosis of infection with *Erysipelothrix,* isolation of the organism is required. Biopsy specimens of infected tissues and/or blood cultures enable isolation of *E. rhusiopathiae* by routine culture techniques. No serologic tests are available.

Treatment

Although erysipeloid usually is self-limited and runs its course within 3 weeks, resolution is facilitated by antibiotic therapy. Most strains are susceptible to penicillins, cephalosporins, ciprofloxacin, clindamycin, and imipenem.[177] For isolated skin involvement, the first-line treatment is with penicillin V 500 mg orally every 6 hours or cephalexin 500 mg orally four times a day for 7 days. Alternatively, ciprofloxacin 250 mg orally twice a day for 7 days is rapidly effective.[12] *E. rhusiopathiae* is resistant to vancomycin, aminoglycosides, chloramphenicol, erythromycin, and trimethoprim-sulfamethoxazole. If arthritis, septicemia, or endocarditis is present, aqueous penicillin G should be administered in a dose of 2 to 4 million units intravenously every 4 hours for 4 to 6 weeks,[138] although oral therapy may be initiated after 2 weeks in patients who do not have endocarditis.

Prevention

Wearing protective clothing and gloves is recommended whenever handling marine mammal skin or body parts. Handle fish with care so as not to be punctured by their spines or lacerated by their scales.

MYCOPLASMA INFECTIONS

Seal Finger

Mycoplasma species are the smallest free-living organisms colonizing animal, plant, and insect kingdoms.[141] They are prokaryocytes lacking cell walls. *Mycoplasma* devolved from gram-positive bacteria through reductive evolution.[141] When initially discovered, they were believed to be viruses.

Definition. Seal finger is the sobriquet given to a unique infection, usually of a digit, acquired by exposure to pinnipeds

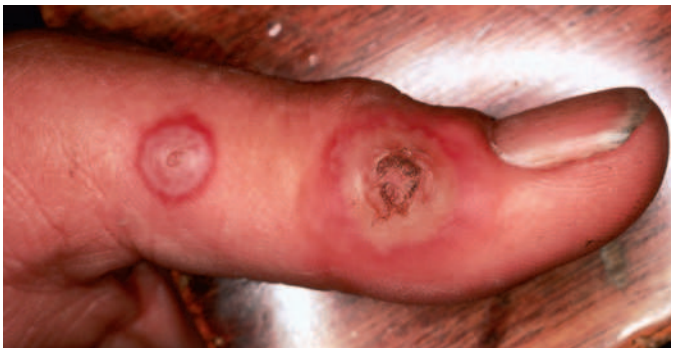

FIGURE 76-37 Seal finger secondary to *Mycoplasma*. *(Courtesy Edgar Maeyens, Jr., MD.)*

(seals, walruses, and sea lions).[180] It is believed that *Mycoplasma* inoculation occurs following direct contact with the skin or mucous membranes of one of these animals. Infection sites, most frequently the digits, become swollen and very painful. If the soft tissue infection is not treated promptly, tenosynovitis, bone marrow edema, periarticular osteoporosis, and interphalangeal effusion may occur.[115]

Pathophysiology. The disorder is believed to be secondary to infection with *Mycoplasma* strains *Mycoplasma phocacerebrale* and *Mycoplasma phocarhinis,* which were initially isolated from seals.[180] These strains are new species of *Mycoplasma* unique to seals and possibly other pinnipeds.[72] Some believe that these *Mycoplasma* species may be part of the normal flora of seals.[72] Several species of *Mycoplasma* are commensals in the animal's genitourinary tract and in the human oral cavity and genital mucosa.[15] Toll-like receptors interact with *Mycoplasma,* provoking an inflammatory response.[112] Antigen-antibody reactions or inflammatory cytokines result in cytolysis.

Clinical Presentation. Clinical manifestations begin after an incubation period of a few hours to 3 to 4 days, although some report an incubation period of 1 to 15 days.[11] Initially, an inflammatory papule rapidly develops into a nodule with swelling, slight purulence, and severe pain (Figure 76-37). Edema and stiffness of the digit are common sequelae.[54,117] If joint involvement occurs, it is usually in the joint nearest the site of entry of the organism.[72] Untreated, atrophy of cartilage, bone resorption, and, ultimately, arthrosis develop.[117] Secondary bacterial infection may occur in skin lesions, producing purulence and lymphangitis. Fever and leukocytosis may accompany the infection. Seal finger can resolve spontaneously with few or no sequelae or can last for several months. No immunity is conferred.[117]

Differential Diagnosis. Presentation can be with edema and erythema, both local and diffuse, resembling erysipeloid or cellulitis as seen with infection by *V. vulnificus.* The edema of erysipeloid is more pronounced than that of seal finger. Atypical mycobacterial infection may mimic seal finger, but produces much less pain in the initial inflammatory phase.

Parapoxvirus infection most closely resembles seal finger. Viruses within this group include the orf and paravaccinia viruses. Both of these viruses produce pustulovesicular lesions.

Orf virus infection is acquired from sheep (orf), whereas the paravaccinia virus is acquired from cows (milker's nodules). Tanapox virus, a monkey virus, can cause solitary nodules similar to those seen with seal finger. Herpetic whitlow not only resembles seal finger morphologically but is as painful. Bacterial furunculosis and an inflammatory response to foreign bodies must be considered.

Risk Factors. Frequent or prolonged exposure to marine mammals, direct contact with live marine mammals, and contact with secretions, excretions, blood, or tissue will increase the opportunity for trauma and infection.

Diagnostic Tests. Because of its small size, *Mycoplasma* cannot be visualized with routine microscopy. One can acquire material for culture, but the organism has very fastidious growth requirements and is very difficult to grow in a cell-free medium. Specimens for culture should not be allowed to desiccate. If culture material cannot be transported to a diagnostic laboratory immediately on collection, it should be frozen at −70° C (−94° F).[180] If available, molecular-based systems, such as polymerase chain reaction and enzyme-linked immunosorbent assays, can identify *Mycoplasma.*

Treatment. After contact with marine animals or bites from handling marine animals, especially pinnipeds, cleanse the wounds thoroughly with soap and water. If signs of infection occur, treat with tetracycline. Tetracycline is given orally at 500 mg four times a day for 4 to 6 weeks.[72] The sooner that therapy is begun, the greater the chance for resolution of infection and prevention of joint involvement.

Prevention. Be aware of the potential for infection when handling pinnipeds or their by-products. Practice good hygiene by wearing gloves, and washing with soap and water after each exposure. If the skin is damaged while handling pinnipeds, seek immediate medical attention and start empirical treatment with tetracycline.

PARASITES

ANISAKIDOSIS

Definition

Anisakidosis, formerly known as anisakiasis, is caused by accidental ingestion of larval nematodes of the family Anisakidae, which include *Anisakis* and *Pseudoterranova* in raw fish and cephalopods.[98]

Epidemiology and Risk Factors

Anisakis simplex is a parasitic nematode of several marine organisms. Accidental ingestion by humans eating raw fish, cephalopods, or undercooked fish can lead to infestation.[35]

Pathophysiology and Clinical Presentation

Adult stages of *A. simplex* and *Pseudoterranova decipiens* reside in the mucosa of stomachs of marine mammals. It is from here that unembryonated eggs produced by adult females pass into the feces of their hosts. In the water, eggs become free-swimming larvae. Larvae ingested by crustaceans morph a third time, becoming infective to predators. Humans ingesting these fishes and manifesting symptoms will often have larvae infiltrating the mucosal linings of their stomachs. Larvae rarely actually then develop in humans. Instead, once embedded in the gastric or intestinal mucosa they die by means of proteolytic enzymes.[75]

Sensitization to *Anisakis* larvae may cause an acute allergic reaction, such as urticaria, angioedema, or anaphylaxis. If a person has been previously sensitized to *Anisakis* antigens, allergic reactions are faster in onset and much more severe. The wide spectrum of allergic reactions to *A. simplex* include, in addition to the aforementioned, rhinitis, conjunctivitis, asthma, and allergic contact dermatitis (Figure 76-38). Consumption of raw and smoked fish may increase sensitization to Anisakidae (Figure 76-39).

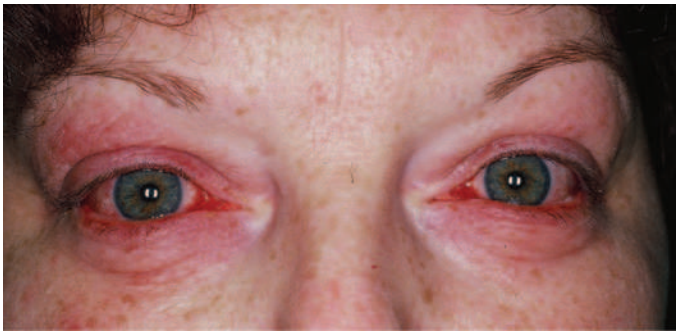

FIGURE 76-38 Anisakidosis. Conjunctivitis from an allergic response to *Anisakis simplex.*

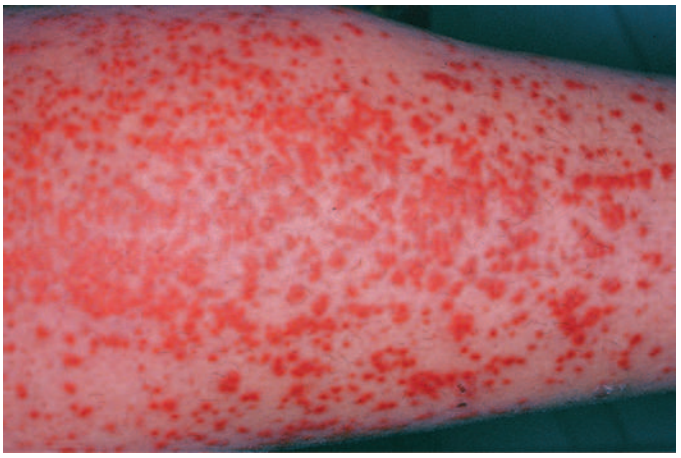

FIGURE 76-39 Cutaneous manifestations of a severe allergic response to *Anisakis simplex* antigens after ingestion of smoked salmon (same person with conjunctivitis).

Differential Diagnosis

Allergic reactions to seafood are the primary differential diagnoses. Most purported seafood allergies are actually reactions to *A. simplex* or the marine larval nematode *Pseudoterranova*.

Treatment

In the majority of persons, symptoms fade spontaneously. Endoscopic removal of worms results in a prompt cure. Treatment of allergic responses is with symptomatic and supportive therapies. Although not approved by the Food and Drug Administration, albendazole 400 mg orally twice daily for 6 to 21 days was successful in cases.[126]

Prevention

Thoroughly cooking seafood for at least 10 minutes over 65°C (149°F) or freezing it at −28.9°C (−20°F) for 24 hours is necessary to destroy all larvae. Adequate cooking or freezing does not destroy larval antigens and therefore will not prevent allergic reactions.

SCHISTOSOME CERCARIAL DERMATITIS

Definition

Schistosome cercarial dermatitis, known as swimmer's itch, is an inflammatory response to cutaneous infestation with any of several blood flukes (schistosomes) of the genera *Trichobilharzia, Ornithobilharzia, Gigantobilharzia, Orientobilharzia, Austrobilharzia, Bilharziella, Heterobilharzia,* and some species of the *Schistosoma* genus.[76] The particular flukes discussed here are animal pathogens that do not parasitize humans beyond the skin to cause systemic infection. The geographic distribution of these dermatoses is worldwide, occurring in Arctic, temperate, and tropical zones. Swimmer's itch is most commonly seen after exposure to cercariae-laden fresh or brackish water or, less often, saltwater.[107] This process is nearly exclusively cutaneous with only localized pruritus. Rarely, there may be fever, lymphadenopathy, and edema, particularly in those with repeated exposures.

Epidemiology

The definitive hosts of these nonhuman schistosomes are aquatic birds, such as ducks, gulls, and geese, in addition to mammals, such as beaver, mice, muskrats, and ungulates. The life cycle begins when eggs of the adult schistosomes are eliminated via feces of infested hosts. When eggs are deposited in water, they hatch and release small swimming larvae (miracidia). On finding their specific intermediate hosts (snails), miracidia penetrate the snails' soft flesh and metamorphose into forked-tail cercariae. Mature cercariae exit the snail in search of a definitive avian or mammalian host to complete their life cycle (Figure 76-40).[16]

The probability of infection is highest in the morning hours when cercarial emergence is greatest[166,178] and increased when more time is spent in the water. Prevalence is higher in warmer summer months when both human water activities and emergence of the cercariae peak. Shallow waters where snail populations are most numerous are sites of the highest infection risk, though infection can still occur at deeper water depths.

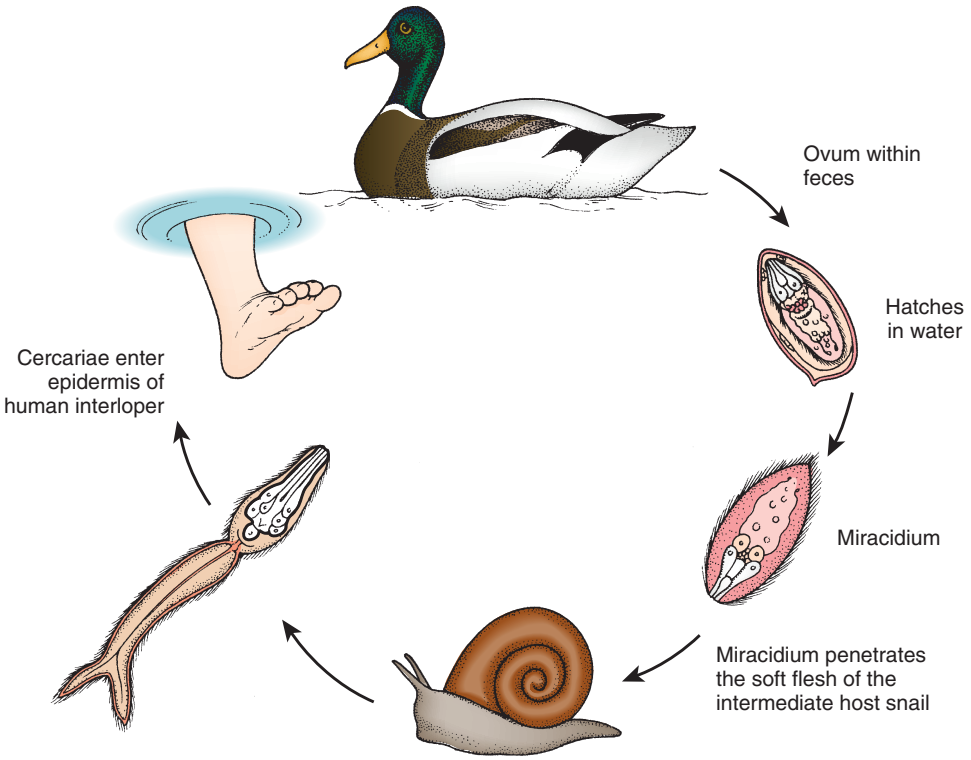

FIGURE 76-40 Schistosome cercarial life cycle. *(Courtesy Edgar Maeyens, Jr., MD.)*

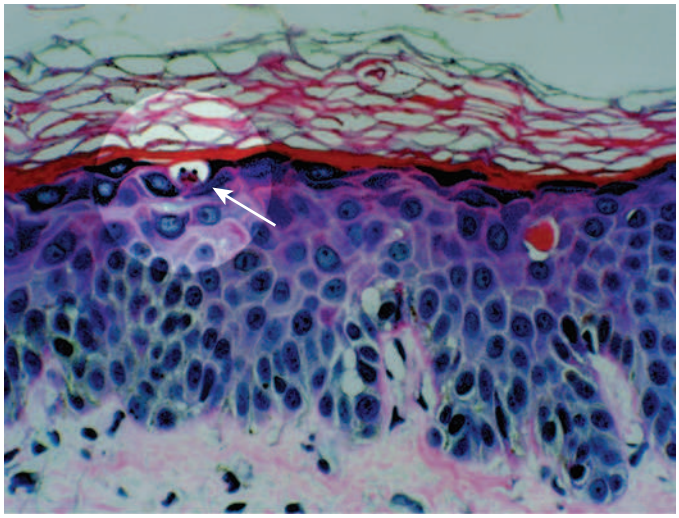

FIGURE 76-41 Schistosomiasis. Schistosome cercaria beneath the stratum corneum of the epidermis (H&E, original magnification ×10). *(Courtesy Ronald Rapini, MD.)*

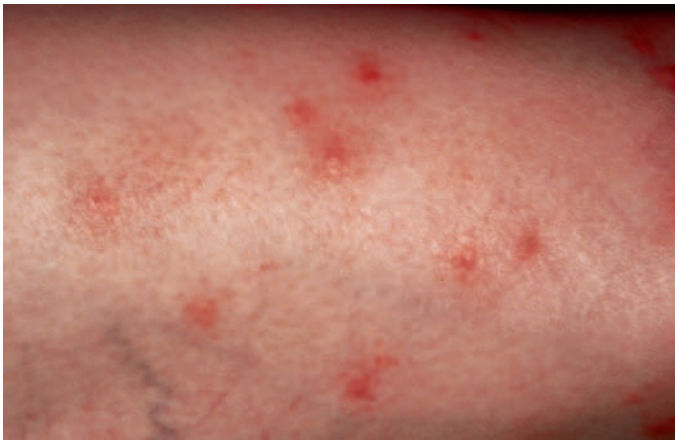

FIGURE 76-43 Schistosome cercarial dermatitis: Multiple papulovesicles in a sensitized individual following clam digging. *(Courtesy Edgar Maeyens, Jr., MD.)*

Pathophysiology

Penetration of human skin by cercariae induces a localized inflammatory response. The immunologic response is IgE-mediated histamine release. The degree of inflammation varies depending on previous exposure to and the numbers of penetrating cercariae. A primary exposure results in development of pruritic macules and papules within 1 to 2 days of infection, whereas infection in a previously sensitized individual results in transient eruption of macules inside of 20 minutes, followed by a papular and then vesicular eruption associated with intense pruritus in the following hours to days.[97] Once in human skin, these nonhuman cercariae are unable to develop further and are destroyed by the inflammatory infiltrate.

Histopathologically, the epidermis shows varying degrees of spongiosis. Extremely rarely, cercariae are found on histopathologic examination. Cercariae are located in the epidermis (Figure 76-41). There is edema of the upper dermis and superficial perivascular inflammatory infiltrate composed of lymphocytes, histiocytes, and eosinophils.[25] Histopathologically, swimmer's itch resembles arthropod assaults and seabather's eruption.

Clinical Presentation

Within minutes of cercarial penetration, tingling, burning, and itching appear. Initially, an erythematous macule develops, which promptly evolves into a papule. When the allergic response is severe, papules vesiculate (Figures 76-40 to 76-43). Without therapy, the eruption disappears in 7 to 14 days.[76] Exposed body surfaces are the primary areas of involvement, helping to differentiate this from seabather's eruption; however, covered surfaces may also be involved. Pruritus with scratching can lead to secondary infection. *Staphylococcus aureus* and *Streptococcus* species are the most common bacteria associated with secondary infection.

Differential Diagnosis

The differential diagnosis includes papular urticaria, arthropod assaults, nettle dermatitis, and *Toxicodendron* (poison ivy, poison oak, and poison sumac) contact dermatitis.

Diagnostic Tests

The complete blood count may show mild eosinophilia; otherwise, there are no specific diagnostic tests.

Treatment

Because the inflammatory response is self-limited, therapy need only be symptomatic. The use of over-the-counter antihistamines plus antipruritic lotions or creams (Table 76-2) is usually all that is needed. If moderate to severe dermatitis occurs, topical corticosteroid creams (see Table 76-1) in conjunction with oral corticosteroids (Table 76-3) may be indicated.[36] Secondary bacterial infection, depending on the degree and extent, is treated with topical antiseptic (mupirocin or bacitracin) ointment or cream or systemic antibiotics. An empirical trial of oral cephalexin or clindamycin may be indicated if secondary infection is severe.

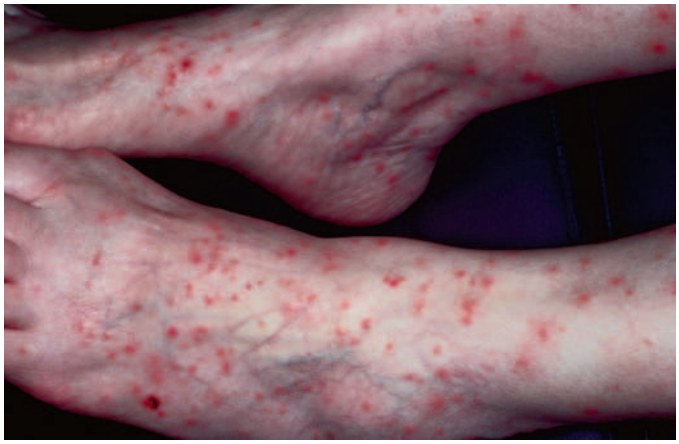

FIGURE 76-42 Schistosome cercarial dermatitis of the feet and ankles. *(Courtesy Edgar Maeyens, Jr., MD.)*

TABLE 76-3 Systemic Steroids

Steroid	Dose
Oral Steroid	
Prednisone	Dosing schedule A: 40 mg orally every morning for 7 days Dosing schedule B: 2-week tapering course starting at 35 mg orally every morning for 2 days; then decrease by 5 mg every 2 days
Intramuscular Steroid	
Kenalog (Triamcinolone)	40-60 mg deep intramuscularly into a large muscle mass (gluteus maximus)

Prevention

Methods to reduce the risk of cercarial dermatitis include the following[36,37]:

- Avoid wading or swimming in marshy areas and areas with dense vegetation, or other areas where snails are plentiful.
- Swim as far away from shore as safety allows, thereby minimizing exposure to vegetation and snails.
- Obey posted signs that indicate that water is unsafe.
- Use of waterproof sunscreens has been reported to prevent infestation.

CUTANEOUS LARVA MIGRANS

Definition

Cutaneous larva migrans (creeping eruption) is a superficial infestation of skin caused by the dog and cat hookworms *Ancylostoma braziliense, Ancylostoma caninum, Uncinaria stenocephala,* and *Bunostomum phlebotomum*.[74,145] Rarely, the human hookworms *Gnathostoma spinigerum* and *Strongyloides stercoralis* can cause similar findings. Although not directly related to water environs, this infestation may be acquired by humans while participating in water-related activities.

Epidemiology and Risk Factors

Ancylostoma braziliense larvae reside in the intestinal tract of dogs and cats. Second-stage, noninfectious larvae are excreted in feces and then mature in soil. Mature, third-stage infectious larvae are able to survive in sand or soil when adequate conditions prevail. Larvae penetrate the skin of humans who come in direct contact with such soil. The condition is more common among children living in warm, humid climates. Cutaneous larva migrans is the most common dermatologic disorder affecting vacationers to tropical countries.[83]

Pathophysiology

On percutaneous penetration, larvae migrate within the superficial dermis, causing a strong inflammatory reaction along the course of migration. Migration is random, forming curvilinear lines of edema and erythema. The leading edge is frequently vesicular. Larvae are rarely found on histopathologic examination, because they are usually 1 to 2 cm (0.4 to 0.8 inches) beyond the vesicle. Larvae are able to advance several centimeters a day (Figure 76-44). The inflammatory response is intensely pruritic.

Clinical Presentation

Larval penetration of the skin causes a tingling sensation, followed by pruritus, inflammation, and vesicle formation. As the larvae migrate, they leave in their wake a serpiginous, inflamed, and edematous tract. Common locations include the feet, buttocks, and back.[153] There may be a single tract or multiple tracts, or a folliculitis-like presentation. The folliculitis-like presentation occurs when multiple larvae penetrate the skin simultaneously in a localized area, such as the back of a person who had been lying on infested sand. Previously sensitized individuals develop an exaggerated allergic response with accentuation of all symptoms. Animal hookworm larvae do not survive in human skin and die in a few weeks, at which time there is spontaneous clearing of signs and symptoms.

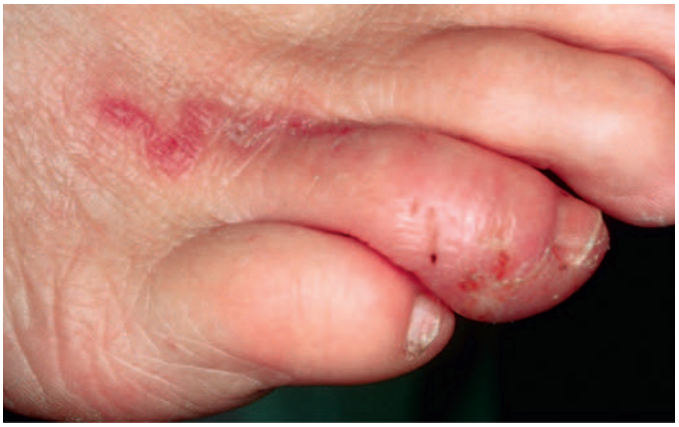

FIGURE 76-44 Cutaneous larva migrans. *(Courtesy Edgar Maeyens, Jr., MD.)*

Diagnostic Tests

Skin biopsies are nondiagnostic because larvae are virtually never found. Rarely, peripheral eosinophilia is present with a massive infestation or in a severely allergic person infested with numerous larvae.

Differential Diagnosis

The differential diagnosis of migratory skin lesions is either infectious or inflammatory. Infectious migratory diseases include: strongyloidiasis, myiasis, hookworm, gnathostomiasis, dracunculiasis, fascioliasis, sparganosis, erythema chronicum migrans, and dermatophytosis. Inflammatory dermatoses include photodermatitis and phytophotodermatitis.

Treatment

This is a self-limited infection; however, symptoms may persist for months if the infection is not treated early. Therapy for cutaneous larva migrans includes ivermectin 12 mg as a single dose, albendazole 400 mg daily for 5 to 7 days, or topical 10% thiabendazole (two 0.5-g tablets crushed and mixed with 10 g of petrolatum) twice a day until clear.[19,32,109,147,175] Antibiotics may be needed if secondary infection occurs.

Prevention

In sandy areas frequented by dogs and cats, do not sit or lie on damp sand or soil, especially during rainy season. Wear footgear in similar situations. Cover the ground with an impenetrable material before sitting or lying down.

LEECHES

Leeches are annelids of the class Hirudinea. Approximately 600 species have been identified. Many are blood-sucking endoparasites and ectoparasites that attach themselves to vertebrae hosts and suck blood.

Definition

Leeches vary in shape and color. They are typically cylindrical and elongated, but can be broadly ovoid. The ventral surface is flat and dorsal surface is convex. Leeches possess suckers at both anterior and posterior ends of their body. Sizes range from 5 mm to 45 cm (0.2 to 18.0 inches) in length. Colors vary from dark brown to black to brightly colored or mottled. The crop (stomach) of the leech can store up to five times its body size in blood. They are hermaphroditic or protandrous (at first male, than later female).[124]

Epidemiology and Risk Factors

Worldwide, there are many different types of leeches. They can be divided into freshwater, marine, and land leeches. The typical freshwater leeches attach themselves to humans and animals entering ponds or muddy-bottomed rivers. At the time of attachment, leeches secrete an adhesive mucoid substance enhancing suction power. They possess blade-like jaws having 60 to 100 small teeth. Land leeches live in the tropical rain forests of South America and southeast Asia on shrubs and under stones. Marine leeches live on and feed on fish.

The one leech known as an internal leech, *Limnatis nilotica,* is found in western Asia, northern Africa, and southern Europe. *L. nilotica* attaches to mucous membranes of the nasal pharynx and esophagus when ingested via contaminated water.

Pathophysiology

After attachment and beginning of feeding, leeches secrete at least three anticoagulants: seratin, hirudins, and ornatins.

Hirudins block collagen-mediated platelet activation. They are antithrombotic agents secreted from buccal glands. Seratin inhibits platelet-collagen interactions, and ornatins are glycoprotein IIb-IIIa antagonists and platelet aggregation inhibitors. Feeding is painless, as leeches secrete an analgesic substance currently not identified.[68,163] Spontaneous detachment occurs on engorgement, usually within an hour or less, leaving behind bleeding attachment sites. The anticoagulant effect lasts for up to 12 hours before spontaneous cessation of bleeding occurs.

Clinical Presentation

The telltale sign of having been parasitized by a leech is a puncture wound oozing blood. Puncture sites may become painful, erythematous, edematous, and pruritic.[114] Bacteria and viruses from prior blood feedings can survive within a leech and be transmitted to humans, thereby causing secondary infectious diseases.[128]

Treatment

Mechanical removal is the treatment. Remove the leeches carefully so as not to leave behind pieces of teeth in the skin. Leeches have very sensitive taste and smell receptors. The key to successful removal is breaking suction of the leech at each attachment site with little or no trauma to the organism. Too aggressive removal can cause regurgitation of crop contents and resultant infection. A drop of any essential oil near the mouthpart causes rapid release by the leech. Overzealous use of essential oils may cause the leech to regurgitate and potentially contaminate the attachment site. If without essential oils, use a fingernail or sharp object to break the sucker seals and cause the leech to release its jaws. Do not apply caustic chemicals, such as alcohol, or a lit cigarette to the leech, as these techniques can also result in regurgitation of stomach contents.[125] Do not forcibly pull off the leech, as this also may result in regurgitation. Cleanse puncture sites thoroughly with soap and water and observe for signs of infection. If oozing is continuous, apply a hemostatic dressing, such as QuikClot gauze, under pressure for 15 minutes.

Prevention

Protect skin from leech attachment by wearing or adjusting clothing when in leech-infested environs. "Leech socks" (any long, light-colored socks pulled over pant legs to allow visualization of leeches and prevent their attachment to skin) should be worn when walking in infested areas. These are light colored to allow visualization of ascending leeches.

Sequelae

Some individuals experience severe allergic reactions or even anaphylaxis from leech bites. Allergic reactions manifest locally as swelling and itching at the attachment sites or as generalized urticaria.

YEAST

PITYROSPORUM FOLLICULITIS

Definition

Pityrosporum folliculitis is a condition most commonly occurring in young or middle-aged adults characterized by follicular papulopustules involving the upper torso.[8] The condition is the result of overgrowth of normal skin yeast of the genus *Pityrosporum*. Two species commonly associated with *Pityrosporum* folliculitis are *Pityrosporum ovale* and *Pityrosporum orbiculare*. Together they are classified as *Malassezia furfur,* of which there are other group members making up the *M. furfur* complex.[103]

Pathophysiology

M. furfur is a lipophilic, dimorphic, gram-positive, double-walled, and saprophytic budding yeast.[8] Growth and proliferation occur in an environment rich in free fatty acids. Sebaceous glands produce triglycerides, which break down into free fatty acids. Any condition creating an increase in free fatty acids encourages proliferation of *M. furfur*.

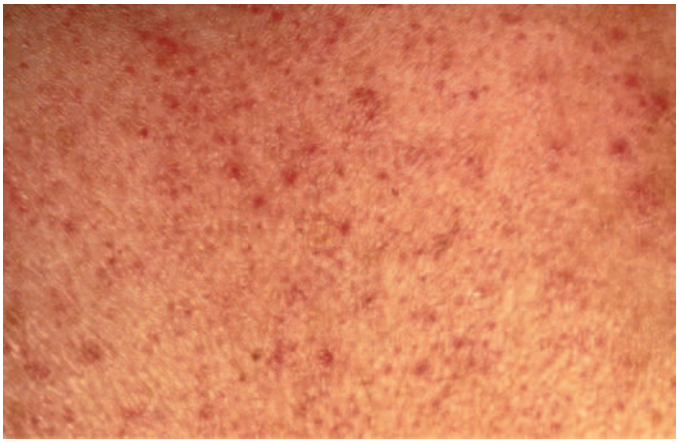

FIGURE 76-45 *Pityrosporum* folliculitis. Follicular papulopustules on the back of a scuba diver after his wetsuit had been removed. *(Courtesy Edgar Maeyens, Jr., MD.)*

Epidemiology and Risk Factors

The surface of normal skin is colonized by *Pityrosporum* in 90% to 100% of humans. Individuals living in humid and hot climates experience increased incidence of *Pityrosporum* folliculitis.[8] Conditions or agents facilitating overgrowth of these yeasts include cosmetics, sunscreens, body lotions, occlusive clothing, and having hot, moist skin from wearing wetsuits.[8]

Medical disorders that can predispose a person to *Pityrosporum* folliculitis include diabetes, leukemia, lymphoma, and immunodeficiency states.[27] Medications known to be associated with the occurrence of *Pityrosporum* folliculitis include antibiotics, anticonvulsants, immunosuppressants, and systemic steroids.[27] All of these medications tend to alter normal skin flora, thereby favoring yeast proliferation.

Clinical Presentation

Pityrosporum folliculitis manifests clinically as an acneiform eruption. The distribution is usually on the upper torso, and infrequently on the neck and face. The lesions are typically dome-shaped papules of 2 to 4 mm in diameter. Some papules are topped by tiny pustules. Pruritus is common (Figure 76-45).

Differential Diagnosis

Pityrosporum folliculitis closely resembles acne, but is unresponsive to acne therapy. *Pseudomonas* and *Staphylococcus* folliculitis are simulators.

Diagnostic Tests

Gram's stain of purulence from the follicular ostia reveals numerous yeast forms, and potassium hydroxide (KOH) preparation from a skin scraping may show a characteristic "spaghetti and meatball" appearance of the hyphae and spores. Skin biopsies stained with hematoxylin and eosin show numerous yeasts within the follicular ostia. Conventional culture techniques rarely detect *M. furfur* because the organism requires free fatty acids for growth.

Treatment

Treatment is with a topical antifungal or systemic antifungal, or both. Ketoconazole 2% cream or miconazole cream twice daily for a month, as well as twice weekly application of selenium sulfide shampoo, may be effective. For disease not responsive to topicals, oral itraconazole 200 mg daily for 7 days is effective.[134] Alternately, fluconazole prescribed either as 100 mg daily for up to 3 weeks may result in clearance.[144]

Prevention

When in hot and humid climates, wear light, loose-fitting clothing and avoid occlusive sunscreens and body lotions. After diving, remove wetsuits promptly, dry the skin thoroughly, and stay cool and dry.

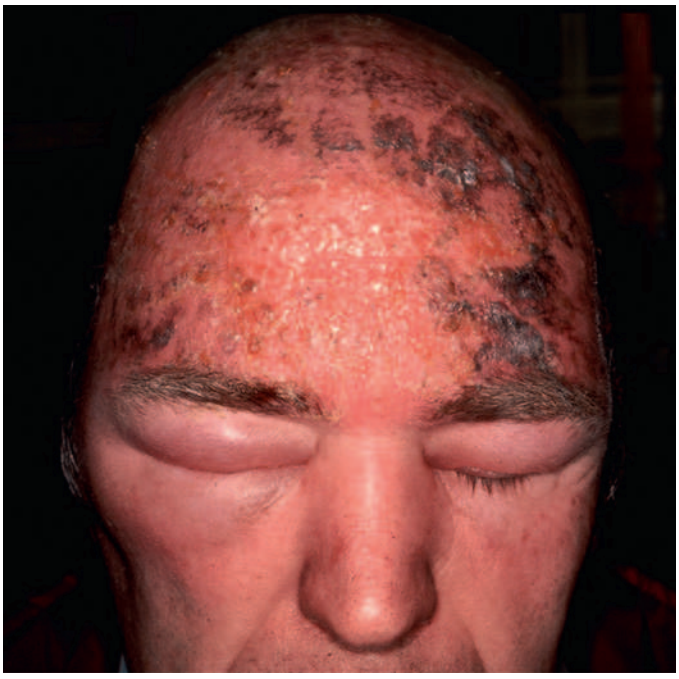

FIGURE 76-46 Severe allergic contact dermatitis secondary to a neoprene hood. *(Courtesy Edgar Maeyens, Jr., MD.)*

DERMATOSES RELATED TO DIVING

ALLERGIC CONTACT DERMATITIS

The use of wetsuits, masks, rubber mouthpieces, and swim gear predisposes a person to development of allergic contact dermatitis. Clinically, the majority of these allergic reactions manifest as clearly delineated areas of dermatitis of the body surfaces in contact with diving gear.

Definition

Allergic contact dermatitis related to diving gear is due to allergies to one of several chemicals used in the development and processing of rubber (Figure 76-46). Dermatitis associated with wetsuits can also be nonallergic, for example, intertrigo, maceration, and folliculitis.

Pathophysiology

Rubber is an organic substance obtained from plants or is artificially synthesized. More than 99% of the world's natural rubber is extracted from the *Hevea brasiliensis* tree. There are many types of natural and synthetic rubber, each with its unique processing technique and chemical content. Many chemical additives are potent allergens. Rubber itself does not cause allergic contact dermatitis. It is the chemical additives used to cure rubber that are the antigenic components of rubber products. Local heat, maceration, and perspiration enhance the potential for developing allergic contact dermatitis. Sensitivity is acquired most easily if the allergen is applied to damaged skin.

Clinical Presentation

Rubber allergic contact dermatitis is a cell-mediated immune response by T lymphocytes to the presence of inciting antigens. The onset of dermatitis becomes apparent hours after antigen exposure. Depending on an individual's previous antigen exposure and the degree of his or her rubber sensitivity, clinical manifestations will be more or less acute.

The acute phase of rubber dermatitis manifests as erythema, edema, pruritus, and vesiculation. In the context of neoprene diving suits, goggles, and so forth, dermatitis is clearly confined to areas of contact with rubber. Chronic allergic dermatitis is characterized by inflammation, pruritus, and cutaneous lichenification. Edema seen in chronic contact dermatitis is usually less than that of acute dermatitis and appears as diffuse thickening and accentuation of skin tension lines (Figures 76-46 to 76-48).

Differential Diagnosis

Irritant contact dermatitis due to direct chemical damage is the primary differential diagnosis. However, it has a different clinical spectrum than does allergic contact dermatitis. Acute irritant dermatitis can present in a spectrum from mild erythema and irritation to florid dermatitis with marked inflammation, edema, pain, and vesiculation. Onset of irritant contact dermatitis is rapid without delay, versus the relatively slow onset of allergic contact dermatitis.

Treatment

Basic methods of treatment apply regardless of whether the dermatitis is secondary to diving masks, goggles, mouthpieces, or wetsuits. Reversal of the T-cell–driven response is the objective. Whether inflammation is mucosal or cutaneous, the mainstay of therapy is removal or elimination of the inciting chemicals and suppression of the inflammatory response. For mild allergic reactions, topical corticosteroids are effective (see Table 76-1). Systemic corticosteroids, such as prednisone, are used to treat severe allergic reactions (see Table 76-3). Mucosal reactions, if with ulceration, respond to application of triamcinolone acetonide 0.1% in dental paste (Kenalog in Orabase) three times a day and at bedtime for 5 to 7 days, in addition to 10 to 20 mg oral prednisone for 2 to 3 days. Triamcinolone acetonide 40 to 60 mg deep intramuscularly may be needed for extensive blistering reactions. Systemic antihistamines provide symptomatic relief from pruritus (see Table 76-2). Secondary infection presents as purulence, pain, or lymphangitis.

Prevention

Avoidance of known allergen(s) is the only prevention.

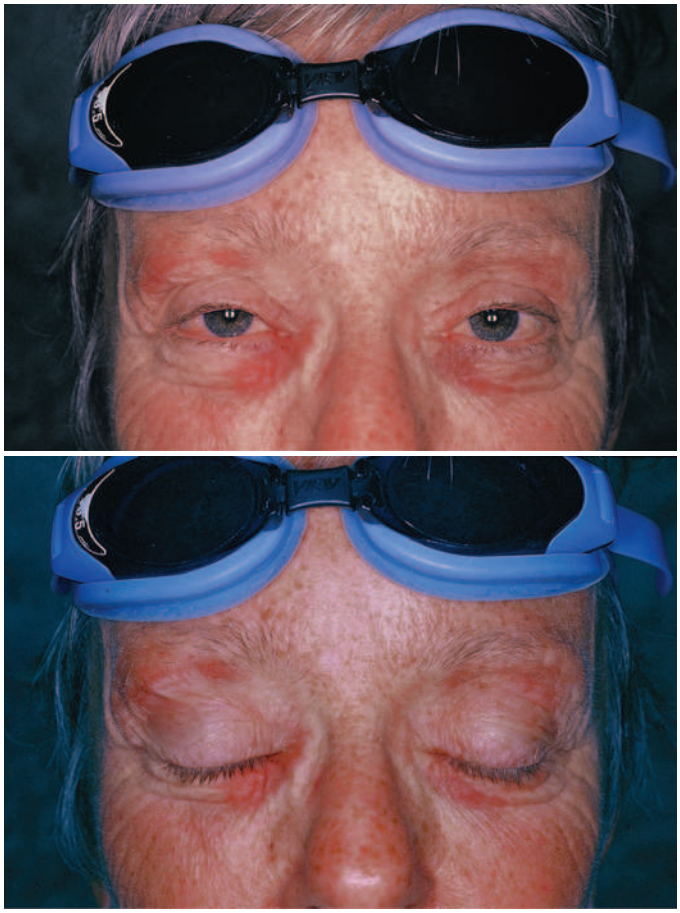

FIGURE 76-47 Allergic dermatitis. Periorbital allergic contact dermatitis from rubber goggles.

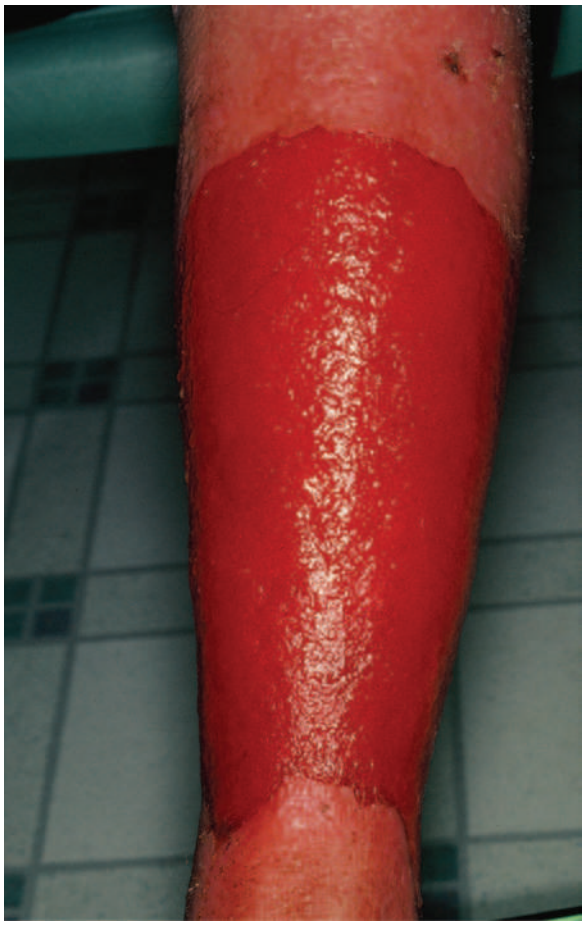

FIGURE 76-48 Allergic dermatitis. Allergic contact dermatitis of a leg caused by an elastic wrap. Notice the clear cut-off distribution of the dermatitis, differentiating this from a diffuse cellulitis.

CUTANEOUS DECOMPRESSION SICKNESS: AN OVERVIEW

Definition

Cutaneous decompression sickness (CDS) is defined as a disorder of the skin occurring in scuba divers or caisson workers as a consequence of depressurization. This results in bubbles forming in the skin from dissolved gases coming out of solution. CDS may occur as an isolated occurrence or in conjunction with other organ system "bubble diseases," such as decompression sickness with or without associated arterial gas embolism. Thermal cooling is also a contributory factor. Excessive skin gas pressure over ambient pressure (called gaseous supersaturation) is critical in development of bubbles occurring during or after ascent from depth. Once bubbles form, they may initiate the release of inflammatory mediators, obstruct vascular or lymphatic vessels, or directly or indirectly stimulate the release of neurotransmitters.

Epidemiology and Risk Factors

Although there is little written about the rates of CDS, in a study of more than 5000 patients treated at a Chinese hyperbaric unit, cutaneous abnormalities were the most common symptom of decompression sickness.[194] Additionally, a majority of divers who suffer from CDS also have a right-to-left cardiac shunt, typically as a patent foramen ovale, although some have pulmonary shunts.[187]

Pathophysiology

Tissue solubility of compressed gases varies. Nitrogen is highly lipid soluble. After a person dives while breathing nitrogen, the greatest amounts of this dissolved gas are deposited in lipid-rich tissues, which become supersaturated. The rash of CDS clinically favors body areas with larger amounts of subcutaneous fat, such as the trunk, thighs, abdomen, arms, and buttocks. The precise pathophysiology of CDS remains unverified. In one proposed scenario, for individuals with a right-to-left cardiac shunt, the mechanism may be due to venous microbubble emboli entering the arterial circulation. Upon entering the circulatory system, bubbles are absorbed into tissues and/or amplified peripherally, becoming emboli. Buttolph and colleagues used a swine model to study CDS, and were able to demonstrate vascular congestion on tissue histology as the most common finding.[27] They also described neutrophil adhesion to vessel walls and vascular occlusion. They demonstrated a perturbation of the endothelium or neutrophils, or both. These authors concluded that "the marbling or cutis marmorata forms of cutaneous presentations in CDS are principally vascular congestion, possibly as a result of inflammation."[27]

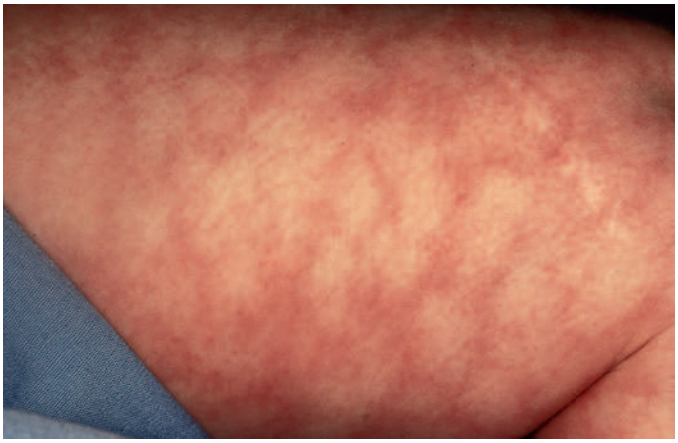

FIGURE 76-49 Cutis marmorata. *(Courtesy Edgar Maeyens, Jr., MD.)*

Clinical Presentation

Clinically this condition presents as a broad, purple marbled, or mottled appearance of the skin and is usually confined to parts of the body with larger amounts of subcutaneous fat, in particular the trunk and thighs. If the diver experiences CDS in future dives, the same sites are typically involved.[187] Clinical manifestations include itching and varying degrees of pain. The term cutis marmorata is often used erroneously to describe CDS. True cutis marmorata presents as a reddish-blue reticulated vascular pattern surrounding central pale areas. The cause of this process involves cooling of the skin and subcutaneous fat with subsequent vasodilation of the deep dermal venous plexus and contraction of superficial arterioles and venules, not gas emboli. This is a transient, asymptomatic normal physiologic process that occurs with drops in ambient temperatures (Figures 76-49 and 76-50). In contrast, CDS almost universally demonstrates an erythematous, blotchy appearance. Depending on the location of the bubbles, cutaneous manifestations vary. For example, when bubbles are present in larger vessels of the deep dermis or subcutaneous

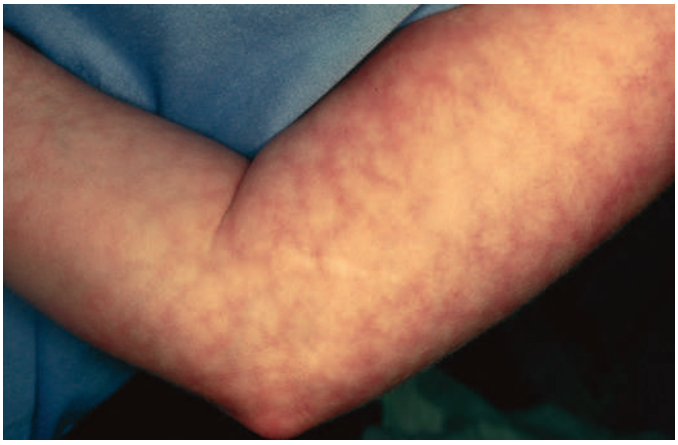

FIGURE 76-50 Cutis marmorata. *(Courtesy Edgar Maeyens, Jr., MD.)*

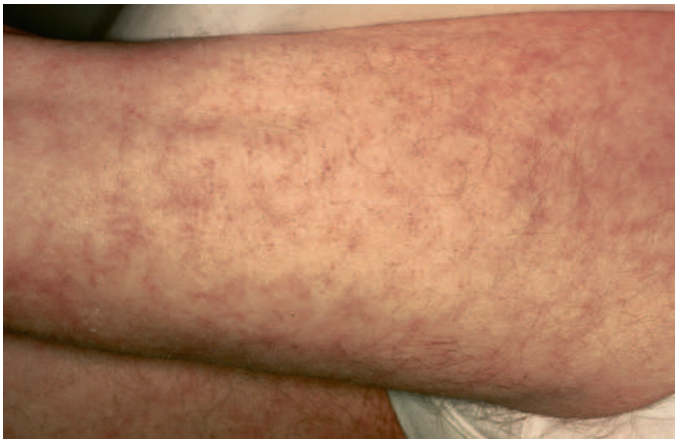

FIGURE 76-51 Marbling of the thigh in cutaneous decompression sickness. *(Courtesy Edgar Maeyens, Jr., MD.)*

tissue, the clinical presentation is that of marbling (Figure 76-51). If the capillaries or venules of the superficial plexus are affected, the skin develops blotchy erythema (Figure 76-52).

Treatment

The initial response is first-aid treatment by having the diver breathe 100% oxygen. Definitive therapy is recompression to increased pressure while the diver breathes 100% oxygen[176] (see Chapter 71).

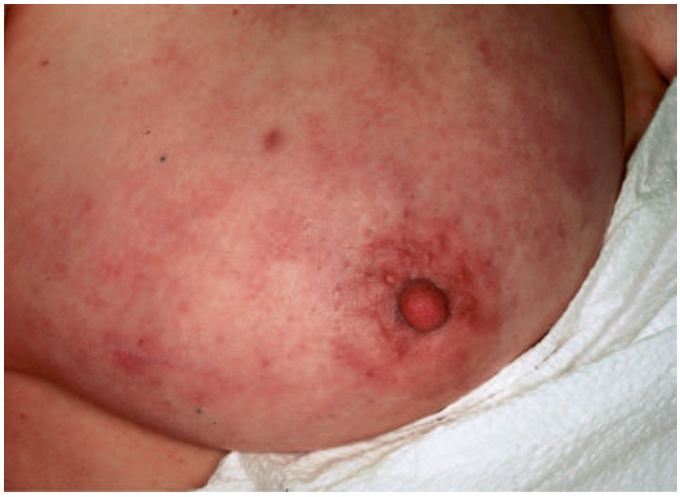

FIGURE 76-52 Blotchy erythema of the breast in cutaneous decompression sickness. *(Courtesy Edgar Maeyens, Jr., MD.)*

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CHAPTER 77
Seafood Toxidromes

ALICIA B. MINNS, MICHAEL J. MATTEUCCI, BINH T. LY, AND RICHARD F. CLARK

At least three-quarters of the world's population live within 10 miles (16 km) of a coast. One of many reasons why populations congregate near the sea is the abundance of food beneath the ocean's surface. Seafood provides a significant percentage of the protein in the diets of many cultures. Presently, 200 to 240 million tons of fish are harvested each year, with 50% of the total coming from coastal regions. Per capita fish consumption has increased in recent decades. Americans consume 7.3 kg (16.4 lb) of fish per person per year.[190] The ocean is one of our last plentiful food resources. International trade has dramatically increased year-round availability of assorted seafoods, many of which come from distant geographic locations.[446]

Throughout time, humans have recognized that toxic seafood is associated with seasons of the year, phases of the moon, water temperature, weather conditions, waterfowl deaths, the color of waves that wash onto shore, and many other circumstances. Unfortunately, none of these factors has proven entirely reliable in predicting when seafood poisoning occurs.

Marine creatures whose consumption can lead to poisoning include dinoflagellates, coelenterates, mollusks, echinoderms, crustaceans, fishes, turtles, and mammals. Most marine biotoxins are naturally occurring poisons derived directly from marine organisms, including phytotoxins (plant poisons) and zootoxins (animal poisons). Ingestible toxins may be classified by specific toxin or by the donor organ of origin ingested by the victim. *Ichthyosarcotoxin* is a general term for poison derived from the fresh flesh (muscle, viscera, skin, or slime) of any fish. The geographic location, dietary and clinical histories, and appropriate index of suspicion figure prominently in diagnosis and treatment of fish poisoning.

Data on food-borne disease outbreaks in the United States show that fish are the vehicle of transmission in 19% of cases, mollusks in 7%, and crustaceans in 4%.[81] Some 90% of outbreaks of seafood-related illnesses and 75% of individual cases come from contaminated raw molluscan seafood (e.g., oysters, clams), histamine poisoning (scombroid), and ciguatoxin found in reef fish species.[349] In general, marine toxins are heat stable and largely unaffected by cooking. Marine poisoning causes mostly gastrointestinal and neurologic symptoms. Many marine toxins target voltage-gated sodium channels in myelinated and unmyelinated nerves, resulting in a range of peripheral neurologic effects.[226]

MONITORING MARINE ALGAE THAT PRODUCE PHYTOTOXINS AND SEAFOOD THAT MAY CAUSE POISONING

Despite the increasing risk of human poisoning from contaminated seafood, standards and methods of screening and law enforcement vary worldwide.[497] According to the U.S. Department of Agriculture, imports account for more than 55% of total U.S. seafood consumption. The largest sources of seafood

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imported into the United States are Canada, Asia, and Latin America. The U.S. Food and Drug Administration (FDA) has been criticized for inadequate inspection of all food imports.[349] In 1995, the FDA switched to a new program for seafood safety known as the Hazard Analysis and Critical Control Point (HACCP) system. This program became mandatory for the seafood industry on December 18, 1997.[155] The HACCP focuses on the following: (1) identification of sources and points of contamination; (2) levels of the hazard(s) of concern, transmission rate, and transport of microorganisms; and (3) possibility of exposure of the consumer to the contaminant. The HACCP concentrates on preventing hazards rather than relying on spot checks and random sampling of products. The most effective control strategies can then be implemented. For shellfish- and virus-associated diseases, data suggest that harvesting from unapproved sources is associated with more than 30% of outbreaks.[301] Among imports, the biggest risks relate to histamines and scombroid poisoning, mainly from tuna and mahi-mahi imported from Argentina, Taiwan, and Ecuador. For foods traveling great distances, refrigeration is the most critical aspect of controlling illness. Although there has been progress in improving standards for imported seafood in the United States, only 5% to 7% of the 8500 firms importing seafood in the country during 2002 and 2003 were inspected by regulators.[114]

The United States is the second largest importer of shrimp worldwide. Shrimp aquaculture currently accounts for approximately 30% of the world's supply. The FDA has amended the food additive regulations to provide for the safe use of ionizing radiation for control of food-borne pathogens in fresh or frozen molluscan shellfish.[156]

Molluscan poisoning is mainly a problem with domestic seafood. In 1991, California was the first state to require restaurants that serve or sell Gulf Coast oysters to warn prospective customers about possible deleterious effects from *Vibrio* contamination, particularly *Vibrio vulnificus*.[389] Other states have since adopted these warning regulations. In addition, fishermen are now required to refrigerate oysters within 6 hours after harvesting from the Gulf of Mexico. Regulations require oyster lot tagging, labeling, and record retention to facilitate trace-back investigations of outbreaks. The United States and Canada allow the sale of oysters if there are less than 10,000 colony-forming units per gram (CFU/g) of *Vibrio parahaemolyticus*. However, in outbreaks in the Pacific Northwest in 1997 and New York in 1998, oysters had less than 200 *V. parahaemolyticus* CFU/g of oyster meat, suggesting that human illness can occur at lower levels.[77]

Approximately one-third of U.S. shellfish beds carry bans or limitations on harvesting because of high levels of fecal coliform bacteria. The fecal indicator system for shellfish-harvesting waters has been effective in protecting consumers against general types of bacteria in fecal contamination. However, several pathogenic bacteria are not predicted by the system. The efficacy of methods for virus recovery may range from 2% to 47%.[517] The most promising of the new detection methods are based on molecular techniques. Deoxyribonucleic acid (DNA) hybridization and polymerase chain reaction (PCR) have the advantages of specificity for particular pathogens, sensitivity, and speed (most assays are completed within a few hours). The PCR has been used in shellfish to detect *Salmonella, Vibrio* species, and viruses, including hepatitis A virus and norovirus. High-performance liquid chromatography (HPLC) has also been used to detect and quantify many shellfish toxins.[18,23,105,289,375,418] Phytotoxin-producing marine algae are responsible for the syndromes of paralytic, neurotoxic, and diarrhetic shellfish poisoning. Closure of fisheries (product harvest areas) depends on the density of algae. In some cases, the decision to close a fishery is based on the toxicity level in shellfish; in others, algae in the water and toxin in shellfish must both be found. In Florida, more than 5000 cells/L of *Ptychodiscus brevis* must be detected before fisheries are closed. The quarantine level of saxitoxin (a neurotoxin found in marine dinoflagellates) varies between countries and ranges from 40 to 80 mg of toxin per 100 g (3.5 oz) of seafood, as determined through mouse bioassay.[21] The higher number is used in the United States and is monitored by the Interstate Shellfish Sanitation Conference and the FDA.

The maximal acceptable concentration of diarrhetic shellfish toxin (okadaic acid) also varies between countries because of lack of precise analytic methods for quantification. Countries with established regulations apply 4 to 5 mouse units or 20 to 25 mg equivalents of okadaic acid as an acceptance limit. In the United Kingdom, the Ministry of Agriculture, Fisheries, and Food shellfish surveillance program tests harvested shellfish weekly from April to October and sporadically during the winter for the presence of toxins.[421] The United States, Canada, and Portugal monitor for domoic acid (the cause of amnesic shellfish poisoning) and use 2 mg/100 g of seafood as the threshold. Ciguatoxins are monitored infrequently because of difficulties associated with the assay. In French Polynesia, ciguatoxin at 0.06 ng/g of seafood as determined by mosquito bioassay is considered toxic; in the United States (Florida, Hawaii), detection of the toxin at any level by immunoassay renders the fish unmarketable. Two primary features render toxin surveillance difficult: performance problems of the assays and impracticality of surveying every fish.

SUSTAINABLE AND SAFE SEAFOOD INITIATIVES

Recently, there have been numerous initiatives by private nonprofit organizations to promote practices that will result in sustainable fisheries, restoration of marine ecosystems, and safer seafood arriving to markets. These initiatives include the industry-centric FishWise (fishwise.org), which encourages sustainable use of fisheries by educational and certification programs primarily directed toward producers/harvesters, distributors, and retailers in the industry. In addition, FishWise periodically publishes an updated list of fish containing a low level of mercury that is useful for both consumers and industry (Box 77-1). Other initiatives, such as those by the Blue Ocean Institute (blueocean.

BOX 77-1 Fish Containing a Low Level of Mercury*

Abalone (United States farmed)
Arctic char†* (farmed)
Catfish (farmed)
Clams
Cod, black/sablefish,† Pacific† (United States and Canada)
Crab, Dungeness/king/Tanner/snow (United States and Canada)
Crawfish (United States farmed)
Flounder, arrowtooth/starry (United States and British Columbia, Canada)
Haddock (United States handline)
Hake (United States Atlantic)
Halibut (Pacific†)
Herring (United States Atlantic)
Lobster, American (United States and Canada)
Lobster, spiny (United States, Mexico [Pacific], and Bahamas)
Mackerel (United States Atlantic)
Mahi-Mahi (United States and international handline)
Mussels, blue† (farmed)
Oysters (Pacific, Eastern-wild†)
Pollock† (United States)
Salmon (Alaska-wild† and British Columbia, Canada†)
Sardines (Pacific†)
Scallops (United States wild and farmed)
Sea bass, black† (north of North Carolina)
Shrimp† (United States and Canada)
Sole (English†)
Squid†
Tilapia† (United States, South and Central America farmed)
Trout (United States farmed, Rainbow†)
Tuna, albacore (United States and Canada [Pacific], international handline)
Tuna, skipjack (United States and international handline)
Tuna, tongol (Malaysian and international handline)
Tuna, yellowfin (Handline)

*See fishwise.org for further information.
†These fish are also low in polychlorinated biphenyls.

BOX 77-2 Representative Ichthyocrinotoxic Fish Hazardous to Humans

Phylum Chordata
Class Agnatha
Order Myxiniformes: hagfishes, lampreys
Family Myxinidae
Myxine glutinosa: Atlantic hagfish
Petromyzon marinus: sea lamprey, large nine-eyes
Class Osteichthyes
Order Anguilliformes: eels
Family Muraenidae
Muraena helena: moray eel
Order Perciformes: perch-like fishes
Family Serranidae
Grammistes sexlineatus: golden striped bass
Rypticus saponaceus: soapfish
Order Tetraodontiformes: triggerfishes, puffers, trunkfishes
Family Canthigasteridae
Canthigaster jactator: sharp-nosed puffer
Family Diodontidae
Diodon hystrix: porcupinefish
Family Ostraciontidae
Lactoria diaphana: trunkfish
Lactoria fornasini: trunkfish, boxfish
Family Tetraodontidae
Arothron hispidus: puffer, toadfish, blowfish, rabbitfish
Fugu xanthopterus: puffer
Order Batrachoidiformes: toadfishes
Family Batrachoididae
Opsanus tau: oyster toadfish
Thalassophryne maculosa: toadfish

org), include a more consumer-based focus with educational outreach that includes smartphone applications that provide instant, color-coded guides to sustainable seafood.

ICHTHYOSARCOTOXISM

The term *ichthyosarcotoxism* describes a variety of conditions arising as the result of poisoning by fish flesh. Many toxins are generally not destroyed by heat or gastric acid. Various toxins are found in the musculature, viscera, blood, skin, or mucous secretions of the fish. Further classification is based on the specific organ system poisoned, for example, ichthyocrinotoxins (glandular secretions), ichthyohemotoxins (blood), ichthyohepatotoxins (liver), ichthyootoxins (gonads), ichthyoallyeinotoxins (hallucinatory), and gempylotoxins (purgative).

ICHTHYOCRINOTOXICATION

Ichthyocrinotoxic fish poisoning is induced by ingestion of glandular secretions not associated with a specific venom apparatus; this usually involves skin secretions, poisonous foams, or slimes. Examples of these toxic fish are certain filefish, pufferfish, porcupinefish, trunkfish, boxfish, cowfish, lampreys, moray eels, and toadfish (Box 77-2). Cyclostome poisoning results from ingestion of the slime and flesh of certain lampreys and hagfishes. Pahutoxin and homopahutoxin have been isolated from secretions of the Japanese boxfish *Ostracion immaculatus*.[163]

Ichthyotoxic skin secretions may cause a bitter taste.[183] Ingestion of ichthyocrinotoxins causes gastrointestinal symptoms within a few hours of ingestion, characterized by nausea, vomiting, dysenteric diarrhea, tenesmus, abdominal pain, and weakness. Most victims recover within 24 hours; however, some individuals have symptoms for up to 3 days. Therapy is supportive and based on symptoms. Additionally, some slime, such as "grammistin" from the soapfish (*Rypticus saponaceus* of the family Grammistidae), can cause contact irritant dermatitis.[209] This dermatitis is managed with cool compresses of aluminum sulfate and calcium acetate (Domeboro). All suspect fish should be washed carefully with water or brine solution and skinned before being eaten.

ICHTHYOHEMOTOXICATION

Ichthyohemotoxic fish are perfused with "poisonous blood," the toxicity of which is usually inactivated by heat and gastric juice. Examples are various eels, such as morays, anguilliforms, and congers. The syndrome is predominantly gastrointestinal and should be treated according to symptoms. Hematologic complications are rare. Risk of intoxication is increased by ingestion of raw or undercooked fish.

ICHTHYOHEPATOTOXICATION

Ichthyohepatotoxic fish carry toxin predominantly in the liver. The remainder of the fish may be nontoxic. Fish that are always toxic fall into two basic groups: (1) Japanese perch–like fish (e.g., mackerel, sea bass, porgy, sandfish) and (2) tropical sharks (e.g., requiem fish, sleeperfish, cowfish, great white shark, catfish, hammerhead, angelfish, Greenland fish, dogfish).[371] Some skates and rays, whose phylogeny is similar to that of sharks, harbor ichthyohepatotoxins.

Ingestion of the Japanese perch–like fish group causes an onset of symptoms within the first hour, with maximal intensity over the ensuing 6 hours.[445] Symptoms include nausea, vomiting, headache, flushing, rash, fever, and tachycardia. No fatalities have been reported.

Ingestion of tropical shark liver (and occasionally of the musculature), such as that of the Greenland shark *(Somniosus microcephalus),* results in "elasmobranch poisoning" (Box 77-3).[25] Symptoms are noted within 30 minutes of ingestion and include nausea, vomiting, diarrhea, abdominal pain, malaise, diaphoresis, headache, stomatitis, esophagitis, muscle cramps, arthralgias, paresthesias, hiccups, trismus, hyporeflexia, ataxia, incontinence, blurred vision, blepharospasm, delirium, respiratory distress, and coma; death may ensue. Recovery varies from several days to weeks. If only the flesh is eaten, the symptoms are mild and gastroenteric, with spontaneous resolution.

In 1993, 200 people in Madagascar were poisoned after ingesting a single shark identified as *Carcharhinus leucas*. They all experienced symptoms, and 30% died. Two lipophilic toxins were isolated from the shark liver and named carchatoxin-A and carchatoxin-B.[47] Trimethylamine oxide, found in shark liver and

BOX 77-3 Representative Poisonous Sharks (Elasmobranchs) Hazardous to Humans

Phylum Chordata
Class Chondrichthyes
Order Squaliformes: sharks
Family Carcharhinidae
Carcharhinus melanopterus: blacktip reef shark
Carcharhinus menisorrah: gray reef shark
Galeocerdo cuvier: tiger shark
Prionace glauca: blue shark
Family Dalatiidae
Somniosus microcephalus: Greenland shark, sleeper shark, nurse shark
Family Hexanchidae
Hexanchus griseus: cow shark, gray shark, mud shark
Family Isuridae
Carcharodon carcharias: white shark
Family Scyliorhinidae
Scyliorhinus canicula: dogfish, lesser-spotted cat shark
Family Sphyrnidae
Sphyrna diplana: hammerhead shark
Family Squatinidae
Squatina dumeril: monkfish, angel shark
Family Triakidae
Triaenodon obesus: white-tip houndshark

flesh, has also been implicated in shark poisoning.[14] A similar syndrome has occurred in sled dogs that ingest large quantities of shark flesh.

Therapy is supportive and based on symptoms. If the victim is treated within 60 minutes of ingestion of the shark liver or other viscera, gastrointestinal decontamination with activated charcoal (50 to 100 g [1.8 to 3.6 oz]) may be of value. Fish liver or any shark viscera should not be eaten. However, drying the flesh properly may minimize toxicity.

ICHTHYOOTOXICATION

Ichthyootoxic fish possess toxic gonads that may vary in toxicity with the reproductive cycle. The musculature is generally nontoxic. Examples are sturgeon, alligator gar, salmon, pike, minnow, carp, catfish, killifish, perch, and sculpin. Sea urchins may be toxic during the reproductive period.[25] This toxicity is exemplified by *Paracentrotus lividus* (Europe), *Tripneustes ventricosus* (West Africa), and *Diadema antillarum* (West Indies). Heat does not inactivate the toxin.

Symptoms begin within an hour of ingestion and include nausea, vomiting, diarrhea, headache, dizziness, fever, thirst, xerostomia, bitter taste, tachycardia, seizures, paralysis, and hypotension; death occasionally occurs. Treatment is supportive and based on symptoms. The roe of any fish should not be eaten during the reproductive season.

ICHTHYOALLYEINOTOXICATION

Ichthyoallyeinotoxic fish induce hallucinatory fish poisoning. These are predominantly reef fish of the tropical Pacific and Indian reefs; they carry these heat-stable toxins mainly in the head, brain, and spinal cord and in lesser amounts in the musculature. Typical species include surgeonfish, chub, mullet, unicornfish, goatfish, sergeant major fish, grouper, rabbitfish, rock cod, drumfish, rudderfish, and damselfish. Hallucinatory mullet poisoning has been described as a seasonal condition that occurs only during the summer months in restricted areas on the Hawaiian islands of Kauai and Molokai.[211] Symptoms can develop within 5 to 90 minutes of ingestion and include dizziness, circumoral paresthesias, diaphoresis, weakness, incoordination, auditory and visual hallucinations, nightmares, depression, dyspnea, bronchospasm, brief paralysis, and pharyngitis.[25] No fatalities have been reported. Various toxins, including indoles akin to lysergic acid diethylamide, have been implicated, the sources being algae and plankton eaten by the fish.[438] Heating the fish does not appear to lessen the severity of poisoning.

Therapy for ichthyoallyeinotoxic fish poisoning is supportive and based on symptoms. Haloperidol or benzodiazepines may be administered if the victim is agitated, psychotic, or violent. The victim should be observed until normal mental status is regained. The head, brain, or spinal cord of any tropical fish should not be eaten.

GEMPYLOTOXICATION

Gempylotoxic fishes are pelagic mackerels that produce an oil with a pronounced purgative effect. The "toxin" is contained in both the musculature and bones. No particular characteristic distinguishes a gempylotoxic fish from a nontoxic fish of the same species. The castor oil fish *(Ruvettus pretiosus)* is named for its purgative properties.

The victim suffers from abdominal cramping, bloating, mild nausea, and diarrhea, usually within 30 to 60 minutes of ingestion. The disorder is self-limited and resolves in 12 to 18 hours. Diarrhea often occurs without concomitant systemic effects. Fever, bloody or foul-smelling stools, or protracted vomiting suggest infectious gastroenteritis. No specific antidote is available. If the victim cannot tolerate oral fluids because of nausea or severe abdominal cramping, administration of intravenous fluid and antiemetics may be indicated. Antimotility agents are not recommended unless the diarrhea is debilitating because inhibition of peristalsis prolongs transit time of the toxin through the gut and may increase the duration of the disorder.

SPECIFIC TOXIC SYNDROMES RELATED TO SEAFOOD CONSUMPTION

Three specific toxic syndromes related to fish consumption are scombroid poisoning, tetrodotoxin (puffer fish) poisoning (both described in Table 77-1) and grass carp gallbladder poisoning.

SCOMBROID POISONING

Scombroid, the most commonly reported seafood poisoning in the United States, occurs after eating fish with high levels of accumulated histamine or other biogenic amines. The first report of scombroid poisoning was published in 1830 and involved five sailors who consumed bonito fish, a member of the Scombridae family; hence the name of the syndrome.[285] Other members of the family Scombridae include albacore, bluefin and yellowfin tuna, mackerel, saury, needlefish, wahoo, and skipjack. Fish not from the Scombridae family that can produce scombroid include mahi-mahi (dolphinfish), kahawai, sardine, black marlin, pilchard, anchovy, herring, amberjack (yellowtail or kahala), and the Australian ocean salmon *Arripis truttaceus*.[322,428,443,471] Most of these fish species are rich in free histidine in their muscle tissues.[222] Scombroid poisoning accounts for 3% of food-related outbreaks reported to the Centers for Disease Control and Prevention (CDC) in Atlanta.[79] Underreporting is likely because of the short duration of illness and its resemblance to an allergic reaction. Because greater numbers of fish that were previously considered not to be a risk for scombroid poisoning are now recognized as potentially "scombrotoxic," it has been suggested that the syndrome be more appropriately called *pseudoallergic fish poisoning*.[388]

Pathophysiology

During conditions of inadequate preservation or refrigeration, the musculature of dark-fleshed or red-muscled fish undergoes bacterial decomposition.[33,371] The normal surface bacteria *Proteus morganii, Klebsiella pneumoniae, Aerobacter aerogenes, Escherichia coli, Alcaligenes metalcaligenes,* and others have been implicated in the putrefactive process, which includes decarboxylation of the amino acid L-histidine to histamine and saurine (a phosphate salt of histamine).[471,551] This most often occurs when fish is held at ambient or high temperatures for several hours.[114] The term *saurine* originated because of association of scombrotoxism with saury, a Japanese dried fish delicacy.[220] Because of this process, the "scombrotoxin" was initially thought to be histamine, which is commonly found in large amounts in the flesh of the fish usually implicated. Evidence initially suggesting that histamine may be the causative toxin of scombroid fish poisoning was presented in an investigation of a small outbreak.[336] The urinary excretion of histamine and its metabolite, *N*-methylhistamine, was measured in three persons who had scombrotoxism after ingestion of marlin. There was no increase in the principal metabolite of prostaglandin D_2 (a mast cell secretory product considered to indicate release of histamine from mast cells), supporting the hypothesis that the excess histamine was from the fish rather than endogenously produced in the victims. Histamine levels greater than 20 to 50 mg/100 g are frequently noted in scombrotoxic fish, and it is not unusual to record levels in excess of 400 mg/100 g.[428] However, it is possible that some other compound may be responsible for scombroid symptoms, because the syndrome cannot be reproduced solely by administration of equal or even massive doses of histamine by the oral route. Histamine is rapidly inactivated by enzymes in the gastrointestinal tract and on first pass through the liver, with very little reaching the systemic circulation. Other compounds, such as cadaverine, putrescine, or *cis*-urocanic acid, may be present in the decomposed fish flesh and may either facilitate absorption or inhibit gastrointestinal or hepatic degradation of histamine.[43,407,471] Whatever the causative toxin, it is heat stable and not destroyed by cooking. Affected fish typically have a sharply metallic or peppery taste but may be normal in appearance and color. Not all persons who eat a scombrotoxin- or histamine-contaminated fish become

TABLE 77-1 Seafood Toxidromes

Toxidrome	Seafoods	Regions	Causative Organisms	Toxins Produced	Mechanisms of Action	Clinical Manifestations	Time of Symptom Onset After Ingestion	Duration of Illness	Treatment
Fish-Related Toxic Syndromes									
Scombroid	Albacore, tuna, wahoo, mackerel, skipjack, bonito, mahi-mahi	Worldwide	Presumably, bacteria within the fish transform histidine to histamine	Histamine, saurine	Histamine response	Diffuse erythema, flushing, nausea, vomiting, pruritus, headache, urticaria, bronchospasm	Minutes	Resolves in 8-12 hr	Histamine-1 and -2 blockers, antiemetics
Tetrodotoxin	Puffer fish (fugu), porcupinefish, sunfish	Tropical and subtropical	*Pseudomonas* species	Tetrodotoxin	Na^+ channel blocker, blocks axonal transmission	Paresthesias of lips and tongue, hypersalivation, weakness, ataxia, tremor, dysphagia, seizure, bronchospasm, hypotension, nausea, vomiting, diarrhea, death	10 min to 4 hr	Hours to days	Supportive, aggressive airway management, intravenous fluids, inotropic agents, ? anticholinesterase agent
Algal Bloom–Related Toxic Syndromes									
Ciguatera	Tropical and semitropical reef fish such as barracuda, grouper, snapper, jack	Worldwide, most common in Indian Ocean, South Pacific, Caribbean	*Gambierdiscus toxicus* and other species	Ciguatoxin, maitotoxin, GT1-4, palytoxin	Na^+ channel blocker	Gastroenteritis followed by neurologic symptoms: dysesthesias, hot/cold reversal, weakness, respiratory paralysis	2-6 hr	Days to months	Supportive, ? intravenous mannitol
Clupeotoxin	Herring, sardines, anchovies, tarpons, bonefish	Caribbean, Indo-Pacific, Africa	*Ostreopis siamensis*	Palytoxin	Inhibits Na^+,K^+-ATPase	Metallic taste, nausea, vomiting, diarrhea, paresthesias, hypotension, death	30-60 min	Days	Supportive, ? early gastric emptying
Paralytic shellfish poisoning	Shellfish	Northeast and northwest coasts of United States, Philippines, Alaska, North Sea	*Protogonyaulax, Alexandrium catarella, Pyrodinium, Saxidomus, Gonyaulax*	Saxitoxin, neosaxitoxins, gonyautoxins	Na^+ channel blocker, may suppress atrioventricular nodal conduction	Paresthesias of face and extremities, numbness, dysphonia, dysphagia, ataxia, weakness, paralysis, death from respiratory failure	30-60 min	Weeks	Supportive, activated charcoal, ventilatory support

Neurotoxic shellfish poisoning	Shellfish	Gulf of Mexico, Florida, Texas, North Carolina, New Zealand	*Ptychodiscus brevis*	Brevetoxins	Modulate Na^+ channel	Circumoral paresthesias, ataxia, gastrointestinal symptoms; if aerosolized, may cause conjunctivitis, bronchospasm	Minutes to hours	Several hours to a few days	Supportive
Diarrhetic shellfish poisoning	Shellfish	Japan, Spain, The Netherlands, Chile	*Dinophysis, Prorocentrum*	Okadaic acid and others	Phosphatase A_1 and A_2 inhibitors	Acute gastroenteritis	30 min-2 hr	2-3 days	Supportive
Amnestic shellfish poisoning	Shellfish	Canada, Japan, northeast and northwest coasts of United States	*Nitzschia pungens, Pseudonitzschia australis*	Domoic acid	Glutamate antagonist	Gastroenteritis, seizures, coma, anterograde memory disorder	1-24 hr	24 hr-12 wk	Supportive, benzodiazepines for seizures
Possible estuary-associated syndrome	Estuarine fish	Coastal waterways in eastern United States and Gulf Coast	*Pfiesteria piscicida*	Unidentified	Unknown	Headache, skin lesions, eye irritation, respiratory irritation, learning and memory deficits, cognitive impairment	Within 2 wk of exposure	Improves within 3-6 mo	No treatment; cholestyramine for persistent symptoms
Haff disease	Buffalo fish	United States, Russia, Sweden	? Blue-green algae	Unknown	Unknown	Severe muscle pain, rhabdomyolysis, weakness, tachycardia, hypotension	6-12 hr	Days	Supportive, intravenous fluids, ? diuretics
Azaspiracid poisoning	Shellfish	Europe, United States	*Azadinium spinosum*	Azaspiracid	Cytotoxic	Nausea, vomiting, diarrhea	Within hours	2-3 days	Supportive, intravenous fluids
Yessotoxin	Shellfish	Japan, United Kingdom, New Zealand, Chile, Italy, Spain, Canada, the Mediterranean	*Protoceratium reticulatum, Lingulodinium polyedrum, Gonyaulax spinifera*	Yessotoxin	Unknown	Restlessness, dyspnea, shivering, cramps	Within hours		

ATPase, adenosine triphosphatase.

ill, possibly because of uneven distribution of decay within the fish.

Clinical Presentation

The effects of scombroid fish poisoning occur within minutes after consumption of the fish. Symptoms are similar to an allergic reaction (which it is not) and typically include headache, diffuse erythema, a sense of warmth without elevation in core temperature, nausea, vomiting, diarrhea, abdominal cramps, conjunctival injection, pruritus, dizziness, and a burning sensation in the mouth and oropharynx.[30,254,322] Flushing of the head, neck, and upper torso is characteristic. Severe effects, such as bronchospasm, generalized urticaria, hypotension, palpitations, and dysrhythmias, have been reported but are not frequent.[176,119,220,548,] In most healthy victims, the syndrome is self-limited, resolving within 6 to 12 hours. In rare cases, symptoms can persist beyond 24 hours.[222] In patients with preexisting respiratory or cardiac disease, effects of the poisoning can precipitate more severe illness.[50,322] Scombroid reactions may be markedly more severe in patients taking isoniazid because of this compound's blockade of gastrointestinal tract histaminase.[495] Death has never been reported after scombroid poisoning. Assays of histamine and its metabolite in urine samples of scombroid-poisoned patients demonstrated elevated levels compared with controls, although histamine measurement is neither common in clinical practice nor recommended. Histamine levels poorly correlate with clinical manifestations and do not affect management decisions.

Treatment

Gastric decontamination for scombroid poisoning is not indicated, because symptoms occur rapidly and vomiting can be a primary effect of the toxin. Symptoms can be lessened or controlled with administration of histamine-1 (H_1) receptor antagonists, such as diphenhydramine or hydroxyzine, administered initially in doses of 25 to 50 mg orally or intravenously. Histamine-2 (H_2) receptor antagonists (e.g., ranitidine, famotidine) have also been shown to relieve most of the symptoms; a combination of H_1 and H_2 receptor antagonists may be most effective.[45,193] Vomiting is usually controlled by an antihistamine, but occasionally requires addition of a specific antiemetic, such as ondansetron. The persistent headache of scombroid poisoning may respond to famotidine or a similar drug if standard analgesics are not effective.[19] Intravenous fluids and inhaled bronchodilators should be used as needed. Vasopressors are rarely necessary because hypotension is usually mild and responds to intravenous fluid administration. Corticosteroids are generally not indicated.

Prevention

The only effective method for prevention of scombroid fish poisoning is consistent temperature control at less than 40° F (4.4° C) at all times between catching and consumption.[114] It has been difficult to reduce the occurrence of scombroid poisoning in the United States; recreational catches likely play a major role.[222] No fish should be consumed if it has been handled improperly or has the smell of ammonia. Fresh fish generally has a sheen or oily rainbow appearance; "dull" packaged fish should be avoided. If an episode of scombroid poisoning is recognized, it is important to report it promptly to local public health authorities to prevent additional exposures, particularly if the food was served in a public eating establishment.[221]

TETRODOTOXIN POISONING

Tetrodotoxin (TTX) is a potent neurotoxin found in a variety of creatures and has been isolated from animals of four different phyla, including puffer fish, California newt, blue-ringed octopus, poison dart frogs, ivory shell, and trumpet shell. TTX is characteristic of the order Tetraodontiformes.[458] The suborder Tetraodontoidei contains three families of fish (Tetraodontidae, Diodontidae, and Canthigasteridae), including puffer fish (toadfish, blowfish, globefish, swellfish, balloonfish, toado) and porcupinefish. Sunfish (*Mola* species) are members of the suborder Moloidei. Tetrodotoxin was named around 1911 after searching for the active ingredient in fugu ovaries.[160] Isolation of the chemical was achieved in the 1950s. In the 1970s, the major toxin in certain poison dart frogs was identified as TTX. Crystalline TTX was isolated in 1978. The puffer fish, sometimes called a globefish, is one of the better-recognized species that contains TTX. These fish can be found in both freshwater and saltwater and can inflate their bodies to a nearly spherical shape using air or seawater.[198] Human TTX poisonings have also occurred after consumption of gastropod mollusks.[534] Envenomation from the blue-ringed octopus is rare, but poisonings have occurred from their consumption.[154,531]

Puffer fish poisoning has been recognized for millennia. Ancient Asian literature documents the dangers of eating puffer fish.[198] There are references to puffer fish in hieroglyphics of the ancient Egyptian dynasty of 2700 BC. Scholars suggest this fish was known to be poisonous during Egyptian times. Mosaic sanitary laws against eating fish without fins and scales may have been derived to avoid fish containing TTX; the TTX-containing fish in the region inhabited by the Israelites were scaleless.[198]

Captain James Cook, the British explorer, recorded in 1774 his experience after eating a piece of liver from a puffer fish purchased from a native fisherman during his voyages in the Pacific Ocean.[505] Before preparing the fish for eating, it was described and drawn. Cook tasted the liver and wrote of a vivid feeling of extraordinary weakness and numbness.[198] There has been some contention that TTX (also known as puffer powder) was used as a component of the Haitian voodoo potion in the zombie ritual.[484] This has been challenged on grounds, among others, that under the usual conditions of extreme alkaline storage, any TTX in a "zombie potion" would be decomposed irreversibly into pharmacologically inactive products.[251,537]

In humans, the most common exposure to TTX is through the ingestion of fugu, a special preparation of puffer fish.[73] Sporadic cases have been reported in the United States.[85] In Japan, chefs must undergo a rigorous certification process before they are allowed to prepare fugu. The fillet of the puffer fish contains very small concentrations of TTX. Fugu is served raw with paper-thin slices placed into an ornate configuration. The presence of small quantities of TTX gives the desired effect of slight oral tingling. Importation of fugu into the United States is illegal, but smuggling has resulted in cases of poisoning. At least 50 of the more than 100 species of these fish have been involved in poisonings of humans or may be intermittently toxic.[406] Many species other than fish also contain TTX (Box 77-4).

Many years ago, when TTX was believed to be present exclusively in puffer fish, it was controversial whether TTX was endogenous. It is now known that TTX is accumulated through the food chain, in a several-step process starting with marine bacteria as the primary source.[351] TTX may be produced by *Pseudomonas* species that live on skin of the puffer fish.[544] This would explain the transmittal of toxicity between toxic and nontoxic fish through skin contact. Other investigators have found that *Vibrio* and other species isolated from intestines of puffer fish produce TTX.[512] The exact origin of TTX in the food chain, however, remains unknown. Distribution of TTX in the body of a puffer fish appears to be species-specific. In general, the liver and ovaries have the highest toxicity, followed by intestines and skin.[351] Female fish are considered more toxic than are males because there are especially high concentrations of TTX in ovaries. The musculature is less toxic but still may contain a significant amount of TTX. The toxin is heat stable and not inactivated by freezing. There occurs seasonal variation of TTX concentration, with peak levels during spawning season. TTX is likely accumulated as a biologic defense agent.[351]

Pathophysiology

TTX blocks the action potentials in nerves by binding to the pores of voltage-gated, fast sodium channels in nerve cell membranes. TTX has a unique nonprotein structure and is widely used as a research tool to study sodium channels. Mouse bioassays demonstrate that the minimal lethal dose of TTX by intraperitoneal injection is 8 to 20 mg/kg.[337] Interaction of TTX with the sodium channel is thought to be stoichiometric, with each TTX molecule interfering with one channel. TTX affects the

BOX 77-4 Non-Tetraodontiformes Containing Tetrodotoxin

Phylum Chordata

Order Caudata

Family Salamandridae
- *Taricha granulosa:* rough-skinned newt
- *Notophthalmus viridescens:* eastern newt
- *Triturus:* European newts
- *Pleurodeles:* ribbed newts
- *Cynops:* fire belly newts
- *Paramesotriton:* warty newts
- *Tylototriton:* crocodile newts

Order Anura

Family Bufonidae
- *Atelopus:* stubfoot toad

Phylum Mollusca

Order Caenogastropoda

Family Buccinidae
- *Babylonia japonica:* ivory shell

Family Naticidae
- *Natica lineata:* lined moon shell
- *Natica vitellus:* calf moon shell
- *Polinices didyma:* bladder moon shell

Family Ranellidae
- *Charonia sauliae:* trumpet shell

Order Octopoda

Family Octopodidae
- *Hapalochlaena maculosa:* Australian blue-ringed octopus

Phylum Echinodermata

Order Paxillosida

Family Astropectinidae
- *Astropecten polyacanthus:* starfish

Phylum Nemertea

Order Paleonemertea

Family Cephalothricidae
- *Cephalohrix linearis:* ribbon worm

Phylum Platyhelminthes

Order Polycladida

Family Planoceridae
- *Planocera multitentaculata:* flat worm

Phylum Arthropoda

Order Decapoda

Family Xanthidae
- *Atergatis floridus:* xanthid crab

Order Xiphosura

Family Limulidae
- *Carcinoscorpius rotundicauda:* mangrove horseshoe crab

Data from Dunn J: Algae kills dialysis patients in Brazil, BMJ 312:1183, 1996; Edwards C, Beattei KA, Scrimgeour CM, et al: Identification of anatoxin-A in benthic cyanobacteria (blue-green algae) and in associated dog poisonings at Loch Insh, Scotland, Toxicon 30:1165, 1992; Gessner BD, Middaugh JP: Paralytic shellfish poisoning in Alaska: A 20-year retrospective analysis, Am J Epidemiol 141:766, 1995; Rosen L, Loison G, Laigret J, et al: Studies on eosinophilic meningitis. 3. Epidemiologic and clinical observations on Pacific Islands and the possible etiologic role of Angiostrongylus cantonensis, Am J Epidemiol 85:17, 1967; and Tatsumi M, Kajiwara A, Yasumoto T, et al: Potent excitatory effect of scaritoxin on the guinea-pig vas deferens, taenia caeci and ileum, J Pharmacol Exp Ther 235:783, 1985.

spike-generating process of sodium channels, not the resting or steady-state voltage.[249]

TTX interferes with both central and peripheral neuromuscular transmission. Although it is not a depolarizing agent, in animals it causes depression of the medullary respiratory mechanism, intracardiac conduction, and myocardial and skeletal muscle contractility. At the microcellular level, the mechanism of action of TTX is linked to the axon rather than to the nerve end plate. TTX blocks axonal transmission by interfering with sodium conductance within the depolarized regions of the cell membrane, perhaps by acting at a metal cation binding site in the sodium channel, without affecting presynaptic release of acetylcholine or its effects on the neuromuscular junction.[4,212] There is no apparent effect on potassium permeability.[404] Saxitoxin, implicated in paralytic shellfish poisoning, has essentially the same action as does TTX on the nerve membrane, although it is believed to have a discrete receptor.[254] The poison in freshwater puffers may be composed of TTX or saxitoxin, the predominant toxin depending on the species. The lethal dose (LD_{50}) for mice is 10 mg/kg when TTX is administered by intraperitoneal, intravenous, or subcutaneous routes.[482]

Animal studies suggest that TTX has a peripheral effect that results in vasodilation independent of α- or β-adrenergic receptors.[233,250,301] Further studies suggest a dose-dependent action. At low doses, systemic blood pressure is lowered, although perfusion pressure is initially maintained. Higher doses of TTX result in a profound fall in blood pressure.[249] Experiments with animal models using TTX from blue-ringed octopi demonstrate a similar profound hypotension. Agonists (norepinephrine or phenylephrine) have been the most effective agents in raising blood pressure in models of TTX poisoning.[154]

Clinical Presentation

Clinical manifestations typically develop within 30 minutes of ingestion but may be delayed by up to 4 hours. In a 2002 outbreak in Bangladesh of 37 people (from eight families) who were poisoned from inadequately prepared puffer fish, 31 victims developed symptoms within 2 hours and 8 died.[2] Death has been recorded within 17 minutes of exposure. The extent and type of symptoms vary according to the individual and amount of TTX ingested. Usually, paresthesias of the lips and tongue are followed by several signs; they may be as mild as diaphoresis or as life-threatening as hypotension, respiratory failure, and coma.[85] Other commonly described symptoms include weakness, headache, body paresthesias, and gastrointestinal symptoms such as nausea, vomiting, and abdominal pain. Hypersalivation, ataxia, cyanosis, dysphagia, aphonia, dyspnea, blurred vision, bronchorrhea, and bronchospasm have been described.[2,85,94,101] Early miosis may progress to mydriasis with poor pupillary light reflex.[482] A disseminated intravascular coagulation—like syndrome is heralded by petechial skin hemorrhages that can progress to bullous desquamation and diffuse stigmata of prolonged coagulation. Hypotension can be profound and may be refractory to treatment. Bradycardia and atrioventricular node conduction abnormalities may be present. Complete cardiovascular collapse with respiratory paralysis precedes death. Normal consciousness may be maintained until shortly before death.[160,482] In some older reports, 60% of victims died, most within the first 6 hours. Survival past 24 hours is a good prognostic sign.

Treatment

Treatment of TTX is primarily supportive, with aggressive airway management and assisted ventilation.[439] Decontamination may be considered with 1 g/kg of activated charcoal given as soon as practical following presentation if no contraindications (such as vomiting or altered mental status) are present. Atropine may be used to treat bradycardia in conjunction with adequate oxygenation (SaO_2 > 92%). Intravenous fluid resuscitation should be initiated for hypotension; however, use of vasopressors may be required to maintain perfusion. α-Agonists, such as phenylephrine or norepinephrine, are more likely to be effective. No antidote is currently available to treat TTX poisoning.

Cholinesterase inhibitors, such as edrophonium and neostigmine, have been used to treat victims of TTX poisoning, with mixed results. Some case reports suggested subjective improvement in neurologic symptoms after administration of cholinesterase inhibitors.[91,482] A recent case series suggested that neostigmine may help overcome respiratory muscle paralysis, which is the predominant cause of death.[91] Other case reports noted no improvement after infusion of these compounds.[2,310,479] Antihistamines and steroids have also been used without clear benefit.[310]

A minor intoxication with TTX may be limited to paresthesias and mild dysphagia. In such a case, the victim should be observed in the emergency department or intensive care unit for at least 8 hours to monitor for deterioration, particularly in respiratory

function. The victim should not be discharged until symptoms are clearly improving. Although it is water soluble, TTX is very difficult to remove from fish, even by cooking. It is prudent to avoid all puffers, even when prepared by an expert.

GRASS CARP GALLBLADDER POISONING

Fish gallbladder has long been used as a folk remedy in China and Southeast Asia. In a case series of 17 patients from Vietnam, the most common reason for ingestion was for symptoms of arthritis.[533] The toxin is found in the bile of freshwater fish of the family Cyprinidae. Grass carp *(Ctenopharyngodon idellus)* accounts for 80% of freshwater fish gallbladder poisonings in China.[276] Serious illness is attributed to the nephrotoxic and hepatotoxic properties of a toxin found in bile.[88] The toxic ingredient is 5-α-cyprinol sulfate, a 27-carbon salt, which is heat stable and not destroyed by ethanol.[19,272] Most cases have occurred in Hong Kong, Taiwan, and South Korea. Two cases were reported in the United States in immigrants who ate raw gallbladders from carp caught in Maryland.[70] One of the patients required hemodialysis for acute renal failure.

Several hours after ingestion, abdominal pain, nausea, vomiting, and watery diarrhea develop. This can be accompanied by marked elevations in concentrations of liver enzymes (aspartate and alanine aminotransferases).[121] The hepatitis is usually self-limited, although fulminant liver failure and death have been reported.[253,533] Nephrotoxicity occurs in moderate to severe poisonings and may be profound, leading to oliguric or nonoliguric renal failure within 48 to 72 hours after ingestion.[409,533] Renal and liver biopsies demonstrate acute tubular necrosis and hepatocellular injury. With appropriate supportive care, including dialysis, patients typically recover. Acute renal failure accounts for more than 80% of deaths, although the mortality rate has declined, likely due to advances in intensive care and renal salvage therapy.[276]

POISONINGS ASSOCIATED WITH ALGAL BLOOMS

Although there are thousands of species of microalgae that form the base of the food chain, fewer than 60 species are toxic or harmful. These toxic species may cause significant rates of death in fish and shellfish, seabirds, and marine mammals, as well as human illnesses and death. Algal toxins have resulted in more than 500,000 incidents per year, with an overall mortality rate of 1.5% on a global basis.[510] In the United States, harmful algal blooms now threaten virtually every coastal state, and the number of toxic species is increasing. Algae can reproduce rapidly, even to the point of discoloring the sea, producing "red tides."[446] Several distinct clinical syndromes exist: ciguatera fish poisoning, clupeotoxic fish poisoning, paralytic shellfish poisoning, neurotoxic shellfish poisoning, diarrhetic shellfish poisoning, amnestic shellfish poisoning, possible estuary-associated syndrome, and Haff disease (see Table 77-1). Besides these more familiar syndromes, several newer syndromes have been characterized recently, including illness due to azaspiracid toxins, yessotoxin, and palytoxin.

Most dinoflagellate toxins are neurotoxins, causing toxicity via their interaction with voltage-sensitive ion channels or specific receptors associated with neurotransmitter release. Some block the channel pore physically and prevent ion conductance (hydrophilic low-molecular-mass toxins and large polypeptide toxins). Others alter voltage-dependent gating through binding to intramembranous receptor sites (alkaloid toxins and related lipid-soluble toxins) or intracellular sites (polypeptide toxins).[510]

CIGUATERA POISONING

The word *ciguatera* is derived from the Spanish name *cigua* for the sea snail *Turbo pica* found in the Caribbean Spanish Antilles.[26,475] Ciguatera poisoning, a neurotoxic syndrome, has been recognized throughout history, with one of the earliest cases reported in the 4th century when Alexander the Great refused to allow his soldiers to eat fish, and another during the Tang Dynasty in China.[452] One of the earliest written records of suspected ciguatera poisoning is from the journal of Captain William Bligh, who described symptoms consistent with ciguatera in 1789 after eating mahi-mahi.[452] In addition, it was also quite possibly ciguatera that was illustrated by Captain James Cook while sailing on the *Resolution* in the South Pacific in 1774.[368]

Ciguatera fish poisoning is an important cause of food-borne disease and is endemic throughout subtropical and tropical regions of the Indo-Pacific and Caribbean. More than 400 species of fish have been implicated to cause ciguatera fish poisoning. In the United States, it is a prominent nonbacterial type of food poisoning associated with fish, second only to scombroid, with cases having been reported in many states.[79,171,215,332,507] Outbreaks of ciguatera are most common between the months of April and August. In endemic areas, the incidence is estimated to be between 500 and 600 cases per 10,000 people.[278] Worldwide, ciguatera may affect more than 50,000 persons each year. Most cases in the United States occur in Hawaii and Florida, with the incidence in Florida estimated to be five cases per 10,000 people.[142] The true incidence of ciguatera fish poisoning is difficult to ascertain because of underreporting. It is believed that only 2% to 10% of cases are reported to health authorities.[159] Outbreaks of ciguatera have been associated with ingestion of warm-water, reef-dwelling fish caught in the zone between the latitudes of approximately 30 and 35 degrees.[29,199] In addition, the advent of flash-freezing and shipping of fish around the world has accounted for several cases of ciguatera in nonendemic areas.[215]

The most frequently implicated reef fishes are listed in Box 77-5. Of reported cases, 75% (except in Hawaii) involve barracuda, snapper, jack, or grouper. Hawaiian carriers of the toxin include parrot-beaked bottom feeders and surgeonfishes, particularly those inhabiting waters with high dinoflagellate populations, such as those with disturbed coral reefs.[232] Other fish that have been reported as ciguatoxic are listed in Box 77-6. Ciguatera has also been reported after ingestion of farm-raised salmon.[130] There is one report of ciguatera from consumption of jellyfish.[550]

Pathophysiology

The blue-green and free algal dinoflagellate *Gambierdiscus toxicus* is thought to be responsible for producing ciguatoxins.[452] *G. toxicus* adheres to dead coral surfaces and marine algae that are consumed by smaller herbivorous fish.[182,278] Although *G. toxicus* is very likely responsible for the majority of ciguatoxins encountered in fish, the cyanobacterium *Trichodesmium erythraeum* can produce water- and lipid-soluble precursors to the

BOX 77-5 Reef Fish Frequently Implicated in Ciguatera Poisoning

Phylum Chordata

Order Anguilliformes
Family Muraenidae: moray eels

Order Mugiliformes
Family Mugilidae: mullets

Order Perciformes
Family Acanthuridae: surgeonfishes
Family Carangidae: jacks
Family Labridae: wrasses
Family Lethrinidae: emperor fish
Family Lutjanidae: snappers
Family Scaridae: parrotfishes
Family Serranidae: groupers
Family Sparidae: porgies
Family Sphyraenidae: barracuda

Order Tetraodontiformes
Family Balistidae: triggerfishes

From Gilbert DN, Moellering RC, Sande MA: *The Sanford guide to antimicrobial therapy*, ed 34, 2007, Sperryville, Virginia, Antimicrobial Therapy, Inc., pp 98-99.

BOX 77-6 Some Fish Other Than Those in Box 77-5 That Are Known to Be Ciguatoxic

Albulidae (ladyfishes)
Chanidae (milkfishes)
Clupeidae (herrings)
Elopidae (tarpons)
Engraulidae (anchovies)
Synodontidae (lizardfishes)
Congridae (true eels)
Ophichthidae (snake eels)
Belonidae (needlefishes)
Exocoetidae (flying fishes)
Hemiramphidae (halfbeaks)
Aulostomidae (trumpetfishes)
Syngnathidae (seahorses)
Holocentridae (squirrelfishes)
Apogonidae (cardinalfishes)
Arripidae (sea perches)
Chaetodontidae (butterfly fishes)
Cirrhitidae (hawkfishes)
Coryphaenidae (dolphins)
Gempylidae (oilfishes)
Gerridae (silverfishes)
Gobiidae (gobies)
Istiophoridae (sailfishes)
Kuhliidae (bass)
Kyphosidae (rudderfishes)
Mullidae (goatfishes)
Pempheridae (sweeperfishes)
Pomacentridae (damselfishes)
Pomadasyiidae (grunts)
Priacanthidae (snapper)
Scatophagidae (spade fishes)
Sciaenidae (croakers)
Scombridae (tunas)
Scorpaenidae (scorpionfish)
Siganidae (rabbitfishes)
Xiphiidae (swordfishes)
Zanclidae (idol)
Bothidae (flounders)
Aluteridae and Monacanthidae (filefishes)
Ostraciontidae (trunkfishes)
Batrachoididae (toadfishes)
Antennariidae (sargassumfish)
Lophiidae (goosefish)
Ogcocephalidae (longnose batfish)

toxins that may generate ciguatera syndrome.[141] Other dinoflagellates, such as *Prorocentrum concavum, Prorocentrum mexicanum, Prorocentrum rhathymum, Gymnodinium sanguineum,* and *Gonyaulax polyedra,* may generate toxins that play a role in ciguatera syndrome.[383,480]

Larger reef fish eat the contaminated smaller fish, thereby becoming vectors as ciguatoxin is bioconcentrated up the food chain. It has long been assumed that smaller fish within a given species are safer to eat than the larger ones. However, a recent study sampling different species from French Polynesia found no relationship between toxicity of the fish and size.[164,209,220,371] Although the entire fish is toxic, viscera (particularly the liver) and roe are considered to carry the highest concentrations of toxin.[28] No plankton feeders have so far been reported to be ciguatoxic.

It has been suggested that proliferation of toxic algae may be triggered by contamination of water from a number of sources, including industrial wastes, golf course runoff, metallic compounds, ship wreckage, or other pollutants.[199] In the Marshall Islands (Micronesia), consequent to nuclear testing, the incidence of toxin-producing plankton has tripled.[393] Similar observations have been made with respect to various military activities (dumping and explosives) in the Line Islands and Gilbert Islands (Kiribati, Central Pacific), Hao Atoll (Tuamotu Archipelago, French Polynesia), Gambier Islands (French Polynesia), and others.[403] Yet another cause of toxic dinoflagellate proliferation may be transfer and dumping of ballast water from large ocean-going vessels.

Ciguatera is associated with more than five toxins, including fat-soluble quaternary ammonium compounds (ciguatoxins), a water-soluble component (maitotoxin, from the Tahitian vernacular name *maito* for the striated surgeonfish *Ctenochaetus striatus*), a maitotoxin-associated hemolysin (lysophosphatidylcholine, or lysolecithin), and a ciguatoxin-associated adenine triphosphatase (ATPase) inhibitor.[202,290,296,413] Scaritoxin (isolated from *Scarus gibbus*) is similar to the fat-soluble component and is specific to parrotfishes.[86] Lipid-extracted toxins from *G. toxicus* have been designated GT-1, GT-2, and GT-3; a water-soluble toxin is designated GT-4.[126,327] Chemical analysis of ciguatoxins demonstrates that they closely resemble brevetoxin C (from *P. brevis*) and okadaic acid, isolated from marine sponges and the dinoflagellate *Prorocentrum lima*.[152,339] Identification of okadaic acid from the Caribbean dinoflagellate *P. concavum* lends support to the notion that this toxin may be more significant in ciguatera poisoning than previously thought. Another compound, named prorocentrolide, has also been found in reef-dwelling fish with okadaic acid and has been implicated in diarrhetic shellfish poisoning, another common fish-borne illness.[152,219]

Three major ciguatoxins (CTX-1, CTX-2, and CTX-3) are usually found in the flesh and viscera of ciguateric fishes. Each is found in variable concentrations; this may account for the inconsistency of reported clinical signs and symptoms.[296] CTX-2 is a diastereomer of CTX-3.[295] Ciguatoxins may result from oxidation of gambiertoxins, possibly through the cytochrome system in fish liver.[297] The lipid components have been characterized as crystalline, colorless, heat-stable compounds with a molecular weight of approximately 1100 daltons, with functional hydroxyl and quaternary nitrogen groups.

Ciguatoxins are potent Na^+ channel toxins and exert their effects by activating voltage-sensitive Na^+ channels. The Na^+ channels open at resting membrane potentials, leading to spontaneous firing of neurons, giving rise to neurologic signs and symptoms of ciguatera.[226] One mechanism of their action may be that they falsely occupy calcium receptor sites that modulate sodium pore permeability in neural, muscle, and myocardial membranes.[35] This effect could allow increased membrane permeability to sodium and cause sustained depolarization. Electrophysiologic studies of the sural and common peroneal nerves in humans with ciguatera, demonstrating reduced light touch, pain, and vibratory sensation in the extremities, showed prolongation of the absolute refractory, relative refractory, and supernormal periods. These findings indirectly suggest that ciguatoxin may abnormally prolong sodium channel opening in nerve membranes.[62] This influx of sodium is antagonized by the presence of TTX.[40]

In vitro studies have also shown that scaritoxin causes release of norepinephrine and acetylcholine and increases sodium channel permeability.[469] Maitotoxin as well may trigger release of norepinephrine and stimulate cellular uptake of calcium and has been hypothesized to stimulate cholinergic receptors by inhibiting acetylcholinesterase.[40,438] However, evidence suggests that highly purified ciguatoxin preparations may not have anticholinesterase effects in vivo.[288]

Hypertension occurring with ciguatera can be suppressed in animal models with phentolamine (an α-antagonist), suggesting α-adrenergic receptor activity. Although purified ciguatoxin appears to have cardiac stimulatory effects (increasing heart rate and output), maitotoxin is a myocardial depressant in vitro, which may explain variation in clinical presentation. Isolated human atrial trabeculae show concentration-dependent positive inotropy with CTX-1 that is not reversed with mannitol.[294] Cardiac calcium conduction effects have been implicated in the activity of maitotoxin, because its action is inhibited in the presence of verapamil, magnesium ions, or low-calcium-concentration solutions. In mice, injection of maitotoxin can induce a marked increase in the total calcium content of the adrenal glands and a rise in the plasma cortisol concentration.[473] When injected into mice, ciguatoxin targets the heart, adrenal glands, and autonomic nervous system.[475] Ciguatoxin and CTX-4c (a derivative),

administered in repeated doses, cause the mouse heart to suffer septal and ventricular interstitial fibrosis, accompanied by bilateral ventricular hypertrophy.[477] Ciguatoxin is a potent substance, with an LD_{50} in mice of 0.45 mg/kg in purified form. Maitotoxin is even more potent, with an LD_{50} of 0.13 mg/kg in mice. It is interesting to note that ciguatoxins can become toxic to fish in higher concentrations, thus potentially limiting levels of these compounds carried by a fish.[293] However, the toxin or toxins may reside in skeletal muscle or other tissues of the fish in association with proteins that may be protective of the carrier.[195]

All identified toxins associated with ciguatera are unaffected by freeze-drying, heat, cold, and gastric acid and do not affect the odor, color, or taste of the fish. There is some evidence that cooking methods can alter the relative concentrations of the various toxins. For example, boiling fish flesh will remove water-soluble toxins, but frying or grilling the flesh may increase toxicity of lipid-soluble toxins as a result of releasing lipid-soluble components from the cellular compounds to which they are normally bound.[140]

Clinical Presentation

Ciguatera fish poisoning is associated with gastrointestinal, cardiovascular, neurologic, and neuropsychiatric symptoms and signs. The meal containing ciguatoxins is generally unremarkable in taste and smell. Symptoms may develop within minutes of ingestion, although they generally occur within 2 to 6 hours after the meal. Almost all victims develop symptoms by 24 hours.[26,142] The severity of symptoms seems to follow a dose-dependent pattern, with victims who eat larger portions of ciguatoxic fish experiencing more severe symptoms (Box 77-7). In addition, there are variable concentrations of ciguatoxin within a fish, depending on the fish size, age, and part consumed, with higher concentrations in the viscera, especially the liver, spleen, gonads, and roe.[266,282]

The most common initial symptoms reported in cases of ciguatera include acute gastroenteritis, with abdominal cramps, nausea, vomiting, and diarrhea.[26] These symptoms rarely persist for longer than 24 hours but may require fluid resuscitation.[142] Myriad other symptoms reported in ciguatoxic patients are listed in Box 77-7. Headache is a common symptom, and victims often complain of experiencing a metallic taste. In a well-described clinical outbreak affecting a group of scuba divers who consumed coral trout *(Cephalopholis miniata),* the most common symptoms were weakness, cold sensitivity, paresthesias, a taste sensation of carbonation, and myalgias.[2] Two men suffering from ciguatera poisoning had painful ejaculation with urethritis, which in turn may have induced dyspareunia (pelvic and vaginal burning) in their female partners after intercourse.[280] In a North Carolina outbreak in 2007, six of the seven sexually active patients reported onset of painful intercourse beginning in the first few days after onset of illness. Although sexual transmission of ciguatoxin has been documented, painful intercourse as a consequence of ciguatera fish poisoning is not commonly described.[282] Neurologic symptoms seem to develop after initial gastrointestinal symptoms. Paresthesias and myalgias are typically seen within the first 24 hours and usually resolve by 48 to 72 hours after ingestion of ciguatoxins, although there have been reports of neurologic symptoms persisting for weeks to months.[27,286,372,282]

Many case reports of ciguatera describe symptoms of a sensory perception of "hot and cold reversal," and loose, painful teeth. Although the presence of these symptoms is suggestive of ciguatera, their absence does not exclude the possibility of the disease.[27] Although there have been reports of a paradoxic reversal of temperature perception, resulting in cold feeling hot rather than hot feeling cold, other reports demonstrated that gross temperature discernment remains intact and the description of paradoxic heat perception may be misleading.[61] These authors describe the symptoms as intense, painful tingling or "electric shock" rather than true reversal of hot and cold perception.[61] This peculiar symptom may have a delayed onset of 2 to 5 days, may last for months after ingestion, and is otherwise seen only with neurotoxic shellfish poisoning (brevetoxins), caulerpicin (from the green alga *Caulerpa*) toxicity, or turban shell poisoning.[132,536] These symptoms are commonly associated with polyneuropathy, predominantly affecting sensory small fibers.[414] Pruritus is another vague but often described sensation in victims of ciguatera. The onset of pruritus may be delayed for more than 24 hours but is rarely, if ever, seen in the absence of other symptoms.[152,286] Pruritus may persist for weeks and be exacerbated by any activity that increases skin temperature (blood flow), such as exercise or alcohol consumption.[286] Ciguatera-associated pruritus may occasionally become severe and may improve after treatment with histamine receptor antagonists. Delayed symptoms also include hiccups.

Tachycardia and hypertension are often described in ciguatera poisoning, in some cases after transient bradycardia and hypotension, which can be severe.[87] Hallucinations, flushing, flaccid paralysis, and fever occur but are uncommon. More severe reactions tend to occur in persons previously stricken with the disease. Severely affected persons may report intermittent symptoms for up to 6 months, with gradual diminution in frequency and intensity. There may be regional variability to the symptoms of presentation.[27,334] Reappearance or worsening of symptoms after alcohol consumption has been described.[282] Other foods and behaviors associated with symptom recurrence include nuts, caffeine, port wine, chicken, other fish, and physical activity/exertion.[159] Persons who have ingested parrotfish (scaritoxin) have been reported to suffer from classic ciguatera poisoning, as well as a second phase of toxicity 5 to 10 days after the initial onset, consisting of ataxia, dysmetria, and resting or kinetic tremor.[95] Although both gastrointestinal and neurologic effects

BOX 77-7 Signs and Symptoms Associated With Ciguatera Poisoning

Abdominal pain
Nausea
Vomiting
Diarrhea
Chills
Paresthesias (particularly of the extremities and circumoral region)
Pruritus (particularly of the palms and soles)
Tongue and throat numbness or burning
A sensation of "carbonation" during swallowing
Odontalgia or dental dysesthesias
Dysphagia
Dysuria
Dyspnea
Weakness
Fatigue
Tremor
Fasciculations
Athetosis
Meningismus
Aphonia
Ataxia
Vertigo
Pain and weakness in the lower extremities
Visual blurring
Transient blindness
Hyporeflexia
Seizures
Nasal congestion and dryness
Conjunctivitis
Maculopapular rash (erythematous, with occasional desquamation)
Skin vesiculations
Dermatographia
Sialorrhea
Diaphoresis
Headache
Arthralgias
Myalgias (particularly in the lower back and thighs)
Insomnia
Bradycardia
Hypotension
Central respiratory failure
Coma

are the hallmarks of ciguatera intoxication, there are regionally dependent differences in clinical presentation. Neurologic effects predominate in the Indo-Pacific region, whereas gastrointestinal symptoms predominate in the Caribbean.[226] Consumption of Indian Ocean fish has led to a further syndrome characterized by hallucinations, incoordination, loss of equilibrium, depression, and nightmares. Sensitization with repeated exposure has been described, leading to more rapid onset of effects.[226]

Whether ciguatoxin crosses the placenta is not known, but exposures during pregnancy have resulted in normal fetal outcomes.[424] Transmission via breast milk has been reported.[257] In small children, symptoms of ciguatera poisoning may be no more specific than irritability, sleep disturbance, nausea, and vomiting.[518] Other reported symptoms include carpopedal spasm, ptosis, and inconsolability.

An overall death rate of 0.1% to 12% has been reported with ciguatera, but the lower percentage seems more likely with modern supportive care. Death is usually attributed to respiratory paralysis.[244]

Diagnosis

Diagnosis of ciguatera poisoning is based on clinical symptoms. The differential diagnosis includes paralytic shellfish poisoning, eosinophilic meningitis, type E botulism, organophosphate insecticide poisoning, TTX poisoning, and psychogenic hyperventilation.[27,402] Temperature-related dysesthesia has also been reported in neurotoxic shellfish poisoning from consumption of shellfish contaminated with brevetoxin. Therefore, neurotoxic shellfish poisoning should be considered in the differential diagnosis. Unreliable folklore used in the past to aid in predicting ciguatoxic seafood includes the advice that a lone fish (separated from the school) should not be eaten. Other myths include that ants and turtles refuse to eat ciguatoxic fish, that a thin slice of ciguatoxic fish does not show a rainbow effect when held up to the sun, and that a silver spoon tarnishes in a cooking pot with ciguatoxic fish.[102] Ciguatoxin may be detected in the flesh of fish by two immunoassay techniques, a mouse bioassay where a sample of the fish is injected intraperitoneally into a mouse, and a rapid IgG assay.[215] Rapid immunoassays have largely replaced using mice and other archaic tests (e.g., feeding fish to a mongoose or cat to observe for neurologic symptoms or death). HPLC is also available for ciguatoxins and okadaic acid. Unfortunately, tests for ciguatoxin are still of limited clinical benefit because most institutions do not have the equipment needed for their performance. Multiple individuals presenting with the same symptoms that are consistent with ciguatera fish poisoning after consuming the same fish strongly supports the diagnosis.

Treatment

If possible, a piece of the implicated fish should be obtained in the event that analysis for ciguatoxins can be performed. Treatment of ciguatera poisoning is primarily supportive. Intravenous hydration with crystalloid and electrolyte replacement may be necessary for dehydration. Severe or refractory hypotension may require a vasopressor. Antiemetics such as ondansetron may be beneficial. Atropine has been shown to be effective in patients with symptomatic bradycardia or excess cholinergic stimulation.[152] Gastric decontamination is rarely indicated, because presentation is usually delayed and gastroenteritis has already occurred. Activated charcoal may bind some of the toxin in the gastrointestinal tract, but this is not useful when presentation is more than 1 to 2 hours after exposure.

Many traditional remedies have been used for centuries to treat ciguatera. Edrophonium, neostigmine, corticosteroids, pralidoxime, ascorbic acid, pyridoxine (vitamin B_6), salicylic acid, colchicine, and vitamin B complex have all been tried with variable success; however, there is no current clinical support for these modalities.[334] Local anesthetics (e.g., lidocaine, tocainide) have also been administered for treatment of ciguatera.[63,279] These agents are effective blockers of sodium influx and may antagonize the sodium channel effects of ciguatoxin. In addition, amitriptyline has been used for its sodium channel–blocking effects, as well as its potent antimuscarinic effects.[55,60,115] Nifedipine has been used to counteract cellular uptake of calcium caused by maitotoxin, and to relieve headache.[60] Although there is limited experience with most of these therapies, they may be beneficial in cases refractory to supportive care alone.

Mannitol has become the most widely applied therapy in severe cases of ciguatera poisoning.[53,453] Most reports of its success are based on limited data with small numbers of patients.[135,364,369,519] One series described successful treatment with mannitol in 24 victims of ciguatera poisoning. Each was infused with up to 1 g/kg of a 20% mannitol solution intravenously over 30 minutes. None of the victims received more than 250 mL.[364] The mechanism by which mannitol might be effective in abating the neurologic symptoms from ciguatera poisoning is unknown, but suggested theories have included acting as a free radical scavenger, acting as a competitive inhibitor of ciguatoxin at the cell membrane, and promoting a decrease in Schwann cell edema.[369,519] It is also possible that the osmotic action of mannitol may render ciguatoxin inert.[364,369] Curiously, mannitol therapy seems to have no beneficial effect on mice administered a sublethal intraperitoneal dose of ciguatoxin (CTX-1).[298] A more recent double-blinded, randomized study of mannitol therapy found no difference in resolution of symptoms when compared with saline.[414] Of note, therapy was not initiated until an average of 19 hours after exposure in the mannitol group and 40 hours after exposure in the saline group. In humans, the empirical observation is that mannitol has greater benefit if administered early in the course of illness, so the delay may have diminished the effect in this study. One concern with administration of mannitol in the setting of ciguatera is that patients may present dehydrated. In these cases, patients should be adequately rehydrated before administration of mannitol. During recovery from ciguatera, it is recommended that victims exclude fish, shellfish, alcoholic beverages, and nuts and nut oils from their diet, as these could result in exacerbation of the syndrome.[437] Gabapentin has been used successfully for treatment of chronic symptoms after ciguatera poisoning, but symptoms seem to recur after cession of therapy in some patients.[372]

Prevention

For travelers, common sense dictates avoiding any fish that local fishermen and residents do not eat, or fish caught in areas known to be endemic for ciguatera. Any level of Caribbean ciguatoxin of 0.1 ppb or more of fish tissue is thought to be a health risk.[282] Because of the accumulation of toxin, all oversized fish of any predacious reef species (such as jack, snapper, barracuda, grouper, or parrot-beaked bottom feeder) should be suspected to be toxic. Moray eels should never be consumed. Internal organs of implicated fish seem to concentrate the toxin and should therefore be avoided. Natural events, such as hurricanes and earthquakes, have been associated with an increased incidence of ciguatera, presumably because of reef disturbance. El Niño storms may also affect the incidence of ciguatera in the Pacific.[29]

CLUPEOTOXIC FISH POISONING

Clupeotoxic fish poisoning involves plankton-feeding fish that ingest blue-green algae and dinoflagellates. This poisoning is distinguished from ciguatera on the basis of the severity and high fatality rate of clupeotoxic fish poisoning and identification of the implicated clupeoid fish. These fish of the order Clupeiformes are found in tropical Caribbean, Indo-Pacific, and African coastal waters. Toxicity is reported to increase during warm summer months. Viscera are considered to be highly toxic. Previously, the toxin was poorly characterized as a result of infrequency of the syndrome and rare access to toxic animals. The first case to shed light on clupeotoxism was reported in a Madagascar woman who died after eating a sardine, *Herklotsichthys quadrimaculatus*.[362] This same sardine has been implicated in clupeotoxism in Fiji and the Philippines.[540,539] The causative toxin was identified as palytoxin or its analog, which distinctly differed from ciguatoxin. Palytoxin is an extremely poisonous nonprotein agent of low molecular weight that has been isolated from various zoanthid soft corals of the genus *Palythoa,* and subsequently from many other organisms such as seaweed and shellfish.[194,510]

Palytoxin was found in the dinoflagellate *Ostreopsis siamensis,* which caused blooms along the coast of Europe, resulting in extensive death of edible mollusks and echinoderms, and human illness.[510] Since the structure of palytoxin was reported in 1981, numerous palytoxin-like substances have been described from various marine organisms.[117] Palytoxin has been found in mackerel *(Decapterus macrosoma),* filefish *(Altera scripta),* freshwater puffer fish (*Tetraodon* sp.), triggerfish *(Melichthys vidua),* and several species of crab *(Demania reynaudii, Demania alcalai, Lophozozymus pictor).*[6,117,161,267] Palytoxin poisoning was recently suspected after cowfish *(Lactoria diaphana)* ingestion.[431] Other examples include the families Clupeidae (herrings and sardines), Engraulidae (anchovies), Elopidae (tarpons), Albulidae (bonefishes), and Pterothrissidae (deep-sea slickheads).[25,325]

Pathophysiology

The benthic dinoflagellate *O. siamensis* is the most probable toxin source.[362,535] As with ciguatoxin, the poison typically does not impart any unusual appearance, odor, or flavor to the fish. The exact mechanism of palytoxin effects remains to be elucidated. However, in vitro studies have demonstrated multiple effects. Palytoxin appears to increase cell permeability to sodium in neuronal cells by converting the sodium-potassium ATPase pump to a permeable channel to monovalent cations, allowing potassium efflux and sodium influx. The subsequent membrane depolarization may open voltage-dependent calcium channels in synaptic nerve terminals, cardiac cells, and smooth muscle cells. In addition, there is increased intracellular calcium concentration through the sodium-calcium exchanger. Ultimately, the increase in intracellular calcium stimulates release of neurotransmitters from nerve terminals, histamine from mast cells, and vasoactive agents from the vascular endothelium.[353,510] Palytoxin may also increase cytosolic hydrogen concentration.[510]

Clinical Presentation

Symptoms of palytoxin exposure vary greatly, depending on the route of exposure. This was originally described using several animal species and various routes of exposure.[516] Deaths have occurred due to palytoxin injection in animals and ingestion in humans. Additional symptoms have been observed to be caused by dermal, ocular, and inhalational exposure in humans. Ingestion in humans reportedly causes abdominal cramps, nausea, diarrhea, limb paresthesias, muscle spasm, and respiratory distress. Of this cluster of symptoms, the predominant physical findings appear to be respiratory distress and extreme tonic muscle contractions. Severe debility leading to death may occur within 15 minutes of the onset of symptoms.[199] A case definition for human poisonings was offered by Tubaro and colleagues.[489] Mortality rates have been reported to be as high as 45%. One of the most commonly reported complications appears to be rhabdomyolysis, with peak creatine kinase levels typically occurring 24 to 36 hours after symptom onset.[117,359] A recent case series of confirmed palytoxin poisoning from Taiwan included a patient that had a fatal dysrhythmia attributable to hyperkalemia following ingestion of *Herklotsichthys quadrimaculatus* (goldspot herring).[532] Surviving family members of this outbreak reported persistent myalgias as well as axonal sensorimotor polyneuropathy. A postmortem examination in one case after ingestion of *Sardinella marquesensis* (Marquesan sardine) flesh and viscera demonstrated enterocolitis and the sequelae of hypotension and acute heart failure.[325]

Inhalational exposure has also been described. In the summer of 2005, a massive proliferation of the tropical microalga *Ostreopsis* spp. broke out along the Mediterranean coastline of Liguria, near Genoa, Italy. Approximately 200 people experienced fever, conjunctivitis, and respiratory distress after exposure to this marine aerosol. Palytoxin and a new analog, ovatoxin-A, were later identified.[96] Dermal exposures have also been described, specifically with handling of marine zoanthids containing palytoxin sold in the home aquarium trade.[216,353] There is a great deal of conflicting information regarding the risks of palytoxin exposure from store-bought aquarium zoanthids. Numerous unconfirmed anecdotal stories can be found by affected individuals online at coral reef hobbyist forums. Palytoxins are not found in all commercially available zoanthid species, but they clearly occur in potentially dangerous concentrations in a select few.[117]

Treatment

Therapy is supportive and based on symptoms, with a focus on aggressive hydration to prevent renal failure associated with rhabdomyolysis. Because of the severe nature of this intoxication, early gastric emptying is desirable; however, the disease is so unusual and so rarely suspected that gastric emptying is not often considered. Patients should be monitored for development of hyperkalemia and life-threatening dysrhythmias during the course of treatment. Aggressive management and early intensive care are essential.

Prevention

Clupeotoxic fish should be avoided, especially during summer months. These fish are indigenous to Caribbean, African coastal, and Indo-Pacific waters. The viscera of suspicious fish can be fed to experimental animals to see if illness is generated. Because a rapid and sensitive hemolysis neutralization assay for palytoxin is available, the toxin's presence in seafood should become easier to determine.[41] Persons handling zoanthid coral should wear protective gloves to decrease the risk of local and systemic toxicity.

PARALYTIC SHELLFISH POISONING

Shellfish have been implicated in poisonings for centuries, if not millennia. Epidemics of shellfish toxicity have been linked to proliferation of dinoflagellates and other small marine organisms responsible for red tides or blooms in oceans around the world. The Bible refers to red tides in Exodus 7:20-21, where "the waters that were in the rivers were turned into blood, and the fish that was in the rivers died; and the river stank." The Red Sea was so named by ancient Greeks for its red appearance in certain seasons when red tides occurred. Red tides are described in the *Iliad* and were first recognized by North American Indians as luminescence or "flickering" of ocean waves.[68]

Perhaps the first published description in the Western world of a patient with clinical findings suggestive of paralytic shellfish toxicity dates back to 1689. An article from a French journal named *Ephemeredes des Curieux de la Nature* described a young woman who had ingested mussels.[90,197] The description notes that her symptoms included fever, chest pain, respiratory insufficiency, nausea, seizures, and tachycardia. She had emesis induced, bringing up the mussels, and eventually recovered. For years after this report, the incidence and cause of paralytic shellfish toxicity were undocumented throughout the world, but epidemics were known to occur in certain seasons and under certain conditions. Improvements in monitoring and public health reporting have demonstrated patterns of occurrence. Gessner and Middaugh[173] described 54 outbreaks of paralytic shellfish poisoning in Alaska occurring in 117 individuals between 1973 and 1992. The California Paralytic Shellfish Poisoning Prevention Program has been so successful that it has been a model of surveillance for many other countries.[379] Paralytic shellfish poisoning has been a reportable condition in California since 1927, with more than 500 cases and 30 deaths reported since that time. In California, there is an annual 6-month quarantine (May through October) on locally harvested mussels, clams, and oysters.

Of the several types of neurologic diseases occurring after ingestion of shellfish, PSP is one of the most common. This syndrome is most frequently reported during summer months when water temperature is highest, but has also been recorded from May to November.[184,197] Some authors suggest that the toxin responsible for PSP may be present in significant concentration in some shellfish, such as the Alaskan butter clam, in certain areas year round, and that shellfish harvested from untested waters of these regions never be consumed.[172] The most commonly implicated varieties of shellfish include mussels, clams, oysters, and scallops.[173,197,252] Lobster hepatopancreas toxicity has also been noted.[144] Although almost all outbreaks have been described from shellfish consumption, 13 cases of paralytic shellfish poisoning were diagnosed in Florida in 2002 after ingestion

of puffer fish containing saxitoxin, rather than TTX.[78] To distinguish the puffer fish poisonings from those caused by TTX, the puffer fish syndrome is becoming known in the literature as *saxitoxin puffer fish poisoning*.[144]

Pathophysiology

The major toxin sources of paralytic shellfish poisoning include marine dinoflagellates of the genera *Alexandrium* (formerly *Gonyaulax*), *Gymnodinium,* and *Pyrodinium*. Bacterial origins of the toxin have also been proposed.[144]

Dinoflagellates produce a number of toxins, the most commonly identified of which is saxitoxin. If a single organism predominates, it can discolor the water, creating a black, blue, pink, red, yellow, brown, or luminescent "tide."[97] Organisms can multiply rapidly from a concentration of 20,000/L to more than 20 million/L. These plankton can release massive amounts of toxic metabolites into the water, at times leading to enormous mortality rates in various bird and marine populations, including large mammals such as dolphins and even whales. Large numbers of dead animals on the beach suggest a colored tide. The trend toward increased numbers and magnitude of blooms is attributable to many factors, including coastal development, dumping of sewage, fertilizer runoff, and ocean warming. Kills by the dinoflagellate *Karenia* (formerly *Gymnodinium breve* and *Ptychodiscus brevis*) *brevis* are estimated at 100 tons of fish per day. The problem is markedly increasing in Europe.[498]

A limited number of the approximately 1200 species of dinoflagellates has been implicated in human toxic syndromes.[412] Paralytic shellfish poisoning has been linked to the dinoflagellate *Protogonyaulax,* species *catanella* (U.S. Pacific coast), species *tamarensis* var. *excavata* (U.S. Atlantic coast and Europe), and *Gymnodinium catenatum* (northwestern Spain).[321,470] These creatures are relatively fastidious and prefer to bloom in warm, sunlit water of low salinity. Some algal organisms may release their toxin in the form of microscopic cysts, which can hibernate at the sediment-water interface. In mollusks, the greatest concentration of toxin is found in the digestive organs (e.g., the dark hepatopancreas), gills, and siphon.[426] Toxic benthic dinoflagellate cysts may be transported by dredging operations, potentially introducing a dinoflagellate population into a new region.[541]

Although the origin of paralytic shellfish toxins is assumed to be dinoflagellates, the toxins have been isolated in both marine and freshwater bivalves that are not associated with dinoflagellates. It has not been determined how this has occurred.[356] The bacterium *Moraxella* isolated from *Protogonyaulax tamarensis* has been shown to produce paralytic shellfish toxins in culture. Toxin production can increase in nutritionally deficient environments.[268]

The paralytic shellfish toxins identified to date are 18 related tetrahydropurine compounds produced mainly by dinoflagellates of the genus *Alexandrium*. These include saxitoxin, neosaxitoxin, and the gonyautoxins (GTX1, GTX2, GTX3, GTX4, GTX5), with the best characterized being saxitoxin.[167] Saxitoxin ($C_{10}H_{17}N_7O_4$) takes its name from *Saxidomus giganteus,* the Alaskan butter clam. *P. brevis* is a toxic dinoflagellate that produces a milder toxin. Other dinoflagellates considered poisonous to animals or humans include *Gonyaulax catenella, Pyrodinium phoneus, Pyrodinium bahamense* var. *compressa, Gonyaulax monilata, Gonyaulax polyhedra, Gymnodinium veneficum,* and *Exuviaella maria-lebouriae*.[363] *S. giganteus* and the Washington clam *(Saxidomus nuttalli)* may carry the toxin in their neck parts for up to 2 years; however, no physical characteristic distinguishes a carrier animal.

Unfortunately, a direct human serum assay to identify the toxin responsible for paralytic shellfish poisoning is not readily available to clinicians. Paralytic shellfish poisoning is assessed in foodstuff using a mouse bioassay, in which a 20-g mouse is injected with 1 mL of an acid extract of the shellfish, and the time taken for the animal to die is recorded. One mouse unit (mu), or 0.18 mg, is the amount of injected saxitoxin that kills a test mouse in 15 minutes.[498] In most countries, the action level for closure of a fishery is 400 mu/100 g shellfish. Polyclonal enzyme-linked immunosorbent assays (ELISAs) that measure saxitoxin, neosaxitoxin, and gonyautoxins 1 and 3 may be reasonable screening techniques. Other testing methods under investigation include a sodium channel–blocking assay, spectrometry, thin-layer chromatography, and fluorometric HPLC.[167,309] An automated tissue culture (neuroblastoma cell) bioassay may become a valid alternative to live animal testing.[240]

Saxitoxin and related compounds are water soluble and heat and acid stable. At least 24 saxitoxin-like congeners have been identified, with an array of hydroxyl, carbamyl, and sulfate substitutions on the backbone structure, and also with large variation in potency.[196,144] Like TTX, they can be destroyed to a certain extent in an alkaline medium but not by ordinary cooking. Saxitoxins are chemically distinct from TTX, but both act on site 1 of the voltage-dependent sodium channel, blocking influx of sodium into excitable cells and restricting signal transmission along nerve and muscle membranes.[277] Although the threshold levels for causing illness in humans are not definitively known, it has been suggested that ingestion of 200 to 500 mg would cause at least mild symptoms; 500 to 2000 mg, moderate illness; and more than 2000 mg, serious or fatal illness. However, serious symptoms have been reported after ingestion of less than 100 mg of saxitoxin in adults. During peak red tide seasons, each mussel may accumulate up to 50,000 mu of saxitoxin. Mussel concentrations of saxitoxin have been determined to be too high for consumption when seawater dinoflagellate counts are as low as 200/mL.[426] A saxitoxin concentration of greater than 75 to 80 mcg/100 g foodstuff is considered hazardous to humans. In the 1972 New England red tide, the concentration of saxitoxin in blue mussels exceeded 9000 mg/100 g foodstuff. In cases of paralytic shellfish poisoning in Massachusetts, saxitoxin concentrations of 24,400 mg/100 g were recorded in raw mussels. With oral ingestion of saxitoxin, the LD_{50} for mice is 263 mg/kg. It has been estimated that as little as 0.5 to 1 mg of saxitoxin can be fatal in humans.[426]

Neither steaming nor cooking affects potency of the toxin. Commercial processing of shellfish does not eliminate the toxin or potential for toxicity; therefore, public health agencies in the United States and Canada strictly monitor these canning industries.

Clinical Presentation

Onset of symptoms of paralytic shellfish poisoning is rapid. Within 30 to 60 minutes of ingestion, victims complain of paresthesias, numbness, vertigo, and tingling of the face, tongue, and lips. Cranial nerve dysfunction, including dysarthria, dysphonia, dysphagia, and even blindness, can occur.[173,197,220,321] Other early symptoms include light-headedness, floating sensation, ataxia, weakness, hyperreflexia, incoherence, sialorrhea, thirst, abdominal pain, nystagmus, dysmetria, headache, diaphoresis, sensation of loose teeth, chest pain, high blood pressure, and tachycardia. Neurologic symptoms progress to involve the extremities and trunk over the first 1 to 2 hours. Limb weakness may begin any time after sensory changes, and gradually progresses to ataxia, and finally paralysis. Reflexes are frequently normal throughout progression of the disease, and patients remain awake and alert. Death results from respiratory failure with diaphragmatic and chest wall muscle paralysis.

Although some victims have nausea, vomiting, or diarrhea, lack of gastroenteritis and thus early self-decontamination may in part explain why the mortality rate from paralytic shellfish poisoning approaches 25% in some older series.[26,515] More recent reports cite a lower incidence of fatalities, probably because of improvements in supportive care. Hypotension can result from direct action of the toxin on vascular smooth muscle, although both diastolic and systolic hypertension have been reported.[249,172] Toxicity is generally not delayed more than 10 to 12 hours, with a median onset of 3 hours. The prognosis is good for individuals surviving past 12 hours, but weakness can persist for weeks. Children seem to be more sensitive to saxitoxin than are adults. In milder cases, alcohol ingestion appears to increase toxicity. Saxitoxin is structurally similar to TTX and shares a common mechanism of action. Intoxication causes superimposable symptoms; these two syndromes can only be differentiated by their area of distribution or by isolation and identification of the specific toxin.[149]

Treatment

No antidote is currently available for saxitoxin or paralytic shellfish poisoning. The victim should be closely observed in the hospital for at least 24 hours for respiratory insufficiency. Airway patency and respiratory support are of utmost importance, because even patients with severe symptoms of poisoning often do well if expeditiously supported with mechanical ventilation. Although gastric emptying has been advocated by some authors when shellfish suspected of containing saxitoxin are ingested, airway collapse can be rapid and induction of emesis should not be attempted.[220] These toxins bind well to charcoal, so an oral dose of charcoal should be administered if this can be done safely.[88] Some clinicians suggest that atropine administration may worsen symptoms of paralytic shellfish poisoning and should be avoided, because saxitoxin and its derivatives may have antimuscarinic effects.[425] Several studies have suggested that acidity may enhance the potency of saxitoxin, leading some authors to speculate that serum alkalinization might be of benefit to victims, although the efficacy of this practice has yet to be established.[11,208,316,366]

At least one human case report and some animal data have implied that dialysis or hemoperfusion may benefit some victims of severe PSP.[26,388] Other reports are less optimistic, because in vitro trials have demonstrated that dialysis is not effective in removing saxitoxin.[136,208] Some clinicians have suggested enhancing renal clearance with diuresis, but no study supports this practice. Maintaining normal urine output should suffice in most cases.

Prevention

The most important aspect of managing paralytic shellfish poisoning is prevention. It has been said that one should not eat shellfish in the Northern Hemisphere in months that contain the letter *r*. It has become more apparent with changing ocean conditions that shellfish in many parts of the world may be contaminated throughout the year because of high water concentrations of *Gonyaulax*. Most coastal agencies monitor dinoflagellate concentrations off the shores of developed countries and restrict shellfish harvesting during high-risk periods. Despite aggressive public health monitoring in a known endemic region, a recent outbreak in Washington State was described following noncommercial harvesting in mid-September because posted signs restricting collection of shellfish were not visible in the darkness.[223] In addition, harvesting management strategies, such as harvesting parts of the organisms known to be safe and discarding the parts of the organism that may pose a threat, are in place.[144] Many outbreaks of this illness have occurred on isolated islands where public health monitoring is infrequent and intensive care medicine resources scarce. Saxitoxin found in southern puffer fish off the coast of Florida is much more concentrated within the muscle than in the liver; therefore, even careful preparation of these puffer fish fillets would not prevent intoxication to consumers.[277]

NEUROTOXIC SHELLFISH POISONING

Neurotoxic shellfish poisoning, often described clinically as a milder version of paralytic shellfish poisoning, results from consumption of molluscan shellfish contaminated with brevetoxins produced by the dinoflagellate *Kareni brevi, which* creates a colorful tide when it blooms and is considered endemic to the Gulf of Mexico. Brevetoxins are potent ichthyotoxins associated with large numbers of dead birds, fish, and mammals. In 1996, 149 manatees died along the southwest Florida coast; brevetoxin was implicated as the primary cause of the epizootic.[51] Signs and symptoms of intoxication in fish include violent twisting and corkscrew swimming, defecation and regurgitation, pectoral fin paralysis, caudal fin curvature, loss of equilibrium, quiescence, vasodilation, convulsions, and fatal respiratory failure.[24]

Pathophysiology

K. brevis produces a group of at least 10 toxins, known as brevetoxins.[24] These toxins are designated PbTx-1 to PbTx-10 and are potent, lipid-soluble, cyclic polyether compounds that bind to and modulate voltage-gated sodium channel activity.[116] Brevetoxins produce acute neuronal injury and death in rat cerebellar neurons.[38] In a canine model, brevetoxins produce depolarization of tracheal and bronchial smooth muscle.[394] Intratracheal brevetoxin instillation in rats resulted in systemic distribution of brevetoxin, which suggests that initial respiratory irritation and bronchoconstriction may be only part of the toxicologic syndrome with brevetoxin inhalation.[34]

Although a human assay to detect the presence of brevetoxins is not readily available to clinicians, a number of distinct methods, in addition of the traditional mouse bioassay, have been developed using ELISA, HPLC, or liquid chromatography paired with mass spectrophotometry, receptor binding assay, and radioimmunoassay to detect the presence of brevetoxins in environmental and biologic samples.[493]

Clinical Presentation

Ingestion of shellfish contaminated with brevetoxin can induce neurotoxic shellfish poisoning. The condition resembles ciguatera toxin poisoning in symptoms but does not have a major paralytic component. Death has not been reported in humans. Symptoms include circumoral and limb paresthesias, dizziness, ataxia, muscle aches, and gastrointestinal symptoms. The median incubation time for this illness is 3 to 4 hours, and it lasts several hours to a few days.[333] Most neurotoxic shellfish poisoning outbreaks have occurred along the Gulf of Mexico or on the west coast of Florida, in coastal Texas, in North Carolina, and in New Zealand.[333]

Unlike other shellfish poisoning syndromes, neurotoxic shellfish poisoning can cause a respiratory irritation syndrome. When large blooms of *K. brevis* occur near the shoreline, wind and wave action can aerosolize the toxin; if sea breezes blow the aerosolized toxin onshore, rapidly reversible conjunctivitis, rhinorrhea, and bronchospasm with nonproductive cough can occur in sensitive individuals.[220] Severe respiratory distress is uncommon, but asthmatics may have respiratory effects that may persist for days following just 1 hour of brevetoxin exposure.[259]

Treatment

As with paralytic shellfish poisoning, there are no antidotes available for treatment of neurotoxic shellfish poisoning. Management consists mainly of supportive and symptomatic care. Although death has not been reported, patients should be monitored for respiratory deterioration. Because patients with asthma are at particular risk for more prolonged and perhaps more severe respiratory symptoms, additional precautions to address respiratory dysfunction are advisable in this population.

Prevention

Avoiding consumption of contaminated shellfish in known endemic areas, such as the coastline of the Gulf of Mexico, adjacent areas of the United States, and New Zealand, during warning periods is key. Although neurotoxic shellfish poisoning is mainly a result of consuming contaminated shellfish, certain healthy omnivorous and planktivorous finfish may accumulate and retain high levels of brevetoxins in their muscles and viscera.[334] There are no guidelines warning against consumption of muscle meat from finfish that are harvested during or after red tides, but there are some cultural communities that engage in whole fish consumption. Because the highest levels of brevetoxins found in healthy finfish were detected in the liver and stomach, consuming these parts may place persons consuming whole fish at higher risk for neurotoxic shellfish poisoning.

DIARRHETIC SHELLFISH ILLNESS

Diarrhetic shellfish poisoning is a rapid-onset illness with gastrointestinal symptoms, which although typically severe, are self-limited. Ingestion of shellfish contaminated with dinoflagellates belonging to the genus *Dinophysis (Dinophysis fortii, D. acuminata, D. norvegica,* and *D. acuta)* or *Prorocentrum (P. lima* and *P. minimum)* causes diarrhetic shellfish poisoning. Lipid-soluble toxins accumulate in shellfish fatty tissues and the hepatopancreas of mussels. They exert their effects mainly on the human

small intestine, leading to diarrhea and degenerative changes of the absorptive epithelium.[318,498] Symptoms include rapid onset (30 minutes to 2 hours) of diarrhea, nausea, vomiting, abdominal pain, and chills. Rarely, symptoms are delayed up to 12 hours. The syndrome is self-limited and resolves after 2 to 3 days. From 1976 to 1982, diarrhetic shellfish poisoning was diagnosed in at least 1300 persons in Japan. The period of greatest toxicity appears to be May to August. In 1981, more than 5000 cases were reported in Spain.[538] Other outbreaks have occurred in The Netherlands and Chile.[201] In 1993, a particularly severe episode occurred in Spain with unusual symptoms; analyses revealed a complex toxin profile, with both paralytic and diarrhetic shellfish toxins present.[166]

DSP toxins include okadaic acid, okadaic acid diolester, dinophysistoxins (DTX-1 to DTX-4), and pectenotoxins.[3,315,496,521,538] Okadaic acid was first isolated from a sponge *(Halichondria okadai)* in the Pacific.[461] It is a specific and potent inhibitor of protein synthesis and inhibits phosphatases A_1 and A_2 in vitro. Okadaic acid induces diarrhea because it increases phosphorylation of proteins, which either controls sodium secretion of intestinal cells or influences permeability of cell membranes.[100,124] It is a potent tumor promoter in mouse cells and can act as a genotoxin.[150] Other diarrhetic shellfish toxins exert various effects in experimental animals: pectenotoxins induce liver necrosis, and yessotoxins (from the Japanese scallop *Patinopecten yessoensis*) induce intracytoplasmic edema in cardiac muscle.[474,476] Minimal doses of okadaic acid and DTX-1 necessary to cause diarrhetic shellfish poisoning symptoms are 40 mg and 36 mg, respectively.[203] Metals (e.g., aluminum, copper, lead, mercury, cadmium) in concentration at or below acceptable levels in mussels synergistically increase cytotoxicity of low concentrations of okadaic acid in cultured cells.[485]

Increasing incidents of phytoplankton blooms with a danger of toxin release have necessitated searching for new diagnostic methods that can detect toxin quickly and reliably. A variety of techniques, including radioimmunoassay using antibodies raised in rabbits, competitive ELISA, idiotypic antiidiotypic competitive immunoassay, rapid tissue culture assays, and cytotoxicity assays, can identify the presence of okadaic acid.[92,104,292,429,491] A unified bioscreen for detection of diarrhetic shellfish toxins and microcystins (as from blooms of the cyanobacteria *Microcystis aeruginosa*) uses capillary electrophoresis coupled with a liquid chromatography–linked protein phosphatase bioassay.[48] A protein phosphatase A_2 inhibition assay has been shown to be rapid, accurate, and reproducible; it can detect concentrations as low as 0.063 ng/mL in aqueous solutions and 2 ng/g in mussel digestive glands.[490] The Japanese quarantine standard is 200 ng of okadaic acid per gram of shellfish tissue. Four times this amount of toxin has been identified in northeastern Pacific Ocean mussels. Okadaic acid and related toxins are potent tumor-growth promotors and immunosuppressants in animals, but the effect of exposure in humans is unknown.[110]

AMNESTIC SHELLFISH POISONING

Domoic acid is produced in nature by the phytoplankton algae *Pseudonitzschia* species, which are widely distributed across the world.[275] Domoic acid, the toxin responsible for amnestic shellfish poisoning, is an excitatory neurotransmitter first described in Japan in 1958 and isolated from the red algae *Chondria armata.*[466] The first documented human outbreak of poisoning with this compound was in 1987 from Prince Edward Island, Canada, when more than 150 people became ill after ingesting cultured blue mussels, *Mytilus edulis,* later found to be contaminated with domoic acid.[239,373,472,530] Four of these individuals died, and the clinical description of persistent memory impairment in many survivors prompted the nickname of amnestic shellfish poisoning.[153] The source of the toxin in these cases was found to be *Nitzschia pungens*, a diatom that had been ingested by the mussels before humans ate them.[30,456] The toxin is concentrated in the mussels' hepatopancreas.

Epidemics of domoic acid poisoning have been prominent in other marine life, especially sea birds.[49,514,527] A large number of dead and distressed pelicans and cormorants were noted in Monterey Bay, California in September 1991.[527,528] Autopsies performed on dead birds demonstrated they had consumed large quantities of anchovies from the bay. Subsequent testing showed the anchovies contained high levels of domoic acid. This was the first report documenting the presence of domoic acid in the United States. Water samples taken in the area identified significant quantities of the diatom *Pseudonitzschia australis,* which were able to produce domoic acid when grown in a laboratory environment.[169,527] Three species of *Pseudonitzschia* are now known to produce domoic acid.

Undefined mortality events with signs of neurologic poisoning of California sea lions *(Zalophus californianus)* have been reported over multiple years, with domoic acid identified as a causative agent in 1998. That year, 400 sea lions were found stranded on shore from Monterey Bay to San Diego. The poisoning was correlated with a late spring bloom of the diatom *P. australis,* generating anchovies contaminated with domoic acid. Clinical signs in sea lions included ataxia, head weaving, seizures, or coma. Seizures varied in severity but were continuous during the period of toxicosis, lasting about 1 week, followed by treatment-aided recovery or death.[386]

Domoic acid has also been detected in Gulf shellfish (Gulf Coast oyster, *Crassostrea virginica*) and phytoplankton in the Gulf of Mexico, although no outbreaks of amnestic shellfish poisoning have been recorded in this region. The toxic *N. pungens* forma *multiseries* has also been confirmed in Korea, Japan, Oslofjord, Scandinavia, the northeastern and northwestern United States, eastern and western Canada, and eastern South America.[127]

In the fall of 1991, the latest reported epidemic of domoic acid poisoning occurred in Washington State.[260] More than 20 people who consumed razor clams were affected. Subsequent testing confirmed the presence of domoic acid in razor clams along the coasts of both Washington and Oregon, although mussels tested in these areas were virtually free of toxin. Dungeness crabs collected from these waters were also found contaminated with domoic acid. Many contaminated filter-feeding marine organisms, such as shellfish and finfish, have been identified as domoic acid vectors. However, in terms of human health risks, species such as market squid, scallops, mussels, and razor clams are of most concern because of their demand by the seafood-consuming public.

Pathophysiology

Domoic acid was first isolated in 1958 following investigations on the antihelmintic and insecticidal activity of seaweed extracts. After the 1987 epidemic of neurotoxic illness on Prince Edward Island, Canada, significant evaluation of the surviving victims was undertaken. Chemical analysis at various laboratories ruled out all other known toxic causes of the symptoms displayed by patients.[530] Intraperitoneal injection of extracts of implicated mussels into mice produced a syndrome characterized by reproducible scratching followed eventually by death.[373,472] The toxin was finally identified as domoic acid.

Domoic acid is a water-soluble, excitatory neurotransmitter and a glutamate receptor agonist. It is structurally related to kainic acid, a potent neurotoxic amino acid.[361,419,472,530] This group of compounds is excitatory and acts on three types of receptors in the central nervous system (CNS), with those in the hippocampus being the most sensitive. Domoic acid seems to work by activating kainate receptors in the brain more potently than does kainic acid itself. The result of this stimulation is extensive damage to the hippocampus, as well as less severe injury to portions of the thalamic and forebrain regions.[321,398,472] There may also be mechanisms mediated by non-*N*-methyl-D-aspartate (NMDA).[468]

It was estimated that the mussels implicated in the Canadian outbreak of amnestic shellfish poisoning contained a total amount of domoic acid in excess of 6 kg, with most being concentrated in the digestive glands.[184,530] Other organisms known to produce domoic acid include the phytoplankton *Alsidium corallinum* and *C. armata.* Subsequent research suggests that other phytoplankton, such as *Amphora coffeaeformis,* can also produce domoic acid. Scientists continue to monitor shellfish and marine

microorganisms to determine the presence of other sources. There are 10 isomers of domoic acid identified to date; however, some of these have a significantly lower amount of toxicity than does the parent compound.[287] Domoic acid is relatively stable and does not degrade at room temperature. Also, cooking will not increase the safety of the shellfish product if it is contaminated with domoic acid.[320] There is wide variation in tissue distribution and retention of domoic acid; for example, razor clams have been shown to retain domoic acid for up to a year and contain domoic acid throughout all tissues, whereas most of the toxin is confined to the viscera in mussels and fish.[287]

Clinical Presentation

As a result of the Prince Edward Island event, numerous laboratory-based toxicity studies were performed in order to characterize the toxicity of domoic acid. Multiple regimens that have been investigated include intraperitoneal, intravenous, intra-arterial, intrauterine, and oral dosing and direct brain injections, making a direct comparison of domoic acid toxicity between species difficult. Studies have been performed in monkeys, mice, rats, birds, and fish. The most notable clinical signs of toxicity include scratching and seizures in rodents, vomiting in monkeys, spiral-swimming in fish, and tremors and scratching behavior in birds.[287,373,344]

Humans involved in the Canadian epidemic of amnestic shellfish poisoning had initial symptoms of nausea, vomiting, abdominal cramps, and diarrhea 1 to 24 hours after ingestion.[373,472] Neurologic symptoms initiated with memory loss began within 48 hours after ingestion and progressed in some victims to seizures, hemiparesis, ophthalmoplegia, and coma. Some victims displayed purposeless grimacing and chewing. Follow-up neuropsychological testing on affected patients displayed predominantly an anterograde memory disorder, with most other cognitive functions preserved.[373] The most severely affected individuals also had retrograde amnesia. Labile blood pressure and cardiac dysrhythmias were recorded in a few individuals, suggesting that domoic acid may be cardiotoxic.[381] Elevations in blood urea nitrogen and creatine phosphokinase were also noted in many victims and have been recorded in animals suffering domoic acid poisoning, possibly resulting from exertional myopathies or tremors.[373,528]

The onset of symptoms in victims of the Prince Edward Island epidemic ranged from 15 minutes to 38 hours, with the average approaching 5 hours.[373,472] Increased age was identified as a risk factor for both severity of illness and memory loss. Males were found to be more susceptible.[381] Most fatalities occurred in the oldest victims, with postmortem findings suggesting neuronal loss or necrosis, accompanied by astrocytosis.[373] The most severe damage was to the hippocampus and amygdala, which are brain areas known to participate in memory function. Lesions were also noted in the claustrum and the septal and olfactory regions. Retinal lesions have also been reported.[381] No lesions were found in the motor nuclei of the brainstem. Hippocampal lesions in victims at autopsy resembled those seen in the brains of animals injected with kainic acid.[373,321,442] A follow-up study on patients from the Montreal area suggested that bronchial secretions became so profuse in the hours after mussel ingestion that one-half of the severely affected individuals required endotracheal intubation.[373] Pupillary dilation or constriction, and piloerection were also common findings. Approximately 10% of involved patients demonstrated persistent memory loss or other neuropathies. Of patients exhibiting neurologic toxicity, maximal effects were noted within the first 3 days after mussel ingestion, and maximal improvement in neurotoxicity occurred in 24 hours to 12 weeks after ingestion. At 4 and 6 months following exposure, several patients had distal atrophy, with weakness of the extremities and hyporeflexia. Electromyography findings were consistent with an acute nonprogressive neuronopathy involving anterior horn cells or diffuse axonopathy predominantly affecting motor axons.[381] Another clinical syndrome, called *domoic acid epileptic disease,* is characterized by spontaneous recurrent seizures weeks to months after domoic acid poisoning and atypical behaviors in animals. There is at least one human who had persistent seizures 1 year after his initial poisoning.[386]

Treatment

As with most other shellfish toxins, no antidote exists for amnestic shellfish poisoning. Based on the alleged mechanism of action of both domoic and kainic acid, it is possible that benzodiazepines may be beneficial in controlling some of the excessive hippocampal activity and seizures.[361,528] Animal studies have suggested a lowered mortality rate in groups in which benzodiazepines are used after domoic acid exposure. There may also be a role for NMDA antagonists.[37]

Prevention

Many regulatory agencies worldwide have established biotoxin monitoring programs. Although monitoring programs have been effective at preventing human toxicity, chronic domoic acid toxicity has been characterized in other mammalian species, such as sea lions.[287] To protect seafood consumers, authorities have established an action limit of 20 mcg of domoic acid per gram of shellfish tissue. This is based on retrospective estimations of concentrations of 200 mcg of domoic acid per gram of mussel tissue, which caused illness during the amnestic shellfish poisoning outbreak and incorporates a safety factor of 10. This regulatory limit has been adopted by the United States, the European Union, New Zealand, and Australia. Levels exceeding this limit trigger closure of the affected beaches and shellfish harvesting areas.[287]

POSSIBLE ESTUARY-ASSOCIATED SYNDROME

Pfiesteria piscicida is a toxic dinoflagellate that inhabits estuarine and coastal waters of the eastern United States and has been associated with fish kills and a human illness that has been labeled possible estuary-associated syndrome. Since 1991, *P. piscicida* and other *Pfiesteria*-like species have been implicated in massive fish kills in estuaries of North Carolina, Maryland, and the Chesapeake Bay.[181,186,433] *P. piscicida* is responsible for a fish disease formally known as ulcerative mycosis. *Pfiesteria* is primarily a benthic organism, but can exist in at least 24 different life stages. Fish swimming into an area with *Pfiesteria* may be exposed to a toxin that is produced by the dinoflagellate. These fish develop characteristic ulcerative lesions and erratic swimming behavior. *Pfiesteria* have now been found in coastal waterways extending from Delaware to the Gulf Coast of Alabama.

Although it is not associated with seafood ingestion, possible estuary-associated syndrome is associated with seafood contact. The first report of adverse health effects in humans was described after an accidental laboratory exposure; investigators working with *Pfiesteria* developed respiratory and eye irritation, skin rashes, and cognitive and personality changes.[181] During the 1990s, commercial fishermen who were exposed to waterways with *Pfiesteria* species reported similar symptoms.[186,188,188,433] The route of exposure is unknown, although it is thought to be either by prolonged direct skin contact with toxin-laden water or via aerosols after breathing the air over areas where fish are dying from toxic *Pfiesteria*.

Individuals with high exposure complain of headache, skin lesions, skin burning on contact with water, eye irritation, upper respiratory tract irritation, muscle cramps, and neuropsychological symptoms, including increased forgetfulness and difficulties with learning and higher cognitive function.[188] No consistent physical findings or laboratory abnormalities have been found. When skin lesions appear, they are erythematous, edematous papules on the trunk or extremities that resolve within a few days to a week after exposure. Thorough neuropsychological testing has documented deficits in higher cognitive function and learning and functional memory.[188] The severity of cognitive dysfunction was directly related to the degree of exposure. The exact nature of the neurocognitive deficit is unknown; however, rats exposed to water containing *Pfiesteria* toxins have shown significant learning impairments.[290,291] Deficits may be expected to improve within 3 to 6 months after cessation of exposure to affected waters.[460] The natural history of the syndrome is improvement in most symptoms without treatment; however, cholestyramine has been successfully used in patients with persistent

symptoms.[434] The clinical improvement seen in cases treated with cholestyramine may be due to interruption of enterohepatic circulation of the toxin, although this hypothesis has not been confirmed.[435]

Diagnosis of the syndrome is difficult because the specific causal toxins have not yet been identified and a biomarker of exposure has not been developed. Current recommendations for diagnosis include (1) development of symptoms within 2 weeks after exposure to estuarine water, (2) memory loss or confusion of any duration, or three or more symptoms from the complex as described in the preceding paragraph, and (3) no other cause for symptoms identified.[76] A multiplex PCR assay is being developed for rapid identification of *P. piscicida* and other toxic *Pfiesteria* species.[331] Possible estuary-associated syndrome is not infectious and has not been associated with eating fish or shellfish caught in waters where *P. piscicida* has been found. Brief, direct water contact, including swimming, has not been associated with symptoms. No deaths have been associated with exposure to *Pfiesteria* species. People should avoid areas with large numbers of diseased, dying, or dead fish.

HAFF DISEASE

Haff disease is a syndrome characterized by severe muscle pain and rhabdomyolysis after consuming fish. It was first described in 1924 around the shores of Königsberg Haff, a bay on the Baltic Sea.[551] Further outbreaks have occurred in Sweden, Russia, and Brazil.[36,131,436,444] Twenty-three cases in total have been reported in the United States, most associated with eating buffalo fish *(Ictiobus cyprinellus)* or crawfish, bottom-feeding species found in the Mississippi River and its tributaries. Two cases have been associated with ingestion of a salmon meal.[281] Haff disease is most likely the result of a heat-stable toxin in blue-green algae that is eaten by fish; however, the toxin is currently unidentified.[75]

Haff disease manifests as generalized muscle pain and tenderness, rigidity, weakness, and rhabdomyolysis. Chest and back pain are common complaints.[213,549] Tachycardia, hypertension, tachypnea, and drop in temperature can also occur. Elevated serum creatine kinase occurs with leukocytosis, myoglobinuria, and elevation of lactate dehydrogenase and other muscle enzymes. Symptoms appear approximately 18 hours after eating fish (range, 6 to 21 hours).[75] Pathologically, there is neuromyodystrophy with necrosis in motor neurons of the brain and spine, coagulation necrosis of muscle, and myoglobinuric nephrosis. Treatment includes large volumes of intravenous fluids and diuretics to prevent renal failure from myoglobin toxicity. The diagnosis is based on the clinical presentation, laboratory data, and food history.

BLUE-GREEN ALGAE BLOOMS

Blue-green algae are worldwide freshwater cyanobacteria that proliferate rapidly in a bloom, discoloring the surface of the water and spoiling its odor and taste. Cyanobacteria in terrestrial water, freshwater, brackish water, and seawater produce toxins that are acute and chronic hazards to human and animal health and are responsible for isolated, sporadic animal fatalities each year. Typical algal species include *M. aeruginosa, Anabaena flos-aquae, Nodularia spumigena, Nostoc, Oscillatoria agardhii,* and *Aphanizomenon flos-aquae.*[99,143,345,405]

During conditions of a bloom (warm stagnant water, frequently enhanced by phosphorus and nitrogen fertilizers), the toxins are concentrated enough to become a significant hazard to wild and domestic animals and have been responsible for the deaths of livestock and dogs.[99,139,207,347,499] In most species of toxic cyanobacteria, the toxins are cyclic heptapeptides called microcystins, or cyanoginosins. More than 60 cyanobacterial toxins have been isolated from blue-green algae.[99,440] The toxins are of multiple configurations and include alkaloids, polypeptides, and lipopolysaccharides (endotoxins).[450]

Anatoxin-a and homoanatoxin-a are potent nicotinic agonists that act as postsynaptic, depolarizing neuromuscular blocking agents. Along with saxitoxin, these toxins cause animals to collapse quickly from neuromuscular paralysis, with features of staggering, muscle fasciculations, gasping, and convulsions.[206] Anatoxin-a(s) ("second" anatoxin-a) is an anticholinesterase that causes demonstrable cholinergic toxicity in animals.[67,206] Anatoxin-a and anatoxin-a(s) are both derived from *Anabaena flos-aquae.* Nodularins and microcystins cause hepatotoxicosis. Cylindrospermopsin is a protein synthesis inhibitor that induces necrotic tissue injury of multiple organs. Cyanobacterial lipopolysaccharide endotoxins are responsible for gastroenteritis and skin irritations.[99] In mice, administration of microcystin-LR causes rapid hepatocellular necrosis with hemorrhagic shock.[108,478]

Human exposure to blue-green algae blooms has resulted in allergic reactions, skin irritations, gastroenteritis, pulmonary consolidation, and liver damage.[99,374] A person who swims through a bloom may suffer local effects, such as conjunctivitis, facial swelling, or papulovesicular dermatitis. Ingestion of contaminated water causes dysenteric diarrhea, with green slimy stools. This may be associated with elevation of γ-glutamyl-transpeptidase and alanine aminotransferase levels. Inhalation of toxins is a probable exposure route; microcystin-LR and anatoxin-a cause significant toxicity in mice via intranasal aerosol exposure.[153] In 1996, more than 50 people with associated liver damage died at a hemodialysis clinic in Brazil. Microcystins are thought to have been present in the water used for hemodialysis.[99,134]

Treatment is supportive in humans and animals. Cyclosporine A has been shown to inhibit the fatal effects of microcystins administered to mice. In humans, no specific treatment is recommended other than fluid and electrolyte supplementation as needed, because all sequelae appear to be self-limited.

AZASPIRACID SHELLFISH POISONING

Azaspiracid poisoning was first described in 1995 in the Netherlands after an outbreak of severe vomiting and diarrhea from ingestion of mussels from Ireland. Although the symptoms were typical of diarrhetic shellfish poisoning, concentrations of the toxins associated with diarrhetic shellfish poisoning were very low in these shellfish. Therefore, an alternate, and in this case novel, causative agent was sought.[494] The toxin was originally named "Killary-toxin" based on the origin of these shellfish from Killary Harbour, Ireland. This unique toxin was later renamed azaspiracid toxin based on its chemical structure. Over the last decade, several analogs of this structurally distinct, heat-stable marine toxin have been identified. Shellfish contaminated with azaspiracids have been documented in several European countries and recently in the UnitedStates.[264]

Pathophysiology

The producing organism was originally thought to be *Protoperidinium crassipes.* However, it is now known to be produced by the small dinoflagellate *Azadinium spinosum.*[246] Limited availability of the pure toxins has impeded necessary investigations of azaspiracid poisoning. Initially, AZA1 toxin was isolated from the Killary mussels. Investigations have shown that AZA1 is cytotoxic to many cell types, including the liver, lung, pancreas, thymus, spleen, and especially small intestine. These effects are time and concentration dependent.[494] Several analogs of AZA have been identified. Some studies indicate that AZAs might have different targets. For example, AZA4 inhibits plasma membrane calcium channels.[162]

Clinical Presentation

The symptoms of azaspiracid poisoning appear within hours of ingestion and include nausea, vomiting, severe diarrhea, and stomach cramps. The illness persists for 2 to 3 days. To date, no long-term effects have been reported.[494] Most information regarding AZA toxicology has been obtained from in vitro and in vivo experiments. Mice injected with low doses of AZA developed slowly progressive paralysis, difficulty breathing, and listlessness. Large oral doses in mice demonstrated widespread organ damage, particularly necrosis in the lamina propria within the small intestine.[162] Azaspiracid poisoning remains a rare illness, although underreporting is probably likely because of the short duration and benign course of the illness.

Diagnosis

Levels of AZA vary significantly among mussels harvested from a given region. The European Commission regulatory limit is 0.16 mg/kg shellfish. Previous reports have determined the presence of AZA by liquid chromatography–mass spectrometry/mass spectrometry.[264] Other detection methods, such as ELISA, have been developed for AZA but are not commercially available.[494]

Treatment

At present, there is no specific treatment for azaspiracid poisoning. Treatment is primarily supportive, with a focus on preventing dehydration, and antiemetics for nausea and vomiting.

Prevention

Several incidents of human intoxication were the impetus for implementation of a national surveillance program that monitors levels of AZA in shellfish from all production areas in Ireland weekly. There have since been no further reports of azaspiracid poisoning incidents associated with Irish shellfish. In 2008, an outbreak occurred in France and Ireland following accidental dispatch to consumers of AZA-contaminated shellfish; the shellfish were held in quarantine following AZA confirmation.[162]

YESSOTOXIN POISONING

Yessotoxins (YTXs) were first isolated in 1986 from the Japanese scallop *P. yessoensis* and Norwegian mussels. They have since been observed in several countries, including New Zealand, Chile, Italy, Spain, the United Kingdom, and Canada.[8] Recently, YTX has been identified in French shellfish originating from the Mediterranean.[8] Yessotoxin and its analogs are produced by the dinoflagellates *Protoceratium reticulatum, Lingulodinium polyedrum,* and *Gonyaulax spinifera*.[488,492] YTX and its analogs were initially included in the group of toxins causing diarrhetic shellfish poisoning. However, they have recently been classified and regulated separately, because they do not share the same mechanism of action and only have been shown to be toxic to mice by intraperitoneal injection.[488,492] Similar to other marine toxins, the principal vectors for YTXs are scallops and mussels, which can accumulate large quantities of YTX, particularly in the hepatopancreas, because of their filter feeding nature.

More than 100 YTX analogs have been reported from shellfish and microalgae, although the structures of only about 40 of them have been identified. Although no reports of human poisoning induced by YTX have been recorded, YTX-contaminated shellfish have been reported worldwide.[367] In a mouse model, intraperitoneal injection of lethal doses of YTX or homoYTX caused symptoms similar to those of paralytic shellfish poisoning, with restlessness, dyspnea, shivering, jumping, and/or cramps.[22] Several studies have demonstrated a range of median LD_{50} values of from 80 to 750 mcg/mL.[488] The target organ of YTX appears to be cardiac muscle, where ultrastructural changes in mitochondria and myofibrils have been demonstrated.[488] Other YTX analogs cause fatty degeneration of the liver and pancreas. Oral administration in mice does not seem to cause behavioral changes or death. However, changes in the cardiac muscle were observed with repeated oral dosing. These changes resolved by 90 days.[492] Although the mechanism of action of YTX remains to be elucidated, it appears to exert a modest indirect effect on calcium channels.[488]

Due to the high number of existing analogs of YTX, methods of detection and quantification are complex. Mouse bioassay is the official method accepted to detect YTXs. However, it is time consuming and expensive, and lacks specificity.[367] Several other methods of detection are available and include functional assays, structural assays, and chemical methods. However, some of these methods have not been validated, and the gold standard for detection has yet to be determined.

OTHER TYPES OF SHELLFISH AND INVERTEBRATE POISONING

Callistin Shellfish Poisoning

The Japanese *Callista* clam *(Callista brevisiphonata)* is toxic during the spawning months of May to September, at which time cholinergic compounds in the ovaries are increased. Intoxication resembles cholinergic crisis, with both muscarinic and nicotinic components. Within an hour of ingestion of the heat-stable toxin, patients may experience generalized pruritus, urticaria, erythema, facial numbness and paralysis, hypersalivation, diaphoresis, fever, chills, nausea, vomiting, diarrhea, bronchorrhea, and bronchospasm.[25] Therapy is supportive, and recovery is usually complete within 2 days. In severe cases of cholinergic crisis, particularly with marked bradycardia, atropine (0.5 mg or more intravenously every 5 minutes, titrated to dry secretions, with adequate ventilation) may be administered.

Venerupin Shellfish Poisoning

The Japanese lake-harvested oyster *(Crassostrea gigas)* and clam *(Tapes semidecussatus)* occasionally feed on toxic dinoflagellate species of the genus *Prorocentrum,* posing the greatest risk during the months of December through April.[25,200] The heat-stable toxin induces rapid onset of gastrointestinal distress, headache, and nervousness, followed at 48 hours by hepatic dysfunction, manifested by elevation of liver enzymes, leukocytosis, jaundice, and profound coagulation defects. Delirium and coma may ensue, and death occurs in 33% of victims. Therapy is supportive. Any victim who shows early symptoms of gastroenteritis should be monitored for 48 to 72 hours for signs of liver failure. There is not yet clinical experience with exchange transfusion, chemotherapy, hemoperfusion, or liver transplantation in management of profound liver failure associated with this disorder.

Tridacna Clam Poisoning

Giant clams of the species *Tridacna maxima* are eaten in French Polynesia.[25] This species can cause poisoning characterized by nausea, vomiting, diarrhea, paresthesias, tremor, and ataxia. Severe cases can be fatal. The toxin appears to be concentrated in the mantle and viscera of the clam. Therapy is supportive.

Whelk Poisoning

In Japan, poisoning has followed ingestion of mollusks of the genera *Neptunea, Buccinum,* and *Fusitriton* (whelks, or ivory shells). The toxin is located in the salivary glands and has been characterized as tetramine.[13] Tetramine (trimethylammonium) is a naturally occurring quaternary ammonium compound that has been identified in anemones, gorgonians, jellyfishes, and mollusks.[12] Symptoms include headache, dizziness, nausea, vomiting, blurred vision, and dry mouth. No fatalities have been reported. Therapy is supportive.[25]

Ivory Shell Poisoning

Human poisonings have followed consumption of the ivory shell *Babylonia japonica,* which is widely distributed along the coastline of Japan. The toxin, surugatoxin, is located in the midgut of the animal and reputed to be produced by a gram-negative bacterium on which the snail feeds. Surugatoxin and ivory shell toxins appear to have autonomic ganglionic blocking action. Symptoms include abdominal pain, diarrhea, nausea, vomiting, oral paresthesias, syncope, and seizures.[201] TTX has also been identified in *B. japonica*.

Abalone Poisoning

Abalone poisoning follows ingestion of the viscera of certain Japanese abalone (tsunowata, or tochiri), particularly from the Island of Hokkaido, where *Haliotis discus* and *Haliotis sieboldi* are found. Symptoms include severe urticaria, erythema, pruritus, edema, and skin ulceration. The reaction appears to be of a photosensitive nature, as the lesions are confined to areas of ultraviolet exposure. The toxin may be derived from chlorophyll contained in the seaweeds on which the abalone feed.[25] Therapy is supportive.

Cephalopod Poisoning

In certain areas of Japan, intoxications have resulted from ingestion of squid and octopus. Symptoms develop within 10 to 20 hours and consist of nausea, vomiting, diarrhea, abdominal pain, headache, weakness, paralysis, and seizures. Although most

victims recover within 48 hours, deaths have occurred.[25] Therapy is supportive.

Sea Cucumber Poisoning

Sea cucumbers are eaten throughout Asia and in some Pacific islands, where they are known as trepang, sea slugs, cucumbers, erico, or hai shen. Gastroenteritis is induced by saponins of the triterpinoid variety, such as holothurin. The typically self-limited disorder consists chiefly of abdominal pain, nausea, and diarrhea.

Sea Hare Poisoning

Sea hares are marine gastropod mollusks prevalent in certain South Pacific waters, including Fiji. *Aplysia* species have been considered to be toxic since Roman times. *Aplysia juliana* secretes an antibacterial and antineoplastic protein found in the water-soluble fraction of a fetid secretion lethal to crabs. Human poisoning has been reported after ingestion of *Dolabella auricularia* (known as *veata* in Fiji).[410,448] The symptoms begin approximately 30 minutes after eating and include prickling skin sensations, vomiting, diarrhea, shaking, tremors, fasciculations, arthralgias, dyspnea, visual disorientation, altered sensorium, and fever. The course of illness may exceed a week. It has been suggested that sea hare poisoning in humans might be a form of subacute organobromine intoxication.

Ingestion of the sea hare *Aplysia kurodai* was associated with acute liver damage with sustained elevations of aminotransferases. Microscopic findings in a liver biopsy specimen revealed characteristic apoptotic hepatocytes accompanied by mitotic hepatocytes. Bioactive substances in the sea hare might induce such apoptosis of hepatocytes in the liver.[411]

Anemone Poisoning

In the South Pacific, ingestion of the green or brown anemones *Radianthus paumotensis* or *Rhodactis howesii* (mata-malu samasama) has been associated with severe illness and death. Accidental deaths generally involve small children, whereas adults may be the unfortunate recipients of improperly cooked anemone or may be intentionally stricken in acts of suicide. The toxic substances are found in the nematocysts and the tentacles. Anemones have been used for criminal purposes in the South Pacific.[25] *Physiobranchia douglasi* is poisonous if eaten raw but is reputedly safe if cooked.[201]

Ingestion of the raw anemone induces an altered mental status within 30 minutes, often immediately after ingestion. The victim becomes agitated or confused, delirious, and then comatose. Other symptoms include fever, seizures, myalgias, abdominal pain, respiratory failure, and hypotension; death may follow. Contact with the skin, particularly mucous membranes, is extremely painful, with rapid inflammation and vesiculation.

Treatment is symptomatic and supportive. Because of the rapid onset of symptoms, the rescuer must be prepared to provide advanced life support within the first hour after ingestion.

A toxic protein has been isolated from the sea anemone *Urticina piscivora*. It is a potent cardiac stimulatory protein and potent hemolysin on erythrocytes of the rat, guinea pig, dog, pig, and human, causing toxicity at concentrations as low as 10^{-10} M.[98]

Crab Poisoning

Human intoxications have followed ingestion of crabs in many Indo-Pacific islands. Most of the toxic crab species are members of the family Xanthidae and include the genera *Demania, Carpilius, Atergatis, Platypodia, Zosimus, Lophozozymus,* and *Eriphia*. Clinical symptoms develop 15 minutes to several hours after ingestion and include nausea, vomiting, diarrhea, perioral and extremity paresthesias, ataxia, aphasia, respiratory distress, altered mental status, coma, and rapid death.

A number of toxins have been isolated from crab species, and there is marked similarity to paralytic and TTX shellfish poisonings. Saxitoxin, neosaxitoxin, and gonyautoxins have been isolated from crab species in Okinawa and from *Eriphia sebana* and *Atergatis floridus* from Australian coral reefs.[302-305] TTX and palytoxin have also been characterized from poisonous crabs.[6] In Thailand, TTX was responsible for an epidemic involving 71 persons (2 died) who ate toxic eggs from the horseshoe crab *Carcinoscorpius rotundicauda*.[248] The poisonous mosaic crab *L. pictor* from the Indo–West Pacific region has caused several fatalities in the Philippines and Singapore. The toxins were concentrated in the gut and hepatopancreas, whereas the muscle was less toxic. Captive crabs lose toxicity almost completely by 24 days.

Coconut crab *(Birgus latro)* poisoning is manifested as nausea, vomiting, headache, chills, myalgias, and exhaustion, with occasional deaths. Asiatic horseshoe crabs *(C. rotundicauda)* are eaten in Thailand, where they cause *mimi* poisoning. Symptoms include nausea, vomiting, diarrhea, abdominal cramps, dizziness, palpitations, weakness, lower extremity paresthesias, aphonia, perioral burning, pharyngitis, sialorrhea, syncope, paralysis, and death. Again, the toxin appears highly similar to saxitoxin.[89]

Crab lung has followed aspiration of tiny fragments of North American blue crab shells into the lung, necessitating removal with fiberoptic bronchoscopy. The diagnosis of occult aspiration should be considered in anyone with an unexplained cough who has recently consumed cracked crab, particularly while intoxicated.

Freshwater crabs are a potential source of human paragonimiasis, a parasitic disease that was prevalent in Asia until the 1960s.[93] Paragonimiasis usually causes pulmonary disease with productive cough and bloody sputum. CNS involvement has also been reported.[382] The disease is contracted by eating raw crab infected with the metacercariae of *Paragonimus* species. Areas known to be endemic are Vietnam, China, Japan, Korea, Ecuador, and Liberia.[5,93,106,346,382,408,504]

BACTERIAL AND VIRAL PATHOGENS IN SEAFOOD

Shellfish, particularly bivalve mollusks, contaminated with bacteria or viruses are implicated more than any other marine animal in seafood-related human illness.[301,376] As filter feeders, bivalve mollusks filter large quantities of water unselectively to gather plankton and extract oxygen, which allows concentration of bacteria and viruses (along with biologic toxins, pesticides, industrial chemicals, radioactive wastes, toxic metals, and hydrocarbons). They are sessile invertebrates that generally inhabit shallow waters close to shore and pollution sources. Standard purification (with ultraviolet light or ozone) for 48 to 72 hours may not significantly reduce these contaminants, or effectively remove viruses.[242,418] Viruses and naturally occurring bacteria that cause disease and death are of great concern because they are so common. The greatest risk of death from consumption of raw shellfish is among people with underlying health conditions.

BACTERIA ASSOCIATED WITH FECAL CONTAMINATION

Bacterial pathogens associated with fecal contamination have accounted for only 4% of the shellfish-associated gastroenteritis outbreaks in the United States.[397] In the early 1900s, most reported illnesses in the United States were associated with bacterial pathogens from fecal contamination; the primary causative agent was *Salmonella*. Since the institution of the National Shellfish Sanitation Program in the 1920s, illnesses from typhoid fever have drastically declined.[122,397,520] *Salmonella typhi* is still responsible for outbreaks of illness in other countries.[454,455] Nontyphoidal *Salmonella* species, including *Salmonella paratyphi* and *Salmonella enteritidis,* have been detected in shrimp and bivalves. Eight *Salmonella* shellfish infections were reported in the United States between 1984 and 1993, and *S. enteritidis* phage type 19 was responsible for an outbreak of infections from cockles in the United Kingdom.[189,522]

Other important bacteria include *Shigella, Campylobacter, Yersinia, Listeria, Clostridium, Staphylococcus,* and *Escherichia coli*.[230] *Shigella* was responsible for 111 cases of shellfish illness and four outbreaks in the United States.[397] *Shigella* has a low infectious dose and a long survival time in clams and oysters.

Campylobacter species have been isolated from shellfish, but their role in seafood infections is not known.[520] *Listeria monocytogenes* has been identified in high rates in isolates from fresh and processed fish and shellfish.[228] *Listeria* seafood-borne infections are probably underreported in the United States. *Yersinia enterocolitica* has also been identified in fish and shellfish; however, most *Yersinia* infections are not associated with seafood.[230,397] *E. coli* has not been an important source of seafood-related illness, although *E. coli* is found in shellfish.[59]

Another potential nidus for infection includes fish bone ingestions. A recent case report describes a 37-year-old previously healthy male who presented with fever and abdominal pain from *Streptococcus constellatus* bacteremia. He developed hepatic abscesses and thrombosis of the superior mesenteric vein, and was ultimately found to have ingested a fish bone that perforated his duodenum, pancreas, and superior mesenteric vein. Other similar cases are reported where patients, who unknowingly ingest fish bones, develop hepatic abscesses from perforation and subsequent infection with *S. constellatus*. *S. constellatus* is part of the normal flora of the human oral cavity; however, it can cause abscess formation in deeper tissue spaces. In the setting of bacteremia, abscess formation may occur in distant areas, such as the lung, brain, liver, and kidney.[174]

Vibrio Poisoning and Septicemia

Over the past few decades, naturally occurring bacteria, particularly those belonging to the family Vibrionaceae, are becoming a more important cause of shellfish illness.[234] Three *Vibrio* species, *V. cholerae, V. parahaemolyticus,* and *V. vulnificus,* are the most important vibrios associated with human illness.[122] *Vibrio* organisms can cause gastroenteric disease and soft tissue infections after consumption of raw shellfish. This can lead to bacteremia and death, particularly in immunocompromised hosts. Between 1988 and 1996, 422 infections from *V. vulnificus* were reported to the CDC and 43% of patients presented with primary septicemia.[427] In 2002, 452 patients were reported to the CDC with noncholera *Vibrio* infections. Of these, 45% were hospitalized and 11% died.[509] *V. parahaemolyticus* was found in 35% of the victims, and *V. vulnificus* was found in 73% of the patients who died.[509]

Vibrio species may be the most virulent halophilic organisms that flourish in the marine environment. In general, they are not associated with fecal contamination, so surveillance methods mentioned earlier for bacteria and viruses do not correlate with the presence of *Vibrio*. *Vibrio* species proliferate in warmer water. Infections seem to cluster during summer months, which may be related to increased numbers of people at the seashore.[329] *Vibrio* species grow best at moderate temperatures of 24° to 40°C (75.2° to 104°F), with essentially no growth below 8° to 10°C (46.4° to 50°F).[59] They can grow in brackish waters and require less sodium for maximal growth than do other, more fastidious marine organisms, a factor that allows explosive reproduction in the saline environment of the human body. *V. parahaemolyticus* has also been identified in freshwater habitats.[20]

Gastrointestinal illness has been associated with toxigenic O group 1 (O1) *V. cholerae,* non-O1 *V. cholerae, V. parahaemolyticus, V. fluvialis, V. mimicus, V. hollisae, V. furnissii, V. alginolyticus,* and *V. vulnificus*.[61,187,385,390,427,464,522] Septicemia, with or without an obvious source, has been attributed to infections with non-O1 *V. cholerae, V. parahaemolyticus, V. alginolyticus, V. vulnificus, V. hollisae,* and *V. metschnikovii*.[1,46,86,187,236,263,265,274,307,427]

Whenever a *Vibrio* species is suspected, the microbiology laboratory must be alerted to use an appropriate selective culture medium for stool cultures, such as thiosulfate-citrate-bile salts-sucrose (TCBS) agar or Monsur taurocholate-tellurite-gelatin agar.[308,335] Pathogenic *Vibrio* species generally grow on MacConkey agar. The stool specimen should be collected if possible within the first 24 hours of illness and before administration of antibiotics; specimens should not be allowed to dry. The specimen may be transported in the semisolid transport medium of Cary and Blair; buffered glycerol-saline is not satisfactory, because glycerol is toxic to vibrios. Tellurite-taurocholate-peptone broth is adequate. All *Vibrio* species grow in routine blood culture media and on nonselective media, such as blood agar. New, rapid PCR tests are available for detection of *V. vulnificus* at the point of harvest.[64,365]

Key characteristics that aid in separation of *Vibrio* species from other medically significant bacteria *(Enterobacteriaceae, Pseudomonas, Aeromonas, Plesiomonas)* include production of oxidase, fermentative metabolism, requirement of sodium chloride for growth, and susceptibility to the 0/129 vibriostatic compound.[247] Species that cannot be identified in the hospital microbiology laboratory may be referred to a state laboratory or the CDC. Many sensitive and reliable PCR methods are now used to detect various strains of *Vibrio* species in oyster tissue and water samples.[34,290,503]

***Vibrio vulnificus* Infection.** Illnesses due to *V. vulnificus* are the leading cause of mortality associated with seafood consumption in the United States. The organism accounts for an estimated 100 food-borne cases per year, with nearly all cases being sporadic and linked to consumption of raw oysters harvested on the Gulf Coast during summer months.[122] *V. vulnificus* is a free-living, motile, halophilic, gram-negative bacillus. It is naturally present in marine environments, has a worldwide distribution, and is found throughout the United States.[397,471]

The growth of *V. vulnificus* is favored in waters with intermediate salinity. The optimal temperature for its growth (doubling time 15 minutes) is 35°C (95°F).[338] Below 10°C (50°F), it enters a nonculturable state and is viable but ceases to replicate.[360] The *V. vulnificus* count in the marine environment and in shellfish increases and peaks during summer months, as does the incidence of *V. vulnificus* infections.[217]

V. vulnificus may appear as one of two colonial morphotypes: opaque and virulent, or translucent and less virulent. The opacity of the colony of the virulent morphotype is caused by an acidic mucopolysaccharide capsule. This capsule increases resistance of the organism to bactericidal activity of human serum and to phagocytosis, and thus renders the organism more virulent. At extremely low frequency, some strains can shift between unencapsulated and capsulated serotypes.[542]

Growth of encapsulated isolates is improved in the presence of iron, but these are unable to use transferrin-bound iron. In patients with iron overload and transferrin saturation greater than 75%, free iron is available for use. Additionally, virulent isolates can use the iron in hemoglobin and hemoglobin-haptoglobin complexes.[56,58,547] *V. vulnificus* can bind specifically to human intestinal cells and quickly induce cytotoxic effects.[273] In vivo studies show that 4 hours after inoculation into the duodenum, the organism is found in the systemic circulation via bacterial translocation.[241]

Clinical Presentation. There are two clinical syndromes of *V. vulnificus* infection: primary septicemia and wound infection. The wound infection syndrome consists of flu-like malaise, fever, vomiting, diarrhea, chills, hypotension, and early skin vesiculation that evolves into necrotizing dermatitis, with vasculitis and myositis. Primary septicemia occurs when *V. vulnificus* is acquired through the gastrointestinal tract. Blood cultures are positive for the organism in 97% of patients. Septic shock, disseminated intravascular coagulation, and death may occur.[508] Infections occur 12 hours to 7 days after ingestion of contaminated raw or undercooked seafood, particularly raw oysters. The mortality rate of patients with primary septicemia is 56% and increases to 92% when there is septic shock.[214]

Gastroenteritis was previously thought to exist as an isolated entity in 10% of cases. However, it is more likely that other enteric pathogens are the causal agents and that *V. vulnificus* illness has been erroneously attributed to the asymptomatically carried organism.[233]

V. vulnificus is also implicated in other infectious presentations, including meningitis, spontaneous bacterial peritonitis, corneal ulcers, epiglottitis, osteomyelitis, rhabdomyolysis, endocarditis, and infections of the testes and spleen.[128,148,255,324,486,501,508,526] Necrotizing fasciitis and myositis have been reported after *V. vulnificus*–contaminated seafood ingestion.[162] *V. vulnificus* endometritis has been reported after an episode of sexual intercourse in the water of Galveston Bay, Texas.[481]

The severity of *V. vulnificus* infections is related to both bacterial characteristics and host factors. In patients with liver disease,

such as cirrhosis and alcoholism, portal hypertension allows shunting of the organism around the liver. These patients also have impaired immune systems, thus promoting virulence of *V. vulnificus*.[384] Persons with high serum iron levels (from cirrhosis, hepatitis, thalassemia major, or hemochromatosis) are at increased risk for infection.[58,274,508] Any individual with impaired immunity (e.g., malignancy, human immunodeficiency virus [HIV] infection, diabetes, long-term corticosteroid use) is at greater risk for fulminant bacteremia.[463]

Treatment. Early recognition of *V. vulnificus* infection is essential for effective treatment. Blood and wound cultures should precede immediate and aggressive antibiotic and supportive treatment. Current recommendations include doxycycline (100 mg intravenously every 12 hours) combined with ceftazidime (2 g intravenously every 8 hours) or ciprofloxacin (400 mg intravenously every 12 hours).[178] Other antibiotics that have been suggested include imipenem/cilastatin, meropenem, trimethoprim-sulfamethoxazole, carbenicillin, tobramycin, gentamicin, and many third-generation cephalosporins. Supportive care includes crystalloid and vasopressor agents for hypotension.

***Vibrio parahaemolyticus* Infection.** *V. parahaemolyticus* is a gram-negative rod that can cause mild to moderate gastroenteritis when consumed in raw or partially cooked seafood. It is more widely distributed than is *V. cholerae* or *V. vulnificus,* because it occurs in cooler and more saline waters. It has been reported in temperate, subtropical, and tropical coastal regions.[32,77,205,319] The organisms are found in marine and estuarine waters along the entire coastline of the United States. In the largest reported outbreak in North America of culture-confirmed *V. parahaemolyticus* infections, during July and August 1997 in the Pacific Northwest, 209 persons became ill and 1 person died after eating raw or undercooked oysters.[77] *V. parahaemolyticus* has been recovered at frequencies up to 25% in frozen peeled shrimp.[525] In the past decade, *V. parahaemolyticus* has become the leading cause of bacterial gastroenteritis associated with seafood consumption in the United States.[122] During 2012, a Pacific Northwest strain of *V. parahaemolyticus* was responsible for several outbreaks along the Atlantic Coast. Six percent of patients were hospitalized; none died. The number of food-borne *V. parahaemolyticus* cases traced to Atlantic Coast shellfish was threefold greater in 2012-2013 compared with the annual average number reported during 2007-2011.[350]

Ingestion of raw or partially cooked seafood contaminated with *V. parahaemolyticus* (shrimp, oysters, crab, or fish) is followed in 6 to 76 hours by explosive diarrhea, nausea, vomiting, headache, abdominal pain, fever, chills, and weakness. In immunocompetent persons, *V. parahaemolyticus* causes mild to moderate gastroenteritis with a mean duration of illness of 3 days. Serious illness and death can occur in persons with underlying disease (preexisting liver disease, diabetes, iron overload states, or a compromised immune system).[263] The stools may contain blood and classically demonstrate leukocytes on methylene blue staining. The syndrome generally resolves spontaneously in 24 to 72 hours but may cause significant fluid and electrolyte depletion. Stool cultures should be obtained before initiation of antibiotic therapy. Panophthalmitis with this organism requiring enucleation occurred in a man who suffered a corneal laceration.[462] A course of oral ciprofloxacin, trimethoprim-sulfamethoxazole, or tetracycline may shorten the duration of the severe gastroenteritis.

***Vibrio mimicus* Infection.** *V. mimicus* is a motile, nonhalophilic, gram-negative, oxidase-positive rod with a single flagellum. It can be distinguished from *V. cholerae* by its inability to ferment sucrose, inability to metabolize acetylmethyl carbonyl, sensitivity to polymyxin, and negative lipase test.[113] Multiple toxins are produced by *V. mimicus,* including cholera-like toxin, enterotoxin, and hemolysin.[385,430,523] *V. mimicus* causes a syndrome of gastroenteritis (diarrhea, nausea, vomiting, abdominal cramps, fever, and headache) after ingestion of raw oysters, crawfish, crab, or shrimp. It was identified by PCR in 11 individuals with gastroenteritis from eating raw turtle eggs.[65] Nonfatal bacteremia resulting from *V. mimicus* has been reported.[265] The median incubation period is 24 hours, with delayed diarrhea noted up to 3 days after ingestion of contaminated seafood. Isolates are sensitive to tetracycline, ciprofloxacin, and norfloxacin.[329]

***Vibrio alginolyticus* Infection.** *V. alginolyticus* can cause gastroenteritis in immunocompetent individuals and bacteremia in immunosuppressed patients.[307,390] More commonly, it is implicated in soft tissue infections (such as those caused by coral cuts or surfing scrapes), sinusitis, and otitis media and externa.[168,307,391,487]

***Vibrio cholerae* Infection.** In developing countries, cholera caused by toxigenic *V. cholerae* is a major public health problem. The last several cholera pandemics were caused by consumption of fecally contaminated water.[529] *V. cholerae* is commonly linked to ingestion of raw or inadequately cooked mollusks and crustaceans and is responsible for the third highest number of shellfish-related illnesses, behind other noncholera *Vibrio* species and Norwalk virus.[247,522] Toxigenic O group 1 *V. cholerae* infections are associated with secretory, profuse watery diarrhea, nausea, and vomiting. Because the stool is virtually isotonic, large amounts of fluid and electrolytes are lost, leading to rapid dehydration, shock, acidosis, and renal failure. Treatment consists of aggressive intravenous and oral fluid replacement. In an outbreak in Italy, all strains were resistant to tetracycline, but patients responded to ciprofloxacin.[311] Untreated, the disease remits in 3 to 8 days.

Nontoxigenic, non-O1 *V. cholerae* strains cause gastroenteritis and septicemia.[217] Self-limited (24 to 48 hours) nausea, vomiting, abdominal cramping, and invasive diarrhea with blood and fecal leukocytes are typical. Spontaneous non-O1 *V. cholerae* bacteremia and peritonitis have been reported in patients with cirrhosis after eating raw oysters.[300,377,399] Meningitis and death have also been associated with non-O1 *V. cholerae*.[77,263]

Other Vibrios. *V. metschnikovii* caused bacteremia in a patient with cholecystitis; the authors postulated that it may have been associated with long-term carriage after seafood ingestion.[236] *Vibrio cincinnatiensis* caused meningitis; a relationship to foreign travel, seawater exposure, or seafood ingestion has not been established.[46] *V. fluvialis,* previously designated as enteric group EF-6 or group F, is common in the marine environment. It causes diarrheal disease associated with vomiting, abdominal pain, dehydration, and fever.[464] Fatal gastroenteritis has been reported.[265] This bacterium can be mistaken in the microbiology laboratory for *Aeromonas hydrophila,* from which it can be distinguished by growth in 60 to 70 parts per thousand sodium chloride solution. *V. hollisae* and *V. furnissii* have both been linked to gastroenteritis after seafood ingestion, and *V. hollisae* has been associated with septicemia.[1,181]

Prevention of *Vibrio* Infection. The Interstate Shellfish Sanitation Conference, a shellfish-industry group, has sought to decrease the number of contamination-related illnesses by public education, limiting harvesting to certain periods, facilitating rapid refrigeration of shellfish after harvest, and studying postharvest treatments to prevent bacterial growth.[103] Recently, postharvest high-pressure processing of oysters has demonstrated significant reductions in *V. vulnificus* levels but variable results with other *Vibrio* species; further studies are ongoing.[103] Persons who are immunosuppressed or chronically ill, particularly those with hepatic insufficiency, should not eat raw or partially cooked shellfish. All seafood should be cooked thoroughly, protected from cross-contamination after cooking, and eaten promptly or stored at temperatures above 60° C (140° F) or below 4° C (39.2° F) to prevent proliferation of *Vibrio* species.

VIRUSES ASSOCIATED WITH FECAL CONTAMINATION

Most infections associated with consumption of shellfish are viral in origin. More than 120 enteric viruses can be found in human sewage. These viruses can produce a variety of symptoms, including gastroenteritis, meningitis, paralysis, myocarditis, and hepatitis. Compared with other food-borne illnesses, those caused by viruses are less severe and seldom fatal. Norovirus (previously Norwalk virus) is the leading cause of nonbacterial illnesses in shellfish consumers.[122] Norovirus illnesses occur more frequently during the late fall through winter because of increased stability of the virus at lower temperatures, reduced solar inactivation,

and bioaccumulation of the pathogen by shellfish.[122] Other viruses that have been isolated from seafood include hepatitis viruses (A, non-A, and non-B), enteroviruses (echovirus, poliovirus, coxsackievirus A and B), adenoviruses, rotaviruses, and, most commonly, small round viruses (norovirus, calicivirus, Snow Mountain agent, and small rounded structured viruses).[376]

Harvest areas are surveyed and closed for fecal contamination. However, the relative absence of fecal coliform bacteria in areas of shellfish harvesting does not indicate freedom from viral contamination. Outbreaks of norovirus and calicivirus have been caused by oyster harvesters discharging sewage overboard.[74] In addition, shellfish depuration processes that eliminate bacteria do not necessarily remove viral contaminants.[418] Steamed clams probably pose a significant risk because household cooking techniques are often insufficient to kill viruses. Although it takes 4 to 6 minutes of pressure-cooker steaming for the internal temperature of soft-shell clams ("steamers") to reach 100° to 106°C (212° to 222.8°F), it requires only 60 seconds for the shells to open, at which point they may appear cooked.[258] Poliovirus can survive (7% to 13%) in oysters that are steamed, fried, baked, or stewed.[129]

Methods using PCR amplification of target viral genomes provide a rapid, specific, and sensitive test for detection of viruses.[16,17] Amplification of viral ribonucleic acid (RNA), DNA, and complementary DNA (cDNA) has shown a high prevalence of human viruses that would not be detected by use of classic techniques.[375] PCR has been used to detect the presence of hepatitis A virus in oysters and scallops during an outbreak, and small rounded structured viruses, adenoviruses, enteroviruses, and noroviruses in shellfish.[16,17,20,105,289,375,418]

Hepatitis Viruses

Oysters, mussels, and clams harvested from waters contaminated with raw sewage are the most frequent cause of food-borne viral hepatitis A. Often, there is a long incubation period of 2 to 8 weeks, so it is common for hepatitis A to occur 3 to 4 weeks after gastroenteritis attributed to consumption of shellfish.[397] Symptoms include fever, jaundice, nausea, and abdominal pain; diarrhea is rare. Treatment is supportive.[42]

Enteroviruses

Enteroviruses are commonly isolated from marine water and shellfish. In the United States, up to 63% of shellfish in areas closed for harvesting and up to 40% of shellfish in areas open for harvesting were positive for enteroviruses.[401] In contaminated waters in Venezuela, 40% of harvested shrimp contained enteroviruses.[52] Enterovirus outbreaks have not been characterized, and the impact of enteroviruses on public health is not fully appreciated.[301]

Small Round Viruses

Small round viruses include norovirus, calicivirus, Snow Mountain agent, and small rounded structured viruses. These viruses are a major cause of shellfish-associated gastroenteritis.[74,84,133,270,451,456] Caliciviruses are small, single-stranded RNA viruses and have been responsible for a number of oyster-related gastroenteritis outbreaks in Louisiana.[74,84] Reverse transcription PCR (RT-PCR) assay can easily detect norovirus in contaminated water, shellfish, and stool from infected people.[270,418] The virus may be excreted in the feces of food handlers and harvesters for 48 hours after recovery from infection.[44] Symptoms, including nausea, vomiting, fever, abdominal cramps, and nonbloody diarrhea, appear 24 to 48 hours after ingesting contaminated shellfish and resolve over 1 to 2 days. Antibodies to norovirus have been measured in the serum of patients with gastroenteritis, and electron microscopy or RT-PCR can detect virus in stool.[270] Treatment is supportive and complications are rare.

BOTULISM

Botulism is a paralytic disease caused by the potent natural toxin of *Clostridium botulinum*. Toxins A to G have been identified, but only A, B, E, F, and G cause human illness.[395,447] Seafood-related botulism can be caused by raw, parboiled, salt-cured, or fermented meats from marine mammals (seal, walrus, whale) or fish products (particularly salmon and salmon roe).[210] Toxin type E spores are found in mud and sediment in northern coastal areas and inland lakes, accounting for the prevalence of type E toxin in fish-borne botulism (although types A and B may also be involved). Improperly preserved (smoked, dried, or canned) foods are at high risk for *C. botulinum* toxin proliferation. The technique of hanging meat for decomposition (flavor and texture improvement) supports growth of the nonproteolytic, psychrotolerant forms of *C. botulinum,* which may grow at temperatures as low as 4°C (39.2°F).[210]

In the last four decades in the United States, more than 10% of outbreaks of food-borne botulism have been related to the consumption of fish. Using quantitative PCR analysis, the prevalence of the *C. botulinum* type E gene was 10% to 40% in raw fish samples and 4% to 14% in fish roe samples in Finland.[225] In 1991, 91 patients were hospitalized in Cairo with botulism intoxication associated with eating *faseikh* (uneviscerated salted mullet fish); *C. botulinum* type E was isolated.[513] In 2002, eight individuals from an Alaskan village on the Bering Sea contracted botulism type E from eating fluke from a Beluga whale that had washed up on shore several weeks before.[326]

C. botulinum spores germinate in an environment of appropriate pH (>4.6), warm temperature (> 10°C [50°F]), sufficient moisture, and an anaerobic environment. The toxins are proteins of an approximate molecular weight of 150,000 Da and are absorbed in the proximal gastrointestinal tract.

Clinical Presentation

The toxin affects the presynaptic cholinergic neuromuscular junction, where it blocks release of acetylcholine and causes flaccid paralysis.[28] Signs and symptoms develop within 12 to 36 hours of ingestion and include nausea, vomiting, abdominal pain, and diarrhea, followed by dry mouth, dysphonia (hoarseness), difficulty swallowing, facial weakness, ptosis, nonreactive or sluggishly reactive pupils (third cranial nerve), mydriasis, blurred or double vision (sixth cranial nerve), descending symmetric muscular weakness leading to paralysis, and bulbar and respiratory paralysis. With adequate ventilatory support, mentation frequently remains normal. Death occurs in 10% to 50% of cases, depending on availability of antitoxin and appropriate intensive care facilities.

If botulism is suspected, a careful food history should be obtained and suspected food items collected. Laboratory confirmation of botulism is achieved when botulinum toxin or viable *C. botulinum* is detected in food, toxin is demonstrated in the victim's serum or stool, or the organism is cultured from stool. Toxin types are distinguished using type-specific antitoxin.[28] The standard test is a bioassay involving intraperitoneal injection of toxin into mice and monitoring for development of botulism-specific symptoms. The test is performed in a limited number of public health laboratories, and final results may not be available for up to 48 hours.[446] To determine the clinical need for botulism antitoxin, a number of tests may be helpful. Electromyography should be performed using repetitive stimulation at 40 Hz or greater; a positive test shows diminished amplitude of the muscle action potential with a single supramaximal stimulus, and facilitation of action potentials using paired or repetitive stimuli.[28] Cerebrospinal fluid (CSF) may be examined for white blood cells and protein (to rule out infectious causes), and an edrophonium (Tensilon) challenge test may be performed to rule out myasthenia gravis. The vital capacity should be monitored as a sensitive indicator of clinical deterioration.

Treatment

Ventilatory support should be provided at the first sign of respiratory inadequacy. As of March 13, 2010, heptavalent botulinum antitoxin (HBAT, Emergent BioSolutions) became the only botulinum antitoxin available in the United States for naturally occurring noninfant botulism. HBAT contains equine-derived antibody to the seven known botulinum toxin types with the following potency values: 7500 U anti-A, 5500 U anti-B, 5000 U anti-C, 1000 U anti-D, 8500 U anti-E, 5000 U anti-F, and 1000 U anti-G. HBAT is composed of less than 2% intact immunoglobulin G

(IgG) and 90% or more Fab and $F(ab)_2$ immunoglobulin fragments. BabyBIG (botulism immune globulin) remains available for infant botulism through the California Infant Botulism Treatment and Prevention Program.[80] A physician who seeks antitoxin should first contact the state health department. If this is unsatisfactory, the CDC may be telephoned at 770-488-7100 (24 hours a day). Before administration, the victim should be skin tested for hypersensitivity to horse serum. If horse serum test material is not available, 0.1 mL of a 1:10 dilution of antitoxin in saline may be used. The antitoxin should not be stored at a temperature greater than 37°C (98.6°F).

An adjunct to therapy in type B is administration of guanidine, which increases release of acetylcholine from nerve endings, although use is limited by hemopoietic and renal toxicity, and it has not been well studied after increased availability and use of antitoxin. The dose is 15 to 35 mg/kg/day orally in four divided doses.

Prevention

Prophylaxis with antitoxin is not currently recommended; neither is general pentavalent (A to E) toxoid immunization.[10,380] The best prevention is public health education with respect to food preparation and avoidance of improperly stored food products. Because the spores are frequently detected in fish intestines, it is important to clean fish properly and to avoid consumption of the viscera, even in salt-cured products. To eliminate spores in food, heat or irradiation may be used. Types A and B may survive boiling for several hours (particularly at the lower temperatures associated with higher altitude) and generally require pressure heating at 120°C (248°F) for 30 minutes; type E spores are killed at 80°C (176°F) after 30 minutes. Preformed toxin is inactivated after heating for 20 minutes at 80°C (176°F) or 10 minutes at 90°C (194°F). Germination is inhibited by acidification, refrigeration, freezing, drying, or the addition of salt, sugar, or sodium nitrate; however, heating remains the most reliable technique.[28]

PARASITES IN SEAFOOD

Most parasites of marine animals are of little public health concern to humans. However, there are at least 50 species of helminths found worldwide in fishes, crabs, crayfishes, and bivalves that can cause human infections. With increasing consumption of raw seafood such as sushi and sashimi, the number of documented human infections is increasing. The overall risk of human infection is small.

FISH TAPEWORM

In the United States, consumption of raw fish (sushi) has led to more frequent recognition of infestation with the fish tapeworm, *Diphyllobothrium latum*. Salmon appears to be a popular culprit.[107,138,224,483] Diphyllobothriasis is also reported from eating raw flesh of redlip mullet.[95] The fish tapeworm has a complex life cycle, in which a gravid egg released into freshwater releases a ciliated coracidium, which is eaten by a crustacean intermediate host. The coracidium penetrates the intestinal wall of the crustacean and then develops into a procercoid larva. A fish eats the small crustacean, and the procercoid larva migrates through the intestinal wall of the fish into fish muscle, where it changes into a plerocercoid larva. It is this final larval stage that is ingested by a human and that subsequently attaches to the intestine, where it grows into a mature tapeworm.

Classic symptoms include subacute abdominal pain, nausea, vomiting, diarrhea, and weight loss. Proglottids may be passed in the stool. Chronic *D. latum* infestation may induce megaloblastic anemia, as the tapeworm splits the vitamin B_{12} intrinsic factor complex and prevents absorption of the vitamin.[185] The diagnosis can be made by examination of the stool for typical proglottids or operculate egg forms, which measure 60 to 75 mm in length. Proper identification of the eggs is important to differentiate them from the ova of trematodes, such as *Paragonimus westermani,* endemic in southeast Asia, which may be carried by immigrants to the United States.[1] For documented *D. latum* infestation, praziquantel (5 to 10 mg/kg in one dose for adults or children) is the recommended treatment.[180,358,357] Magnesium sulfate as a purgative has been used to help expel the worm.[483] Niclosamide, 2 g orally as a single dose, can also be used for treatment.[370] Because a worm may not be identifiable if expulsion is delayed or follows a purge, stool analysis should be repeated at 3 months to confirm successful therapy.

Fish tapeworm infection can be avoided by cooking fish until the parts for consumption reach a temperature of at least 56°C (133°F) for 5 minutes, or by freezing the fish to −18°C (0°F) for 24 hours or −10°C (14°F) for 72 hours.[524]

TREMATODES

Humans can acquire intestinal infection from the trematode *Nanophyetus salmincola,* which infests salmonid fishes such as steelhead trout or salmon.[137] Canine infection with this fluke is a well-known phenomenon in the Pacific Northwest of the United States. Humans ingest the flesh of fish infested with the metacercariae, which excyst in the host and attach to the upper small bowel. The worms release eggs that are detected in the stool approximately 1 week after ingestion of infected fish.

Symptoms of nanophyetiasis include diarrhea, eosinophilia, abdominal discomfort, bloating, nausea, vomiting, weight loss, and fatigue. Although symptoms may resolve spontaneously over a period of months, antihelmintic treatment is recommended. Praziquantel (25 mg/kg orally three times a day for 1 day) is the first-line treatment. Other regimens have included bithionol (50 mg/kg orally for two doses), niclosamide (2 g orally for three doses), or mebendazole (100 mg orally twice a day for 3 days).[137]

Numerous other trematode infections cause enormous morbidity worldwide via liver and intestinal flukes. For instance, in Southeast Asia, opisthorchosis caused by the liver fluke *Opisthorchis viverrini* is quite serious. The cercariae are ubiquitous in cyprinid fish.[175] Clonorchiasis occurs when humans eat raw or undercooked freshwater fish harboring the metacercariae of *Clonorchis sinensis*.[422]

NEMATODES

Anisakiasis

Thousands of restaurants serve sushi in the United States, and many do so without specific knowledge of the various parasites that can infest their fare. For instance, many serve raw salmon, squid, shrimp, and mackerel.

The first report of acute gastric anisakiasis caused by penetration of the *Anisakis* larvae through the gastric mucosa was by Van Thiel in 1960.[500] It is a rare problem in the United States, but is increasingly noted in Japan, where raw fish is more commonly eaten.[261,457] In a Japanese series, the fish consumed included predominantly mackerel; less common perpetrators included horse mackerel, bream, squid, sardines, and bonito.[457] In the United States, anisakine nematodes are present in many commercial fish intended for raw or semiraw consumption, such as Pacific herring (thus, herring worm disease), sablefish, Pacific cod (thus, codworm disease), arrowtooth flounder, petrale sole, coho salmon, Pacific ocean perch, silvergray rockfish, yellowtail rockfish, and bocaccio.[345] In rare cases, the anisakine worm can be present in tuna or yellowtail. Preservation of marine mammals along the western coast of the United States has been linked to greater worm burdens in fishes associated with these mammals, such as Pacific rockfish, red snapper, and salmon.[323]

Life and Habits. Anisakine nematodes, members of the order Ascarida (suborder Ascaridae), are found in great numbers in the viscera and muscles of fish.[341] There are 30 genera in the family Anisakidae, including *Anisakis* and *Pseudoterranova* (or *Phocanema*). Adult worms infest the stomachs of marine mammals, burrowing in clusters into the mucosal surface. Eggs passed in the stool embryonate and hatch in seawater to produce second-stage larvae, which are ingested by crustaceans, which are in turn eaten by squid or fish. In these hosts, larvae migrate through the gut wall and encyst in the viscera or musculature.[366] The fish may then pass the parasite to other fish, humans, or back to another marine mammal. The coiled *Anisakis* larva grows

to approximately 2.5 to 3 cm (1 to 1.2 inches) in length and 0.5 to 1 mm in diameter. Fish are usually the intermediate (transport) host for larval anisakines.

The definitive host for *Phocanema decipiens* is the seal; *Anisakis* larvae grow to maturity in the whale. Shellfish are not infested. Only four genera of anisakine nematodes have been implicated in human anisakiasis: *Anisakis, Phocanema, Porrocaecum,* and *Contracaecum.* In the United States, all cases are related to larval stages of *Anisakis simplex* and *Phocanema decipiens.*[323]

Clinical Presentation. Symptoms from ingestion of *Anisakis* may begin within 1 hour of ingestion of raw fish and include severe epigastric pain, nausea, and vomiting. The presentation may mimic an acute abdomen. Asymptomatic gastroduodenal anisakiasis has also been a cause of acute urticaria and severe anaphylaxis in sensitized patients.[111,158,165] If the anisakine worms (such as *Phocanema*) do not implant and the infection is luminal without tissue penetration, the worms may be coughed up, vomited, or defecated, generally within 48 hours of the meal.[109] If the worm is felt in the oropharynx or proximal esophagus, the "tingling throat syndrome" is described.[323] An anisakine worm was documented in the tonsil of a 6-year-old girl with recurrent tonsillitis.[39]

Intestinal anisakiasis is more often delayed in onset (≤ 7 days after ingestion) and marked by abdominal pain, nausea, vomiting, diarrhea, fever, eosinophilia (particularly with gastric anisakiasis), and occult blood in the stool.[109] This may be easily confused with appendicitis, regional enteritis, gastric ulcer, colonic or other gastrointestinal carcinoma, or, most commonly, other causes of small bowel inflammation with partial obstruction.[54,243,432,465] In one study, 29% of patients with Crohn's disease had detectable specific total immunoglobulin (IgG), IgM, and IgA antibodies against *A. simplex.*[192] Anisakiasis has also manifested as small bowel obstruction requiring surgical resection.[416]

Diagnosis and Treatment. Definitive diagnosis of anisakiasis is usually made on the basis of morphologic characteristics of the whole worm when the creature is expelled by the patient or removed from the stomach after endoscopic examination.[411] Contrast-enhanced radiographs of the gastrointestinal tract may reveal threadlike gastric filling defects approximately 30 mm (1.2 inches) in length, which are typical, with a circular or ring-like shape.[54,457] Mucosal edema and pseudotumor formation are also seen. Ultrasonography can be useful in identifying intestinal anisakiasis.[227] However, once the worms have migrated to extragastric sites, the diagnosis can be difficult.

Early fiberoptic gastroscopy is recommended for patients in whom acute gastric anisakiasis is suspected and for those who have eaten raw fish within 6 to 12 hours before the onset of gastric symptoms. The *Anisakis* worm is usually found in the greater curvature of the stomach, often associated with severe mucosal edema.[245] Worms may also penetrate the intestinal wall.

The larvae of *Anisakis* can be visualized on endoscopy and removed with biopsy forceps. Fourth-stage larvae of *A. simplex* and *Pseudoterranova (Phocanema) decipiens* are found in the intestine and stomach of humans.[262] The larva is visible in the mucosa or buried within the submucosa, surrounded by an intense inflammatory granulomatous response.

When laparotomy is performed for presumed appendicitis, the diagnosis is based on identification of the worm in an inflamed segment of appendix, cecum, small intestine, mesentery, or omentum.[66,118] The only effective therapy for inflamed bowel is resection.

Antibodies to the ileal worm have been detected by radioallergosorbent test (RAST), ELISA, and immunofluorescent antibody assay, but these laboratory methods are not widely available.[192] Physical removal by endoscopy or surgery is the treatment of choice. The use of albendazole (400 mg orally, twice daily for 6 to 21 days) is of questionable efficacy.[180]

Prevention. The larvae are extremely difficult to identify in fish flesh, because they are colorless and normally tightly coiled in a spiral of approximately 3 mm. Only cooked (above 60°C [140°F]) or previously frozen (to −20°C [−4°F] for 24 hours) fish should be eaten. Smoking (kippering), marinating, pickling, brining, and salting may not kill the worms.[109] Candling is an inadequate method of surveillance, particularly in dark-fleshed fish infested with *Anisakis* larvae. Fish should be gutted as soon as possible after they are caught to limit migration of worms from viscera into muscle.

Irradiation of fish to limit their infectivity is controversial because of potential generation of long-lived free radicals within the fish, as well as germination of spores of *Clostridium botulinum.*[523] To date, this practice is not legal for seafood in the United States, although it is used in other countries.

Eustrongylides

Eustrongylides is a genus of roundworms that can invade fish in its larval form and thus be consumed by humans in their quest for sushi and sashimi. *Eustrongylides* may also parasitize bait minnows, which are sometimes swallowed whole by fishermen. The worms are released into the human gastrointestinal tract, where they attain lengths of 15 to 30 cm (6 to 12 inches) and penetrate the intestinal wall to enter the peritoneal cavity. Symptoms include unexplained abdominal pain, peritonitis, and fever in a live-bait fisherman. Surgical intervention may be required in pursuit of the acute abdomen, at which time the characteristically bright red worm is identified.[524]

Gnathostoma

Approximately 12 *Gnathostoma* species are responsible for gnathostomiasis, also known as larva migrans profundus or nodular migratory eosinophilic panniculitis. This systemic infection is caused by tissue destruction by migrating larvae.

Gnathostomiasis was first described in humans in 1889 in Thailand and has been endemic in Southeast Asia.[147] However, with advent of increased international travel, reports of gnathostomiasis are becoming more common in other regions of the world. Often, this is the result of travelers becoming infected in Southeast Asia and returning to other countries, as with 16 cases reported in London in 2003.[330] There also appear to be newly endemic regions such as Central and South America. Mexico's first case was reported in 1970, but gnathostomiasis is now endemic in many regions of that country.[125,299] *Gnathostoma* larvae are acquired by ingestion of raw or undercooked freshwater snakes and fish, particularly *Monopterus albus* (swamp eel), *Fluta alba* (eel), *Clarias batrachus* (catfish), or *Channa striatus* (snake-headed fish).[299] In Mexico, gnathostomiasis is particularly related to ingestion of ceviche (a dish made of raw fish marinated in lime juice).[355,400]

Life and Habits. There are 12 known species of *Gnathostoma,* all having similar life cycles. The definitive hosts are dogs, felines, and wild mammals.[299] The first intermediate hosts are crustaceans, which are ingested by the second intermediate hosts, fish. Humans then ingest the larvae found in these second intermediate hosts, leading to gnathostomiasis.

Clinical Presentation. Symptoms, which begin within 24 to 48 hours after ingestion of larvae, are nonspecific: fever, arthralgias, myalgias, malaise, anorexia, vomiting, diarrhea, and abdominal pain.[299] Cutaneous gnathostomiasis manifests as migratory swelling and inflammation, most often affecting the trunk, that appears 1 to 20 weeks after ingestion.[83,299] Visceral gnathostomiasis occurs when larvae migrate through internal organ systems such as the lungs, gastrointestinal tract, genitourinary tract, or CNS. CNS infections may manifest with radiculomyelitis with severe radicular pain followed by paralysis.[49] Eosinophilia is a common but nonspecific finding.

Diagnosis and Treatment. Definitive diagnosis is by isolation of the larvae from lesion biopsies.[83] ELISA has been used with a sensitivity of 93% and specificity of 96.7% in one study.[83] A clinical diagnosis may be made in a patient with a history of ingesting raw or partially cooked fish, migratory swelling, and eosinophilia.[354] The standard treatment for gnathostomiasis is albendazole (400 mg twice daily for 21 days), which results in a cure rate of 92%. Single-dose ivermectin (200 mg/kg) results in a 76% cure rate.[272]

Prevention. Adequate cooking of food is preventive, as is freezing to −20°C (−4°F) for 3 to 5 days. Lime juice is not effective at killing *Gnathostoma.*[299]

OTHER TYPES OF POISONING RELATED TO SEAFOOD

POISONING BY ENVIRONMENTAL CONTAMINATION

In the process of concentrating fish proteins as a food source, a variety of protein-bound, non–water-soluble, or non–alcohol-soluble toxic compounds may be preserved. These include organic mercurials, hydrocarbons, dioxins, polychlorinated dibenzofurans, chlorinated pesticides, and heavy metals (e.g., antimony, arsenic, cadmium, chromium, cobalt, lead, phosphorus, mercury, nickel, and zinc).[23,102,459] The overall public health risk for environmental contamination is concerning; however, the true risk of exposure is unknown.

Higher concentrations of polychlorinated biphenyls and dioxin-like compounds are found in Inuit people in the Arctic because of their traditional diet, which includes large quantities of sea mammal fat.[23] Data suggest that there may be an elevated risk of multiple myeloma in groups with high consumption of dioxin-contaminated fish from the Baltic Sea and Alaska, and accidental exposure in Italy.[420] Dioxin has been found in Dungeness crabs in Humboldt Bay, California.

In Taiwan, high levels of copper, zinc, and arsenic were found in oysters. The long-term exposure to metals from seafood consumption is potentially dangerous, although the real risk is unknown.[204] Urine arsenic levels have been shown to increase twofold to sevenfold after consumption of certain types of seafood (mackerel, herring, crab, and tuna).[15] Consumption of fish rich in amines has been shown to increase excretion of *N*-nitrosodimethylamine in the urine, because of increased formation of carcinogenic *N*-nitrosamines.[502]

Mercury is found in marine organisms in the form of methylmercury (MeHg) and is concentrated in the food chain. Increased fish consumption is associated with higher blood levels of mercury.[312] MeHg is neurotoxic and crosses the placenta and blood-brain barrier. Prenatal poisoning causes mental retardation and cerebral palsy. The risk of this from seafood is unclear. High blood and hair concentrations of mercury have been found in fishermen of coastal villages, and adverse effects have been reported.[342,392] Controversy exists over fetal risk from exposure to low-dose MeHg from maternal consumption of fish.[23] A study of children exposed to MeHg from seafood in a Madeira fishing community did not show mercury-associated deficits.[340] A longitudinal cohort study of children showed no adverse outcome with either prenatal or postnatal MeHg exposure.[112]

In the past several years, benefits of seafood containing long-chain omega-3 fatty acids have become popularized. This is partially responsible for increased seafood consumption. These fatty acids have been shown to decrease the risk of cardiac sudden death and coronary artery disease in both men and women.[6,218] However, small amounts of mercury are commonly found in the same fish, and studies have shown increased mercury levels in persons with increased seafood ingestion.[191,543] These same studies have shown conflicting data on whether elevated levels of mercury diminish the cardioprotective effect of omega-3 fatty acids. More study is needed. Omega-3 fish oil supplements have not been shown to contain elevated levels of mercury.[157]

Spills of toxic chemicals and petroleum by-products will certainly continue to expand the list of carcinogens to which humans are exposed through the marine environment. Although radiation exposure is not known to induce production of new marine poisons, ingestion of radioactive fish poses a potential radiation hazard. Divers are exposed to a variety of environmental contaminants while exploring polluted waters. These hazards include solvents, nuclear wastes, herbicides, chemical effluents, and sewage.

RED SEAWEED POISONING

Seaweed is a common component in the diet of individuals living in the Pacific Islands and the Pacific Rim. It can be eaten raw or cooked. Most *Gracilaria* species are nontoxic and edible, but a number of poisonings and deaths have been reported in Japan, Guam, and Hawaii. Ingestion of the red seaweeds *Gracilaria verrucosa* (ogonori) and *Gracilaria chorda* (tsurushiramo) is associated with a toxic syndrome, including gastroenteritis and death.[352] It is commonly referred to as *Japanese ogonori poisoning*.

In 1991 in Guam, 13 individuals became ill and 3 died after ingesting the red alga *Polycavernosa tsudae* (formerly *Gracilaria tsudae* or *edulis*).[201] Symptoms consisted of diarrhea, abdominal cramping, vomiting, generalized numbness, perioral and extremity paresthesias, numbness of the fingertips, diaphoresis, jaw aching, muscle spasms, tremors, and hypotension. *Gracilaria lemanaeformis* may have been responsible for three illnesses in California in 1992.[71] In Japan, two people became ill with nausea, vomiting, and hypotension and one died after ingestion of *G. verrucosa*. Prostaglandin E_2 is suggested as the toxic component of *G. verrucosa,* and polycavernosides, which are glycosidic macrolides, are the probable toxins in *G. tsudae*.[352,545,546]

An outbreak of acute gastroenteritis from ingestion of the red alga *Gracilaria coronopifolia* occurred in Hawaii in 1994, in which seven individuals reported symptoms of diarrhea, nausea, vomiting, and a burning sensation in the mouth and throat.[71] Aplysiatoxin and debromoaplysiatoxin have been isolated as the causative agents.[343] These toxins are probably produced by blue-green algae that are found on the surface of *G. coronopifolia* and are known to cause contact dermatitis in swimmers in Hawaii. Aplysiatoxin and debromoaplysiatoxin experimentally cause edema and bleeding of the small intestine, leading to hemorrhagic shock.[231]

SEA TURTLE POISONING (CHELONINTOXICATION)

Various tropical Pacific, particularly Japanese, marine turtles are toxic when ingested (Box 77-8).[449] The term *chelonintoxication* comes from the order Chelonii. All portions of the turtle are toxic and the freshness of the meat is irrelevant. In Madagascar, 60 people became ill after eating sea turtle in 1994. The mortality rate was 7.7%.[387] Lyngbyatoxin A has been isolated from meat of a green turtle, *Chelonia mydas,* that was involved in a fatal intoxication.[535] The source of the toxin was suspected to be blue-green algae belonging to the genus *Lyngbya*. The sea turtle may feed on sea grass contaminated with this alga.

Symptoms develop from 1 to 48 hours after ingestion and include ulcerative glossitis and stomatitis, pharyngitis, diaphoresis, hypersalivation, nausea, vomiting, diarrhea, abdominal pain, vertigo, icterus, desquamative dermatitis, hepatosplenomegaly, centrilobular hepatic necrosis with fatty degeneration, renal failure, somnolence, and hypotension. The mortality rate can be as high as 28% to 44%. Therapy is supportive and based on symptoms.

Various *Salmonella* serotypes have been isolated from pet turtles *(Pseudemys* [or *Chrysemys*] *scripta elegans)* imported into and from the United States.[123,269,313] Pet-associated salmonellosis was a significant problem in the 1970s. In 1975, Canada banned importation of turtles, and the FDA prohibited sale of small turtles in the United States the same year. However, the popularity of iguanas and other reptiles is increasing; these reptiles can also

BOX 77-8 Representative Marine Turtles Hazardous to Humans

Phylum Chordata

Class Reptilia

Order Chelonia: turtles
- Family Cheloniidae
  - *Caretta caretta gigas:* Pacific loggerhead turtle
  - *Chelonia mydas:* green turtle
  - *Eretmochelys imbricata:* hawksbill turtle
- Family Dermochelyidae
  - *Dermochelys coriacea:* leathery turtle
- Family Trionychidae
  - *Pelochelys bibroni:* soft shell turtle

transmit *Salmonella* to humans. Reptile-associated salmonellosis causes febrile gastroenteritis, septicemia, and meningitis; one death has been reported from myocarditis from *Salmonella virchow* in a small child.[72,123,348]

LIVER POISONING: HYPERVITAMINOSIS A

Hypervitaminosis A can occur with ingestion of the liver of certain polar bears, seals, sea lions, whales, dolphins, walruses, husky dogs, and Pacific sharks. The vitamin A content of shark liver can reach 100,000 IU/g. A typical ingestion involves exposure to more than 1 million (and occasionally 3 to 8 million) IU of vitamin A. The recommended daily allowance is 4000 to 5000 IU. Symptoms of hypervitaminosis A include formication, headache, apathy, drowsiness, giddiness, irritability, photophobia, nausea, vomiting, diarrhea, polyarthralgia, seizures, desquamative dermatitis, ophthalmoplegia, and elevated CSF pressure with an idiopathic intracranial hypertension type of presentation (acute or chronic, the latter with headache, lip fissuring, papilledema, decreased visual acuity, and tinnitus).[145,328] Elevated levels of serum glutamic oxaloacetic transaminase and serum vitamin A (markedly in excess of 70 mg/dL) may be measured. A normal serum beta-carotene level excludes the possibility of a plant source (e.g., carrots or mangoes) for the vitamin.[328] The syndrome is rarely fatal and resolves in 2 to 8 weeks.

AMEBIC INFECTIONS

Free-living, amphizoic amebas belonging to the genera *Naegleria, Acanthamoeba,* and *Balamuthia* can cause significant CNS pathology in human beings. Approximately 350 cases of human infection have been reported to date.[317,397] These amebas are ubiquitous in nature; they are found in soil, lakes, ponds, swimming pools, hot springs, and warm water around the world. Human infection caused by amebas has significantly increased over the past 10 years.[317]

Free-living amebas are responsible for three disease entities: (1) primary amebic meningoencephalitis produced by *Naegleria fowleri,* (2) granulomatous amebic encephalitis caused by *Acanthamoeba* species and *Balamuthia mandrillaris,* and (3) *Acanthamoeba* keratitis caused by *Acanthamoeba* species.

PRIMARY AMEBIC MENINGOENCEPHALITIS

Primary amebic meningoencephalitis (PAM) is a fulminant, rapidly progressive CNS infection produced by *N. fowleri*. It was first described in 1965 by Malcolm Fowler and Rodney Carter in four human cases of meningoencephalitis from *N. fowleri*.[142] Worldwide, approximately 180 cases of PAM have been reported, with more than 80 cases in the United States alone.[69,120,283,304,398,506] *N. fowleri* multiplies and grows between 40° and 45°C (104° and 113°F). In response to adverse environmental conditions, such as cold temperature, the ameba encysts and remains in the sediment in the bottoms of lakes, rivers, and pools.

Infections occur in healthy children and adults who contact the ameba while swimming in polluted water in manmade lakes, ponds, and swimming pools, or the ameba may be inhaled with dust from air.[317] Infection is more common during summer months. Amebas enter the CNS through the nasal mucosa and olfactory neuroepithelium. Amebic trophozoites travel up the unmyelinated fila olfactoria of the olfactory nerves and through the cribriform plate to the subarachnoid space.[241] They proliferate and penetrate into the CNS, causing edema and necrosis. The incubation period is from 1 to 15 days. Symptoms include severe headache, fever, nausea, vomiting, and stiff neck. Rapid neurologic deterioration, accompanied by signs of fulminant meningitis with seizures, coma, and death, follows within 2 to 3 days.

Diagnosis is made by direct visualization of trophozoites in the CSF, along with polymorphonuclear pleocytosis, elevated protein, and low glucose. *Naegleria* trophozoites typically measure 8 to 12 mm (0.3 to 0.5 inches) in diameter with indistinct cytoplasm, round nucleus, and perinucleolar halo.[317] *N. fowleri* causes acute leptomeningitis and hemorrhagic necrosis of the orbitofrontal cortex, olfactory bulbs, and base of the brain, with edema of the cerebral hemispheres and cerebellum. Computed tomographic (CT) scan of the brain shows nonspecific cerebral edema.[256,415] Early detection and treatment are essential because this disease carries a very poor prognosis, with mortality rate of 98%. To date, there are six cases of successful treatment of PAM in individuals who were treated very early in the clinical course.[57,378,423,511] Treatment includes high-dose intravenous (1 to 1.5 mg/kg/day) and intrathecal (1 to 1.5 mg/day) amphotericin B.[179] Oral ketoconazole (200 to 400 mg/day) and rifampicin (10 mg/kg/day; maximum 600 mg/day) have been used in addition to amphotericin B.[378]

PAM should be suspected in any previously healthy individual who has been exposed to fresh warm water within 7 days of the onset of illness and who has clinical findings of bacterial meningitis with a basilar distribution of exudate by head CT.[69]

GRANULOMATOUS AMEBIC ENCEPHALITIS

Several species of *Acanthamoeba* and *B. mandrillaris* are pathogenic opportunistic amebas that cause granulomatous amebic encephalitis (GAE), mainly in victims who are immunocompromised, debilitated, diabetic, or alcoholic. GAE has been reported in patients with systemic lupus erythematosus, acquired immunodeficiency syndrome (AIDS), or bone marrow transplantation.[9,146,271,467] However, two cases of GAE caused by *B. mandrillaris* occurred in apparently immunocompetent individuals.[398] Approximately 170 cases of GAE have been reported worldwide.[317]

Acanthamoeba species are ubiquitous in nature; they have been found in ocean water, ponds, sewage, rivers, air-conditioner filters, cooling towers, eye-wash stations, and dust. Some of the *Acanthamoeba* opportunistic species include *A. castellanii, A. hatchetti, A. culbertsoni, A. astronyxis, A. polyphaga, A. rhysodes,* and *A. mauritaniensis*.[317] *B. mandrillaris* has not been isolated from the environment, although, like *Acanthamoeba,* it probably exists in cyst form. Trophozoites and cysts can enter through the lungs and ulcerations in the skin. Olfactory neuroepithelium may also act as a portal of entry.[235,317] The incubation period is unknown but is probably weeks.

Both *Acanthamoeba* species and *B. mandrillaris* produce chronic granulomatous encephalitis. The clinical presentation may mimic tuberculous meningitis or viral encephalitis. Symptoms include headache, fever, seizures, personality changes, cranial nerve palsies, hemiparesis, and coma. There may be skin ulcerations. The amebas cause hemorrhagic necrosis and foci of encephalomalacia in occipital, parietal, temporal, and frontal lobes. The lesions are multifocal and most numerous in the basal ganglia, midbrain, brainstem, and cerebral hemispheres.[317] Vasculitis can occur, and trophozoites are often found invading vascular walls.[396] The amebas multiply and can disseminate throughout the body. Other organs involved (at the time of autopsy) include the liver, lungs, kidneys, adrenals, pancreas, lymph nodes, and heart.[9,467]

Magnetic resonance imaging (MRI) and CT scans have shown multiple enhancing lesions in the cerebral hemispheres and cerebellum, but the scans are nondiagnostic.[256,396,415] Diagnosis is difficult, because amebas are rarely observed in the CSF. Examination of the CSF shows a moderate mononuclear pleocytosis, elevated protein, and low glucose. Definitive diagnosis is made by direct visualization of amebic trophozoites and cysts within brain tissue. Unfortunately, there is no effective treatment for GAE, and the mortality rate is 100% in immunocompromised patients.[317] Although pentamidine isethionate, propamidine, sulfadiazine, and ketoconazole are effective in vitro, these drugs do not appear to be useful because of the underlying immunosuppression of most of these patients.[317] Based on tissue-culture studies, pentamidine isethionate appears to be the best choice for treatment of *B. mandrillaris* encephalitis.[417] One case of widespread granulomatous skin lesions in an immunocompromised patient resulting from *A. rhysodes* was successfully treated with intravenous pentamidine isethionate for 4 weeks, topical chlorhexidine gluconate, and ketoconazole cream, followed by oral itraconazole.[441] Miltefosine is a drug that has shown in vitro activity against free-living amebas, but as an investigational drug.

It is not readily available in the United States. However, with CDC assistance, miltefosine has been administered since 2009 for amebic infections as single-patient emergency use with permission from the FDA. Although the number of *B. mandrillaris* and *Acanthamoeba* species infections treated with a miltefosine-containing regimen is small, it appears that a miltefosine-containing treatment regimen does offer a survival advantage for patients with these often fatal infections. The CDC now has an expanded access investigational new drug protocol in effect with the FDA to make miltefosine available directly from the CDC for treatment in the United States.[82]

ACANTHAMOEBA KERATITIS

Acanthamoeba keratitis is caused by *Acanthamoeba*, a genus containing at least 24 species of free-living amebic protozoa.[317] It is ubiquitous in nature, existing both in soil and in nearly all water sources and supplies, and has been found in seawater, lakes, rivers, and streams, and is commonly found in water supplies, such as tap and bottled water, drinking fountains, eye-wash stations, dental units, and dialysis machines. Despite its near universal presence, *Acanthamoeba* infection in humans is relatively uncommon. The combination of corneal epithelium barrier disruption, whether from trauma or from contact lens wear, and exposure to a sufficient inoculum of *Acanthamoeba* substantially increases the risk of keratitis.

Acanthamoeba enters the corneal stroma through minor trauma or abrasion, causing chronic corneal inflammation, which can impair vision and lead to vascularized corneal scarring, perforation, and loss of the eye. Poor lens hygiene and overnight wear are the dominant risk factors for development of keratitis. The incidence of *Acanthamoeba* keratitis is estimated at 0.33 to 1.0 per 10,000 hydrogel contact lens wearers per year.[7]

Symptoms include severe eye pain, photophobia, conjunctival inflammation, and blurred vision. Diagnosis is made by identification of the trophozoites or cysts by corneal scrapings or biopsies. The treatment of choice for *Acanthamoeba* keratitis is 0.02% polyhexamethylene biguanide or propamidine (0.1%) with topical polymyxin B, gramicidin, or neomycin.[177,284] Other topical drugs that have been used for the treatment of this form of keratitis include antibiotics (e.g., aminoglycoside, neomycin) and antifungals (e.g., azole, itraconazole, metronidazole, voriconazole). Oral itraconazole has been used in severe cases to prevent potential spread of trophozoites into adjacent tissues. Penetrating keratoplasty and corneal grafting have been performed.[151] Contact lens wearers should use sterile solutions for lenses and should consider not wearing contact lenses while engaging in water sports.[229]

DISEASES CAUSED BY OCCUPATIONAL EXPOSURE TO SEAFOOD

The number of fishers and fish farmers has been growing at an average rate of 3.5% per year since 1990.[237,238] There is great variation in work activities for the different types of seafood, including working aboard fish trawlers, aquaculture production, working inland as capture fishers or in processing, food preparation activities, laboratory technicians and researchers, pet food production, shell grinders, and jewelry polishers. Adverse respiratory reactions are mainly the result of biologic and chemical agents associated with processing, preserving, storage, and transport of seafood. Several types of seafood cause occupational respiratory allergy, although shellfish are some of the most allergenic species of seafood. Agents with the potential to cause respiratory disease include high-molecular-weight seafood proteins, microbes containing "fish juice," biogenic amines, degradation compounds, and digestive enzymes.[238] Additional contaminants not associated with seafood, such as parasites, protochordates, marine toxins, bacterial toxins, chemical additives, spices, and gasses produced by anaerobic decomposition (hydrogen sulfide), have been reported to cause toxicity.[237,238]

PATHOPHYSIOLOGY

Adverse reactions to seafood can be immune mediated or nonimmune mediated.[306] A number of seafood allergens have been characterized, including shellfish muscle protein, tropomyosin, and other crustacean allergens, including arginine kinase, myosin light-chain kinase, and sarcoplasmatic calcium-binding protein.[306] These proteins can cause typical IgE-mediated symptoms in individuals who have been sensitized through ingestion. By contrast, aerosolized seafood proteins responsible for asthmatic reactions encountered in occupational environments have not been well described.

CLINICAL PRESENTATION

Occupational asthma is the most frequent work-related respiratory disease reported in the seafood industry. The prevalence varies from 2% to 36%, with differences in prevalence partly due to inconsistent definitions of occupational asthma.[237] A higher prevalence is associated with exposure to crab and shrimp. Symptoms may develop from weeks to years after exposure, and are more severe at work, with improvement noted on weekends. Rhinitis, conjunctivitis, and skin rashes on exposed portions of the body accompany or precede respiratory symptoms. The prognosis of occupational asthma is variable and depends on several factors, including duration of exposure, pulmonary function testing at the time of diagnosis, and type of agent involved.

Approximately 75% of workers with occupational asthma are left with permanent hyperresponsiveness, even after removal from the exposure, although the magnitude of their symptoms is generally mild. In patients who remain exposed, asthma is likely to worsen.[314]

TREATMENT

A definitive diagnostic test for occupational asthma does not exist.[31] Questionnaires are very sensitive but not very specific. The specific inhalation challenge test is considered the reference standard. However, it is not widely available and false-negative results occur. Other objective tests include the prick skin test or specific IgE to the offending allergens, or documentation of increased nonallergenic bronchial responsiveness. These tests have positive predictive values of 76% to 89%. Therefore, a negative test does not exclude the diagnosis, whereas a positive test is not confirmatory.[31,237] Monitoring of peak expiratory flow is inexpensive and easily available; however, performance is effort dependent and often poorly performed.[170] Diagnosing occupational asthma should be performed in a stepwise manner, incorporating the compatible clinical history and objective testing. Once the diagnosis of occupational asthma is made, the worker must be removed from the exposure. Inhaled steroids can hasten improvement.

PREVENTION

Atopy is the most important host factor associated with development of sensitization to high-molecular-weight allergens and for development of occupational asthma, although there is a general consensus that there is no place for prescreening and exclusion from employment of atopic individuals.[170] Smoking has also been associated with sensitization to snow crab.[170] Potential primary prevention measures include engineering controls to improve ventilation, administrative controls to reduce the number of workers exposed or duration of exposure, and use of personal protective equipment. There are currently no regulatory exposure standards for seafood allergens.

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CHAPTER 78

Seafood Allergies

ASHLEY R. LAIRD

Seafood, including all edible fish and shellfish, has been a mainstay of diets throughout the world for centuries, playing a key role in the nutrition and economy of nations around the globe. In the United States, fish and shellfish consumption has increased in recent decades, perhaps because of its increasingly recognized nutritional benefits, such as providing low-fat, high-quality protein as well as omega-3 fatty acids essential for heart and brain health. In 2012, the United States was ranked the third largest consumer of seafood in the world, behind China and Japan, consuming a total of 4.5 billion pounds of fish and shellfish.[143] This equated to 14.4 pounds of fish and shellfish per person in 2012, up from 11.8 pounds in 1970. Table 78-1 illustrates trends in per capita seafood consumption in the United States since 1970. Since 2001, shrimp has continued to rank as the most consumed seafood in the United States, with 3.8 pounds of shrimp consumed per person in 2012, down from a record of 4.4 pounds in 2006.[142] Table 78-2 lists the most frequently consumed seafood in the United States in 2012.

Given this trend toward increased fish and shellfish consumption, there has been growing recognition and appreciation of seafood allergies, which can range from mild cutaneous reactions to life-threatening anaphylaxis and death. It is important that clinicians be prepared to recognize, treat, and prevent fish and shellfish allergies. Understanding the epidemiology, pathophysiology, biologic classification, and spectrum of cross-reactivity of seafood with other potential allergens is instrumental in achieving this goal.

EPIDEMIOLOGY

Food allergies pose a significant threat to human health. Bock and coworkers estimate that food allergies are the leading identifiable cause of anaphylactic reactions presenting to emergency departments in the United States. Overall, there are approximately 29,000 anaphylactic reactions per year, resulting in 150 deaths annually.[23] The actual incidence of anaphylaxis due to food allergies depends on the diagnostic criteria used. One study reported a 13% incidence among a sample of patients presenting with food-related allergic reactions,[165] whereas another reported an incidence of 51%.[39] In a study of patients presenting with food allergies to an allergy center in Singapore, 66% had a history of anaphylactic reaction to a food allergen.[193]

Food allergies are common. It is estimated that 4% to 5% of adults and 5% of children under the age of 3 years in the United States have a food allergy.[181] Seafood allergy is the most common food allergy in adults, with as much as 2.3% of the general population reporting a seafood allergy.[180] Unlike many food allergies, seafood allergies appear to be more common in adults than in children. Similar to the situation with peanut allergy, individuals with fish and shellfish allergies generally remain clinically reactive lifelong. A 2002 telephone survey conducted in the United States determined that fish allergies afflicted 0.1% and 0.4% of children and adults, respectively, whereas 0.1% of children and 2% of adults reported a shellfish allergy. Shellfish rank as the leading cause of IgE-mediated food allergies in the U.S. adult population, as well as the leading cause of visits related to a food allergy to an emergency department.[39,180] Another analysis estimated that shellfish are the number one cause of food allergies among individuals older than age 6 years presenting to EDs in the United States with food allergies.[165]

Although the specific causes of food allergies vary in different countries according to regional dietary patterns, seafood allergies appear to be one of the leading causes of food allergies worldwide. In Korea, where whelk is commonly eaten, allergy to this mollusk has been reported.[99] Similarly, barnacle allergy has been identified in the Portuguese population.[121] In a study of patients with food allergies in Singapore, crustacea accounted for 34%, mollusks 19%, and fish 4% of food allergies.[193] A telephone survey in Canada reported a probable prevalence of fish and shellfish allergies to be 0.48% and 1.42%, respectively,[19] similar to the allergy patterns reported in the U.S. population. In a survey of food allergies in schoolchildren in Asia, a high prevalence of shellfish allergy was seen, with rates of 5.23% and 5.12% in 14- to 16-year-olds in Singapore and the Philippines, respectively. This was in comparison to similar groups of children born in Western countries, where peanut and tree nut allergies were found to be much more prevalent,[176] possibly reflecting differences in patterns of seafood consumption in Asian and Western countries.

BIOLOGIC CLASSIFICATION OF SEAFOOD

Seafood can be classified mainly into four categories of organisms: fish, crustacea, mollusks, and echinoderms, with each belonging to a different phylum. Because most individuals with a seafood allergy are not allergic to all types of seafood, basic understanding of the biologic classification of fish and shellfish can be helpful to guide patients regarding selective avoidance diets. Table 78-3 provides an overview of the taxonomic relationships among seafoods.

Fish belong to the phylum Chordata, with most edible fish belonging to the class of bony, ray-finned fish, Actinopterygii (superclass Osteichthyes). Sharks (including dogfish), rays, and skates are the exception, belonging to the Chondrichthyes class of cartilaginous fish. The most frequently consumed fish in the United States fall into several orders: Salmoniformes (salmon, trout, whitefish), Siluriformes (catfish), Pleuronectiformes (flounder, halibut, sole, flatfish), Perciformes (bass, perch, snapper, tuna, mackerel, tilapia, swordfish), Gadiformes (codfish, pollock), and Clupeiformes (herring, sardines, anchovies).[139] Table 78-4 describes the taxonomic relationships among edible fish species.

Shellfish can be broken down into two distinct phyla. Crustacea, which include shrimp, prawns, crab, lobster, barnacles, krill, and crayfish, are classified as arthropods, sharing the Arthropoda phylum with spiders, centipedes, and insects. The Mollusca phylum includes eight classes, three of which are important for human consumption: Gastropoda (snails, abalone), Bivalvia (mussels, oysters, scallops, clams), and Cephalopoda (squid, octopus, cuttlefish).[139,191]

Sea cucumbers and sea urchins and their products, including *uni,* or sea urchin coral, and *roe,* or sea urchin ovaries, make up a very small percentage of marine organisms consumed by humans. Sea urchins and sea cucumbers belong to the phylum Echinodermata, with sea urchins belonging to the class Echinoidea, and sea cucumbers belonging to the class Holothuroidea.[139]

IMMUNOLOGIC MECHANISMS OF SEAFOOD ALLERGIES

Although nonimmunologic reactions to fish and shellfish occur, true seafood allergies are reactions mediated by immunoglobulin E (IgE) that represent a failure of the body's oral tolerance

TABLE 78-1 U.S. Seafood Consumption for Selected Years from 1970 to 2012 (Pounds per Capita)

Seafood	1970	1980	1990	1995	2000	2005	2007	2009	2010	2011	2012
Total	11.8	12.5	15.0	15.0	15.2	16.2	16.3	16.0	15.8	15.0	14.4
Fresh/frozen	6.9	7.9	9.6	10.0	10.2	11.6	12.1	12.0	11.6	10.9	10.5
Canned	4.5	4.3	5.1	4.7	4.7	4.3	3.9	3.7	3.9	3.8	3.6
Cured	0.4	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3

From National Oceanic and Atmospheric Administration: Fisheries of the United States: noaa.gov.

TABLE 78-2 Top Ten Most Frequently Consumed Seafoods in the United States in 2012

Seafood	Weight (lb/capita)
1. Shrimp	3.800
2. Canned tuna	2.400
3. Salmon	2.020
4. Tilapia	1.476
5. Pollock	1.167
6. Pangasius	0.726
7. Crab	0.523
8. Cod	0.521
9. Catfish	0.500
10. Clams	0.347
Total	14.6

Data from National Marine Fisheries Service: Top 10 U.S. consumption by species chart, calculated by Howard Johnson, H.M. Johnson & Associates for NFI: aboutseafood.com/about/about-seafood/Top-10-Consumed-Seafoods.

TABLE 78-3 Taxonomic Relationships Among Seafoods

Phylum	Class	Common Name Representatives
Chordata	Actinopterygii	Bony, ray-finned fish (see Table 78-4)
	Chondrichthyes	Cartilaginous fish (sharks, rays, skates)
Arthropoda	Crustacea	Shrimp, crab, lobster, barnacles, crayfish, krill
Mollusca	Gastropoda	Snails, abalone, whelk
	Bivalvia	Mussels, oysters, scallops, clams, cockles
	Cephalopoda	Squid, octopus, cuttlefish
Echinodermata	Echinoidea	Sea urchin
	Holothuroidea	Sea cucumber

Data from Myers P, Espinosa R, Parr CS, et al: The animal diversity web, 2008: animaldiversity.org.

TABLE 78-4 Taxonomic Relationships Among the Edible Fishes

Class	Order (Suborder)	Common Name
Chondrichthyes	Elasmobranchii	Sharks
Actinopterygii	Acipenseriformes	Sturgeons, paddlefish
	Anguilliformes	Common eels, morays
	Atheriniformes	Silversides, jacksmelts, grunions
	Beloniformes	Sauries, needlefish, flying fish
	Clupeiformes	Herring, sardines, alewives, shad, menhaden, anchovies
	Cypriniformes	Minnows, carp, suckers
	Elopiformes	Tarpons, ten-pounders
	Esociformes	Pike, pickerel, muskellunge
	Gadiformes	Codfish, ling cod, pollock, haddock, tomcod, hake, codling, whiting
	Gonorynchiformes	Awa, milkfish
	Lampridiformes	Opah
	Lophiiformes	Monkfish, goosefish
	Mugiliformes	Mullets
	Osmeriformes	Smelts, eulachon, capelin
	Perciformes (Ammodytoidei)	Sand lances
Actinopterygii (cont.)	Perciformes (Labroidei)	Cichlids (tilapia), tautogs, wrasses, surf perch
	Perciformes (Percodei)	Bass, crappies, bluegills, sea bass, sunfish, perch, bluefish, jacks, pompanos, dolphin fish, snapper, groupers, scups, grunts, porgies, pomfrets, sheepsheads, snooks, robalos, bigeyes, catalufas, croakers, butterfly fish, goatfish, mojarras, rudderfish, weakfish, drums, sauger, threadfins, walleye
	Perciformes (Scombroidei)	Mackerel, tuna, cutlassfish, albacore, bonitos, kingfish, swordfish, sailfish, barracuda, billfish, marlin, spearfish, tenggiri fish
	Perciformes (Stromateoidei)	Butterfish
	Perciformes (Zoarcoidei)	Wolffish
	Percopsiformes	Trout-perch, sand rollers
	Pleuronectiformes	Flounders, halibut, sole, dabs, turbots, flatfish
	Salmoniformes	Trout, salmon, whitefish, graylings, lake herring
	Scorpaeniformes	Rockfish, scorpionfish, greenlings
	Siluriformes	Catfish
	Tetraodontiformes	Pufferfish, boxfish, trunkfish

From Myers P, Espinosa R, Parr CS, et al: The animal diversity web, 2008: animaldiversity.org.

mechanisms. Oral tolerance can be defined as "an active nonresponse to antigens delivered via the oral route."[123] It involves both prevention of uptake of allergenic proteins from the gut into the bloodstream and suppression of the immune system's allergenic response to such proteins once they enter the system.

Under physiologic conditions, luminal barriers within the gastrointestinal tract prevent the uptake of the majority of potential food allergens that enter the gut. Potentially allergenic proteins are degraded into nonimmunogenic forms by gastric acid and digestive enzymes, whereas IgA antibodies secreted by B cells in the gut bind foreign proteins and prevent their uptake. However, even under physiologic conditions, approximately 2% of ingested proteins cross the protective epithelium of the gastrointestinal tract intact and are absorbed into the bloodstream as immunologically active antigens.[80] Usually these antigens do not elicit allergic reactions because of the body's innate mechanisms that suppress the immune response to food allergens. This process of immune suppression begins when an intact antigen escapes the protective barriers of the gut and is taken up and presented by antigen-presenting cells (APCs), including B cells, dendritic cells, and macrophages. APCs then activate regulatory and suppressor T cells, which secrete suppressive cytokines, transforming growth factor β and interleukin-10 (IL-10). Through this series of steps, a state of oral tolerance is achieved whereby the immune system essentially "ignores" the food antigen. In the case of high-dose oral antigen exposure, tolerance is mediated by a different mechanism, specifically, lymphocyte clonal anergy and/or deletion.[29,34]

When oral tolerance mechanisms fail to inhibit the body's immune response to ingested food antigens, food allergies can develop. True seafood allergies are type I immediate hypersensitivity IgE-mediated reactions that result from a chain of molecular and cellular interactions involving APCs, T cells, and B cells (Figure 78-1). Production of allergen-specific IgE (sensitization) antibodies forms the underlying basis of immediate hypersensitivity; atopy is defined as the genetic predisposition to developing allergen-specific IgE antibodies. The sensitization process requires a cooperative effort between CD4 T lymphocytes and B lymphocytes. It begins with presentation of an allergen to CD4 T lymphocytes by APCs in the context of a major histocompatibility complex. Cytokines released from CD4 T lymphocytes as a result of this interaction cause differentiation of B lymphocytes into immunoglobulin-secreting plasma cells. This differentiation leads to isotype switching (production of specific antibody types) within plasma cells. For example, release of cytokines IL-4 or IL-13 from T lymphocytes promotes IgE switching.[50] Once allergen-specific IgE antibodies are produced, subsequent exposure and binding of the allergens to IgE molecules on the surface of mast cells results in cross-linking of the IgE molecules. Consequently, mast cells or basophils degranulate and release both preformed and newly synthesized mediators. The prototype preformed mediator is histamine, and the newly synthesized mediators include those of the arachidonic acid pathway (leukotrienes, prostaglandins, and platelet-activating factor), neuropeptides (e.g., substance P), and cytokines (e.g., IL-4, IL-5).

Release of chemical mediators has various pathologic consequences that can cause both local and systemic clinical manifestations. Histamine causes vasodilation and increased vascular permeability, smooth muscle contraction, stimulation of sensory nerve endings, and glandular secretions, with clinical effects including nasal congestion, rhinorrhea, urticaria, angioedema, laryngospasm, cough, wheezing, and shock. Products of the arachidonic acid pathway have similar effects.

Allergic reactions consist of an early phase characterized by mast cell or basophil degranulation, and a late phase, which occurs 4 to 6 hours after the early phase. The hallmark of the late-phase reaction is influx of inflammatory cells, such as eosinophils, basophils, and T lymphocytes. For example, basophils cause further histamine release, and T lymphocytes release additional cytokines that enhance IgE production (via IL-4) and eosinophil activation (via IL-5). As a result of further inflammatory activity by these cells, there is recrudescence of symptoms many hours after the initial allergen exposure. Leukotrienes, prostaglandins, and cytokines released in the early-phase reaction play an important role in recruiting the late-phase cellular components to the inflammatory site.

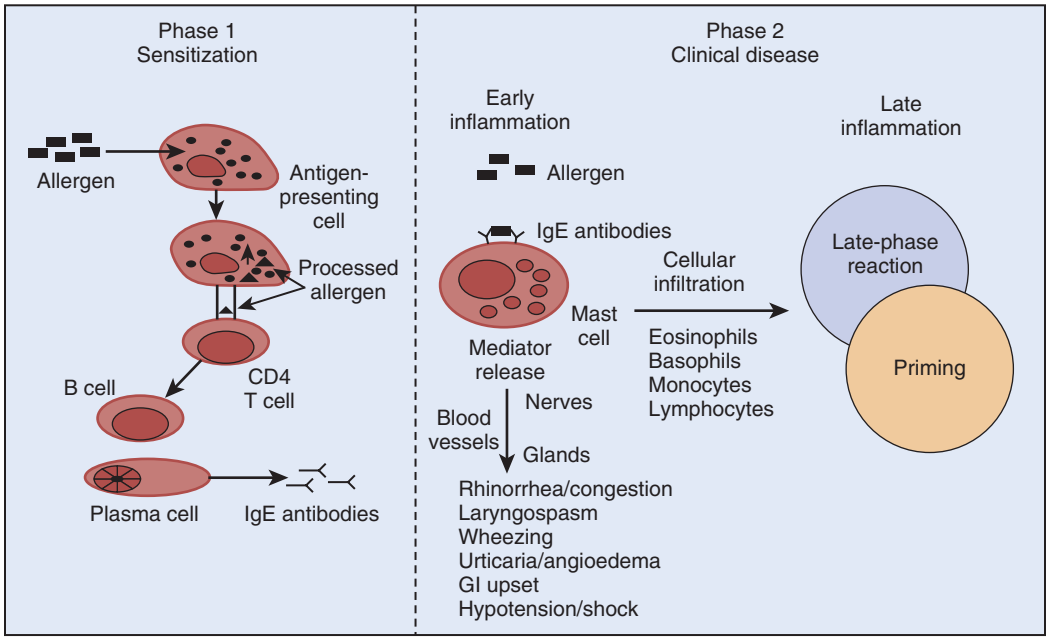

FIGURE 78-1 The natural history of IgE-mediated allergic reaction (simplified schematic). During phase 1, the individual becomes sensitized to an allergen. During phase 2, clinical disease develops. An overwhelming majority of individuals have an early response on reexposure to the allergen. Activation of mast cells and release of mediators dominate the early response. After the early response, most individuals have an influx of inflammatory cells, causing late inflammatory events, including spontaneous recurrence of release of mediators (late-phase reaction) and increased responsiveness to the allergen on reexposure (priming). *Circles* indicate the heterogeneity of these late inflammatory events. *(Modified from Naclerio R: Allergic rhinitis,* N Engl J Med *325:860, 1991.)*

In theory, prior exposure and sensitization to a food allergen must occur before development of a clinically significant allergic reaction. The exposure may occur through cutaneous or inhalation routes, cross-sensitization via similar antigens, placental transfer, or as a result of hidden ingredients or contaminants in other foods. Risk factors for development of food allergies include early age of antigen exposure, extensive delay of oral exposure (possibly causing sensitization by topical exposure rather than inducing tolerance via oral exposure), family history of atopy, presence of asthma or other atopic disease, and medications (e.g., antacids) or medical conditions that reduce acidity within the gut and allow more potential allergens to escape the natural protective barriers of the gastrointestinal tract.[29,181,197] In one study, more than half of patients with food allergy had concomitant allergic rhinitis, asthma, and/or atopic dermatitis.[193] In another study, codfish-allergic individuals were orally challenged with fish digested with gastric enzymes at pH 2.0 and 3.0. Patients experienced allergic symptoms sooner or at a lower dose when the codfish was predigested at pH 3.0 compared with pH 2.0, underscoring the role of gastric digestion in the process of food allergen tolerance.[197]

CLINICAL MANIFESTATIONS

Clinical manifestations of fish and shellfish allergies are similar to those of other IgE-mediated food allergy reactions, ranging from mild urticaria to life-threatening anaphylaxis. In the U.S. telephone survey cited earlier, 55% of finfish reactions and 40% of shellfish reactions were severe enough to cause the sufferers to seek evaluation by a physician.[180] IgE-mediated reactions generally have a rapid onset, with allergic symptoms developing within minutes to an hour of exposure and most reactions occurring within 30 minutes.[1,30,46,74] However, a delayed onset (3 to 24 hours after exposure) of symptoms may occur and has been noted with, among other seafoods, dogfish,[163] cuttlefish,[177] abalone,[119] and limpets.[134] A biphasic reaction may occur, whereby the individual appears to recover and then experiences a late-phase reaction with recrudescence of symptoms after an asymptomatic period. In one pediatric study, a biphasic reaction was seen in 6% of anaphylaxis patients.[98]

Symptoms of seafood allergy are often, but not always, related to the route of exposure and can occur after ingestion, cutaneous contact, and inhalation. Following ingestion of an offending seafood, the most commonly reported signs and symptoms include generalized itching and urticaria; angioedema, particularly swelling of the lips and tongue; pulmonary manifestations, including dyspnea, wheezing, and chest tightness; gastrointestinal complaints, including nausea, vomiting, diarrhea, and abdominal cramping; and shock.[101,180] It is direct contact of the allergenic food with the oral mucosa that causes pruritus and angioedema of the lips, tongue, throat, and palate—a constellation of symptoms known as oral allergy syndrome.[37,52] In patients with underlying atopic disease, exposure to fish and shellfish allergens can cause exacerbations of eczema[169] and, less commonly, asthma symptoms.[84] Because ongoing exposure to a food allergen may cause chronic urticaria, the presence of an undiagnosed food allergy should be sought in patients with chronic urticaria.[52]

In general, ingestion of the allergic seafood leads to gastrointestinal symptoms, urticaria, and possible vascular compromise, whereas skin contact results in mainly dermatologic symptoms. Exposure by inhalation typically causes respiratory symptoms. For example, there are documented cases of patients allergic to fish presenting with skin reactions after handling raw fish,[136,157] as well as symptoms of asthma in fish-allergic children after inhalation of aerosolized fish.[161] However, this is by no means the absolute rule; systemic reactions after cutaneous and inhalational exposure may occur. In one case study, a 2-year-old fish-allergic child experienced facial urticaria and angioedema after her grandfather, who had eaten fish 2 hours earlier, kissed her.[131] In another report, a shellfish-allergic patient experienced anaphylaxis after kissing her boyfriend, who had recently ingested shrimp.[185] In one survey, 8.6% of fish-allergic and 10% of shellfish-allergic individuals experienced more severe reactions following inhalational or dermal, rather than ingestion, exposure. These allergic individuals were able to consume the offending antigen without significant sequelae.[180]

Vascular involvement is not uncommon in patients with seafood allergies. In one review of patients with seafood allergies, 8% of patients with fish allergy and 13% of patients with shrimp allergy developed anaphylactic shock after seafood challenge.[101] Manifestations of vascular involvement may include hypotension, a subjective "sense of doom," respiratory distress progressing to asphyxia, dysrhythmias, and myocardial infarction. Near-fatal and fatal reactions may begin with only mild symptoms, such as oral allergy syndrome, before rapidly progressing to cardiovascular collapse. Risk factors for severe anaphylactic reactions are the presence of other atopic disease(s), inadvertent ingestion of the offending food, rapid onset of symptoms, failure to promptly treat with epinephrine, and a history of prior anaphylaxis to the causative food.[52]

One form of anaphylaxis that occurs in the setting of seafood allergy is *food-associated, exercise-induced anaphylaxis*. Affected patients develop anaphylaxis if they exercise within 2 to 6 hours of ingesting an allergenic food, but remain asymptomatic if the same food is ingested without exercise. Although the mechanism is poorly understood, shellfish and wheat flour are the most common causes of food-associated, exercise-induced anaphylaxis.[18,211]

OCCUPATIONAL SEAFOOD ALLERGIES

Hypersensitivity reactions to fish and shellfish in the seafood processing industry due to occupational exposure are increasingly recognized. Rather than ingestion, most reactions are associated with direct contact or inhalational exposure during cutting, cleaning, cooking, or drying of seafood.[100] Occupational reactions have been reported in a variety of seafood workers, including fishermen, seafood-processing workers, canners, restaurant cooks, delivery persons, and other workers associated with the seafood industry.[31,49,105,174] Occupational seafood allergy can manifest as rhinitis, conjunctivitis, asthma, urticaria, contact dermatitis, or oral allergy syndrome.[4,86] Studies performed on snow crab workers demonstrated a 33% incidence of asthma, 24% incidence of skin rash, and 18% rate of rhinitis or conjunctivitis related to inhalational exposure or skin contact with snow crab meat or by-products.[31] In a survey of occupational allergies in seafood workers in Australia and South Africa, skin reactions accounted for 78% to 81% of reported problems, followed by asthmatic symptoms (7% to 10%) and nonspecific allergic symptoms (9% to 15%).[117] Although rare, vascular involvement related to occupational seafood exposure has been reported.[174]

In most studies, occupational asthma appears to be the most prominent clinical presentation of seafood allergy, with a reported prevalence of 7% to 36%.[86] Seafood implicated in occupational asthma include all the major seafood groupings: oysters,[141] clams,[49] shrimp,[49,105] prawns,[61] fish,[42,51] snow and king crabs,[31,151] lobsters,[105,154] sea squirts,[89] abalone,[40] powdered marine sponges,[16] cuttlefish,[194] and clam liver extract.[91] In one case study, shark cartilage powder was reported to have caused a fatal occupational asthma attack.[153] Hypersensitivity pneumonitis may result from occupational exposure to seafood allergens and has been documented secondary to mollusk shell dust inhalation.[152] Clinical manifestations of hypersensitivity pneumonitis include dyspnea, fever, chills, cough, and malaise. With chronic low-level allergen exposure, fever and chills may be absent, with symptoms of exertional dyspnea, fatigue, and weight loss predominating.[104]

Dermatologic occupational seafood allergy has been less well studied but generally takes the forms of contact urticaria and a chronic recurrent dermatitis known as protein contact dermatitis.[4,78,138] The estimated prevalence of occupational protein contact dermatitis ranges from 3% to 11%.[86] The most frequent clinical presentation is chronic or recurrent eczema that may be limited to the fingertips or extend to the wrists and arms. Initial manifestations include itchy, erythematous, and vesicular lesions, which usually progress to chronic eczema, with episodic acute exacerbations after repeated contact with the culprit allergen.[4,78] Some cases of chronic paronychia (after handling the allergenic

food) may also be a variant of protein contact dermatitis, with redness and swelling of the proximal nail fold.[196] In some cases, percutaneous sensitization to seafood allergens may occur via direct skin contact in the workplace, as may occur with seafood packers or delivery persons. If ongoing exposure occurs, the individual may develop allergic symptoms and even anaphylaxis following ingestion of the offending seafood.[174] Risk factors for sensitization and clinical allergy in seafood workers include the presence of atopy, as well as the duration and intensity of exposure to the potential allergen.[90,182]

DIFFERENTIAL DIAGNOSIS

Diagnosing a seafood allergy can range from a simple to an extremely complex process. There are a number of hidden allergens in foods, as well as seafood allergy mimics (such as seafood toxins and allergens present in seafood parasites), that can easily go unrecognized. When evaluating a patient with a suspected seafood allergy or a patient with an apparent allergic reaction to an unknown allergen, it is important to obtain a careful history and consider a broad differential diagnosis.

Many nonseafood products contain fish and shellfish, often unbeknownst to the consumer. For example, imitation crab meat is usually made of pollock or monkfish. Surimi, which is processed fish meat usually derived from Alaskan pollock in the United States, is commonly used for seafood-flavored snacks, sauces, flavors, "meatless" hot dogs, sausages, pepperoni sticks, imitation crab, and pizza toppings.[205] Anchovies are a routine ingredient in Caesar salad dressing and Worcestershire sauce. Fish gelatin is a common stabilizing and gelling agent in foods, often used in marshmallows, gummy candies, and other desserts. Many pills and medications contain chitin, a component of the outer skeleton of crustacea and other arthropods. Additionally, many products may be unintentionally contaminated with seafood because they are processed in a facility that also handles seafood. Although the allergenic potential of some of these products has not been well studied, it is important to consider them as potential sources in patients presenting with allergic symptoms. A thorough history may help to identify these accidental ingestions, especially in patients with a known seafood allergy who present with an allergic reaction of unknown cause.

Apparent seafood allergies can also be caused by seafood parasites, rather than to the particular fish or shellfish consumed. The parasite *Anisakis simplex* can be a cause of allergic reactions in individuals after consuming parasitized seafood.[10,11,92] *A. simplex* is a nematode that infects fish worldwide and can cause health issues in humans via transient infection after consuming raw or undercooked flesh of infected fish, or via allergy. The allergic reaction is a typical IgE-mediated reaction, presenting as acute urticaria, angioedema, or anaphylaxis following ingestion of infected fish.[11] To date, 13 different *Anisakis* allergens have been characterized.[3] One of the responsible allergens, Ani s 3, is the invertebrate panallergen tropomyosin, capable of cross-reacting with shellfish tropomyosins, adding to the diagnostic dilemma when faced with a patient with a potential seafood allergy.[8,11,68,122,204] Another *Anisakis* allergen, the secretor allergen Ani s 1, has been identified as the major allergen for diagnosing *Anisakis* allergy, with sensitivity and specificity values in vivo and in vitro approaching 100%.[63]

Evidence also suggests that *Anisakis* allergy contributes to occupational respiratory and skin allergies in seafood workers. Armentia and colleagues found *A. simplex* to be the cause of occupational asthma in two seafood workers.[5] In a case report by Scala and coworkers, *Anisakis* was found to be the allergen responsible for contact urticaria and inhalational asthma in a seafood factory worker.[173] In one study looking at the prevalence of *Anisakis* sensitization and related symptoms in fish-processing factories, the prevalence of sensitization to *Anisakis* was found to be higher than that for the fish being processed and was associated with a higher risk of allergic reactions.[145] These findings underscore the importance of considering *Anisakis* allergy in patients presenting with first-time allergic symptoms following consumption of seafood, especially if that seafood has been tolerated in the past. Unfortunately, studies suggest that ingestion of frozen or cooked seafood, which is recommended for anisakidosis prophylaxis, does not prevent IgE-mediated allergic reactions to *Anisakis*. Given the prevalence of parasitism of fish and shellfish by *Anisakis,* for patients diagnosed with *Anisakis* allergy, a seafood-free diet is recommended.[132]

A common mimicker of IgE-mediated seafood allergy is scombroid poisoning (see Chapter 77). Scombroid intoxication results from ingestion of dark-meat fish (tuna, salmon, marlin, mahimahi, bluefish, mackerel, and others) containing high levels of free histamine produced by bacteria in the fish flesh during spoilage.[33] Usually within 10 to 30 minutes of ingestion, the histamine produces symptoms that mimic IgE-mediated allergy, including perioral tingling and burning sensations, flushing, urticaria, and gastrointestinal complaints, and may progress to bronchospasm, tachycardia, and hypotension. Symptoms that suggest scombroid intoxication include headache, dizziness, and perioral tingling and burning, as well as a history of consuming fish that tasted peppery or bitter.[33]

Other types of seafood poisoning (ciguatoxin, fish or diarrheic shellfish poisoning, and others) may result in a variety of physical complaints, but these are usually clinically distinct from IgE-mediated allergic reactions. Similarly, seafood-associated illness may occur secondary to bacterial and viral causes, such as poisoning due to toxins (botulism, *Staphylococcus*) or gastroenteritis from bacterial or viral infection.[33] These illnesses also tend to be clinically distinct from IgE-mediated reactions.

DIAGNOSIS

A critical step in diagnosing seafood allergy, or any other food allergy, is obtaining a thorough and accurate history, including specific symptoms, food(s) ingested around the time of symptom onset, timing of the reaction, prior history of similar reactions, presence of known food allergies, and any exacerbating factors, such as exercise. Patients should also be questioned about possible contaminants or hidden allergenic ingredients in ingested food(s), particularly if the inciting allergen is unknown. Although taking a good history is of utmost importance, research suggests that medical history alone is insufficient in diagnosing food allergy. In one study of children with a self-reported food allergy, the allergic reaction was reproducible in only 40% by double-blind, placebo-controlled food challenge.[22]

Contributing to the challenge of diagnosing food allergies are several confounding factors. Preparation and processing methods, as well as the part of seafood ingested, may all contribute to the allergenicity of any particular seafood. In one study, pomfret and hilsa fish lost their allergenicity significantly when they were boiled and fried compared with raw extracts, and bhetki and mackerel remained strongly, if not more, reactive once cooked.[32] Another study found that patients with salmon and tuna allergies had negative reactions to canned salmon and tuna challenges, suggesting that the major antigen(s) in these fish may be considerably heat labile.[21] Finally, Kobayashi and colleagues demonstrated less allergenicity in fish dark muscle compared to white muscle, suggesting that the part of the fish ingested may lead to variable allergic responses.[95]

In patients with suspected seafood allergy, skin prick tests (SPTs) are a relatively safe, inexpensive, and useful screening tool. Commercial extracts are not available for every seafood species; therefore, mixed extracts are often used. Additionally, actual raw or cooked food itself can be used for skin testing. SPTs may be contraindicated in patients with a history of a severe anaphylactic reaction to the seafood being tested or in patients with significant skin disease. Given the fact that SPTs measure sensitization to a particular allergen, and sensitization is not equivalent to allergic disease, caution must be taken in interpreting SPT results. Multiple studies comparing SPTs with double-blind, placebo-controlled food challenges have found that a positive SPT does not always correlate with symptomatic seafood allergy.[20,22,73] Thus, SPTs have high sensitivity and excellent negative predictive value, but low specificity and poor positive predictive value.[52] Specifically, patients with positive results on SPT may not necessarily have clinically significant allergic disease. However, a study using mean wheal diameters to predict positive

food challenges with shrimp suggested that skin testing for seafood allergy may not be as problematic as was once thought.[88] Mean wheal diameter of 30 mm (1.2 inches) after an SPT provided 80% and 95% predictive probability for positive food challenge in subjects with allergies to black tiger prawn and giant freshwater prawn, respectively. This study suggested that the predictive probability of SPTs can be helpful in cases where food challenge cannot be performed.[88]

In vitro diagnostic methods, such as serum immunoassays to determine food-specific IgE antibodies, can also be useful screening tools, particularly for patients in whom skin testing is contraindicated. Serum immunoassays are fraught with the same diagnostic dilemmas as is skin testing, in that in vitro reactivity, like cutaneous sensitization, does not necessarily correlate with clinical allergy.[130] Thus, many patients with positive serum immunoassay testing may not have allergic disease when exposed to the allergen in question.[20,73] Studies by Sampson and colleagues, however, suggest that quantitative measurement of food-specific IgE antibodies may be a useful predictive tool in identifying patients with clinical reactivity.[170,171] In one study, diagnostic levels of IgE, called "decision points," were established that could predict clinical reactivity with greater than 95% certainty to a variety of allergenic foods, including fish, eggs, peanuts, and milk. Diagnostic IgE levels were identified at 20 kU (A)/L or greater for fish allergy.[171] The predictive value of using diagnostic IgE levels to substantiate clinical reactivity was confirmed in a prospective study in which more than 95% of clinical food allergies, including fish allergy, were correctly identified using quantitative serum food-specific IgE concentrations.[170] These findings suggest that serum immunoassay testing may be a safe alternative to oral challenge in patients suspected of having IgE-mediated food allergy.

Atopy patch tests (APTs) have been evaluated as useful tools for diagnosis of food allergy. In the classic patch test, the suspected allergen is applied to a piece of cloth or paper, which is placed on intact skin and covered with an impermeable barrier for 24 to 48 hours. The patch is then removed and the skin examined.[104] However, recent studies have found that APTs add little predictive value to standard SPT and IgE measurements in the diagnostic workup of suspected food allergies and thus cannot be routinely recommended.[125]

The gold standard test in verifying a particular food allergen is the double-blind, placebo-controlled food challenge.[24] This should not be performed in persons who have experienced life-threatening reactions and should be undertaken only under close physician supervision. Dried or freeze-dried foods are encapsulated in opaque, dye-free capsules; alternatively, the food of interest can be hidden in a food vehicle. Appropriate identical placebo-controls are prepared. Although such testing is time consuming and labor intensive, it permits precise diagnosis.

When a certain type of seafood is suspected of producing symptoms, a diagnostic elimination diet can support the diagnosis. Once the offending allergen is eliminated from the diet, the allergic reactions should not occur. The food is then reintroduced to determine if the allergic reaction is reelicited. Diagnostic elimination diets should only be used in persons who have experienced mild allergic symptoms.

Although the methods described previously are useful in diagnosing food allergies, the diagnosis of occupational allergies often requires a different approach, especially in the case of occupational asthma due to inhalation of a seafood allergen. If the allergic individual notes the onset of asthma symptoms related to work exposure, and there is improvement during weekends or vacation, occupational asthma should be suspected. Asthma is verified by appropriate pulmonary function tests, such as spirometry with and without bronchodilators. If the history of asthma is suspected but not corroborated by physical examination or spirometry, it may be necessary to perform a provocation test with inhaled methacholine or histamine to document airway hyperreactivity. The diagnosis depends ultimately on provocation of symptoms by bronchial inhalation challenge with the suspected allergen to simulate industrial exposure.[104] Such evaluation can be performed at the workplace or in a controlled laboratory environment. If a workplace challenge is performed, the subject's lung function is monitored during the workday with the idea that lung function will decline during the work period because of workplace exposure to the offending allergen. Laboratory challenge is the diagnostic method of choice for diagnosis of occupational asthma, because it allows for identification of a specific etiologic agent (unlike a workplace challenge, where many different allergens may confound the test).[104] Because of inherent dangers of exposing an allergic individual to high doses of allergen, laboratory challenge should occur under close observation in a hospital setting.

Occupational allergic contact dermatitis may also require a specialized approach. Approximately 90% of occupational dermatitis involves the hands, usually the palm and back of the wrist[104]; therefore, dermatitis in a different distribution should raise doubt about the diagnosis. Additionally, location of the dermatitis and location of exposure to the allergen must be matched. Although routine atopy patch testing is not recommended as part of the diagnostic workup of food allergy, in the case of suspected occupational skin disease, patch testing may be useful in demonstrating allergic contact dermatitis to a suspected allergen.[104]

MANAGEMENT

Treatment of acute allergic reaction due to seafood is the same as for any other allergic reaction and depends on the severity and specific symptoms of the reaction. Treatment should begin with assessment and management of the ABCs. For mild cutaneous reactions, antihistamines alone may be sufficient. In patients with severe reactions, epinephrine should be promptly administered intramuscularly or, in refractory cases, intravenously. Intravenous fluids and vasopressors should be used to manage hypotension refractory to epinephrine. Respiratory symptoms, such as wheezing, can be treated with an aerosolized β_2-agonist. To decrease the risk of a delayed, or late-phase, reaction, systemic glucocorticoids should also be given. Because of the risk of a recurrence of symptoms after initial recovery, patients should be observed for a period of several hours up to 24 hours, depending on the severity of the allergic reaction. If severe respiratory or cardiac compromise is present, the patient should be hospitalized.

AFTERCARE

All individuals at risk for anaphylaxis should carry a device for self-injection of epinephrine and carry a medical information card or wear a medical information bracelet. Patients should be referred to an allergist for evaluation and testing to help determine the nature and extent of the seafood allergy.

Avoidance is the only treatment for seafood allergy. Because the allergens present in fish and shellfish are molecularly different (see Molecular Biology section), patients with an allergy to fish generally do not need to avoid shellfish, and vice versa. Allergists typically recommend removing all edible fish from the diet when the patient has a demonstrated history of severe allergic reaction to any fish and/or if there is a positive skin test or serum immunoassay to a fish extract. Similarly, an individual who previously had a severe allergic reaction to a shellfish would be advised to avoid all shellfish. In patients with a history of severe anaphylactic reaction or allergic reactions to many types of seafood, avoidance of all fish and shellfish may be the safest strategy.

In patients with a history of less severe allergic reaction to a particular seafood, research suggests that selective avoidance diets may be reasonable. Studies using double-blind, placebo-controlled fish challenges[20,73] and other tests[48] in fish-allergic children have shown that individuals are not uniformly sensitive to all fish species; hence, sensitivity to one species does not automatically warrant dietary elimination of all seafood. Studies of fish challenges are often negative in children with negative skin tests.[20] Therefore, it seems reasonable to recommend dietary elimination of any seafood species for which there has been a demonstrated allergic reaction or a positive SPT or in vitro test. If a patient tests positive by SPT or in vitro testing to a particular seafood item, but has no history of clinical allergy to that seafood

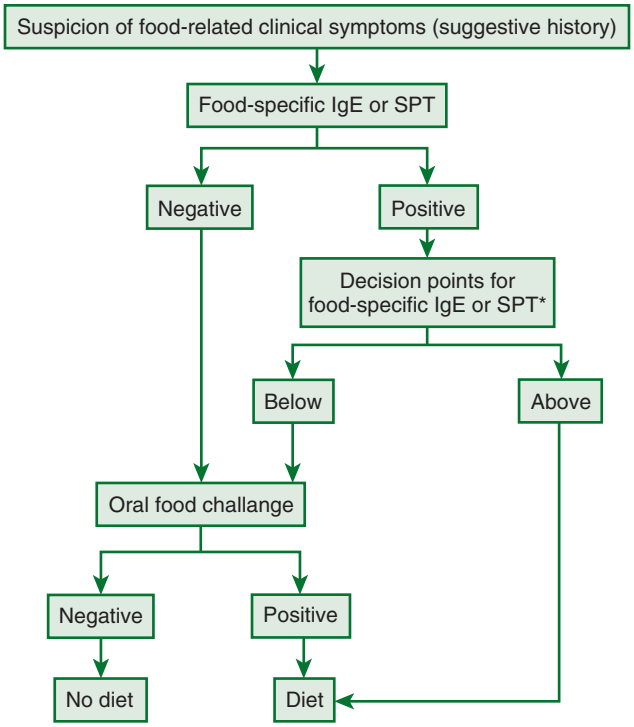

FIGURE 78-2 An algorithmic approach to diagnosing food allergies, including seafood allergies, proceeding from suspicion of food-related symptoms to final recommendations on a specific elimination diet. *Diagnostic decision points appear to be population, age, and allergen dependent. SPT, skin prick test. *(From Niggemann B, Beyer K: Diagnosis of food allergy in children: Toward a standardization of food challenge,* J Pediatr Gastroenterol Nutr *45:400, 2007.)*

species, a double-blind, placebo-controlled food challenge can be performed to determine whether true clinical allergy exists. Given the high negative predictive value of SPTs, seafood species for which patients have no history of allergic reaction and have tested negative by a SPT could be permitted in the diet after oral challenge. In the setting of a newly diagnosed seafood allergy to a particular fish or shellfish species, it is reasonable to allow patients to consume other seafood items that have not previously caused allergic symptoms.

Niggemann and colleagues have proposed an algorithmic approach to diagnosing food allergies, including seafood allergies (Figure 78-2).[146] In this algorithm, all patients with a suspected food allergy should undergo food-specific IgE or SPT. If negative, an oral challenge can be conducted. If the initial IgE or SPT is positive, previously established food-specific IgE or SPT "decision points" should be evaluated. If the patient's quantitative IgE or SPT wheal diameter is above the previously established decision point, the food should be eliminated from the diet, but if it falls below the decision point, oral challenge can be conducted.[146]

Education is crucial following an allergic reaction to seafood. Patients should be counseled to read all food labels for the possibility of hidden or unexpected allergenic ingredients or allergic contaminants. Since passage of the United States Food Allergen Labeling and Consumer Protection Act of 2004, food labels have been required to clearly state the presence of eight specified food allergens, including fish and crustacean shellfish. However, mollusks are not included in this labeling mandate.[60] Patients should be informed about the potential for allergic reaction after aerosolization of the offending allergen, as may occur during cooking of seafood, either at home or in fish markets. Finally, patients should be cautioned about the potential for exposure to seafood allergens via inadvertent cross-contact, as in restaurants where equipment is shared for seafood and nonseafood cooking, or during contact with contaminated saliva during kissing or utensil sharing.[131,185]

MOLECULAR BIOLOGY OF SEAFOOD ALLERGIES

The major allergens responsible for IgE-mediated allergic reactions due to fish and shellfish are the parvalbumin and tropomyosin proteins, respectively.[47,53,54,110,175] Since the original characterization of these allergens in codfish and shrimp models, researchers have continued to characterize these proteins and confirm their allergenicity in a wide variety of species of fish and shellfish, as well as identify new classes of proteins also implicated in the development of seafood allergies. Tables 78-5 and 78-6 list the allergens characterized in fish and shellfish to date.

FISH ALLERGENS

Of the seafood allergens that have been isolated and purified, the best characterized is the major allergen of the codfish, Gad c 1, which belongs to the group of muscle tissue proteins called parvalbumins and was first identified in the Baltic cod *(Gadus callarias).*[54] Parvalbumins are small (12-kD) calcium-binding proteins responsible for mediating the concentration of calcium in white muscle of lower vertebrates and skeletal muscle of higher vertebrates. Parvalbumins exist in two different isoforms, alpha and beta. In fish, parvalbumin beta appears to be a cross-reactive panallergen. Parvalbumins resist heat and enzymatic degradation,[205] making them ideally suited food allergens capable of withstanding extreme temperatures during cooking and proteolytic breakdown in the digestive tract.

Since the original characterization of parvalbumin in codfish, parvalbumins have been identified as allergens in numerous other fish species. Lindstrom and coworkers identified a parvalbumin, designated Sal s 1, as the major allergen in Atlantic salmon *(Salmo salar).*[116] A second cod parvalbumin, Gad m 1, has been characterized in the Atlantic cod *(Gadus morhua)* and was found to have greater homology with Sal s 1 than with Gad c 1 (75% with Sal s 1 compared with 62.3% with Gad c 1).[45,119] Parvalbumin antigens have also been identified as major allergens in three species of mackerel (Sco j 1, Sco a 1, Sco s 1), carp (Cyp c 1.01, Cyp c 1.02), Alaska pollock (The c 1), pilchard (Sar sa 1.0101), threadfin, Indian anchovy, pomfret, tenggiri, and Indian scad.[17,71,113,128, 189,200] Studies performed on red and golden snapper revealed a 51-kD protein as a major allergen that is hypothesized to be a parvalbumin tetramer.[164] Interestingly, the 12-kD protein isolate believed to be fish parvalbumin was only found to be a minor allergen in both species of snapper.[164] Studies on tuna have produced inconclusive results. Bugajska-Schretter and associates demonstrated IgE reactivity to tuna parvalbumins in sera from fish-allergic patients,[27] and another study reported identification of parvalbumin as a major allergen in bigeye tuna (Thu o 1).[178] Other studies have failed to detect allergenicity to tuna parvalbumins, suggesting that tuna fish allergy may be caused by an allergen other than parvalbumin.[198,209]

In addition to parvalbumin proteins, other antigens are also emerging as major fish allergens. A second codfish allergen, p41, has been identified that is a 41-kD IgE-reactive protein homologous to an aldehyde phosphate dehydrogenase.[44,62] The purified p41 protein binds specifically to reaginic IgE from cod-allergic individuals. The p41 protein was also found to bind to monoclonal antibodies specific for the first calcium-binding site of parvalbumins, suggesting that p41 may have a calcium-binding site corresponding to an IgE epitope similar to that of Gad c 1.[62] Fish enolase and aldolase have also been identified as significant fish allergens in cod, salmon, and tuna.[97]

Type 1 collagen, a component of muscle and skin in several fish species, was recently identified as a potential major allergen. Hamada and colleagues identified a high-molecular-weight allergen recognized by one fish-allergic serum sample in surimi made from walleye pollock.[69] IgE immunoblotting and amino acid analysis identified the allergen as collagen. In another study, Sakaguchi and coworkers demonstrated IgE antibodies to fish gelatin (type 1 collagen) in fish-allergic children.[168] Anaphylaxis following ingestion of marshmallows containing fish gelatin has been reported.[96] In a study by Hamada and colleagues, five of eight serum samples obtained from fish-allergic individuals

TABLE 78-5 Allergens Characterized in Fish

Protein	Species	Allergen	Reference
Parvalbumin	Baltic cod *(Gadus callarias)*	Gad c 1	54
	Atlantic cod *(Gadus morhua)*	Gad m 1	44, 199
	Atlantic salmon *(Salmo salar)*	Sal s 1	116
	Mackerel *(Scomber japonicus, Scomber australasicus, Scomber scombrus)*	Sco j 1, Sco a 1, Sco s 1	71
	Alaska pollock *(Theragra chalcogramma)*	The c 1	200
	Carp *(Cyprinus carpio)*	Cyp c 1.01, Cyp c 1.02	188
	Pacific pilchard *(Sardinops sagax)*	Sar sa 1.0101	17
	Indian anchovy *(Stolephorus indicus)*		113
	Pomfret *(Pampus chinensis)*		113
	Tenggiri papan *(Scomberomorus guttatus)*		113
	Threadfin *(Polynemus indicus)*		113
	Indian scad *(Decapterus russelli)*		128
	Bigeye tuna *(Thunnus obesus)*	Thu o 1	178
	Red snapper *(Lutjanus argentimaculatus)*		164
	Gold snapper *(Lutjanus johnii)*		164
Collagen, type 1	Bigeye tuna *(Thunnus obesus)*		70
	Alaska pollock (*Theragra chalcogramma*)		69
Aldehyde phosphate dehydrogenase homologue	Cod	p41	44, 62
Vitellogenin	Trout caviar		58
	Beluga fish caviar	Hus h 1	156
Alpha S1-casein-like protein	Kingfish caviar		35
Aldolase	Cod		97
	Salmon		97
	Tuna		97
Enolase	Cod		97
	Salmon		97
	Tuna		97

TABLE 78-6 Allergens Characterized in Crustacea and Mollusks

Protein	Species	Allergen	Reference
Tropomyosin (Crustacea)	Brown shrimp *(Penaeus aztecus)*	Pen a 1	47
	Indian white shrimp *(Penaeus indicus)*	Pen i 1	175
	Neptune rose shrimp *(Parapenaeus fissurus)*	Par f 1	114
	Sand shrimp *(Metapenaeus ensis)*	Met e 1	110
	Tiger prawn *(Penaeus monodon)*		167
	King prawn *(Penaeus latisulcatus)*		167
	Chinese spiny lobster *(Panulirus stimpsoni)*	Pan s 1	107
	American lobster *(Homarus americanus)*	Hom a 1	107
	Red crab *(Charybdis feriatus)*	Cha f 1	106
	Krill *(Euphausia superba)*	Eup s 1	140
	Krill *(Euphausia pacifica)*	Eup p 1	140
	Amphipods (*Gammarus* and *Caprella* spp.)		135
	Acorn barnacle *(Balanus rostratus)*	Bal r 1	186
	Goose barnacle *(Capitulum mitella)*	Cap m 1	186
Tropomyosin (Mollusks)	Pacific flying squid *(Todarodes pacificus)*	Tod p 1	129
	Octopus *(Octopus vulgaris)*	Oct v 1	83
	Pacific oyster *(Crassostrea gigas)*	Cra g 1, Cra g 2	82
	Razor clam *(Ensis macha)*	Ens m 1	87
	Mussel *(Perna viridis)*	Per v 1	38
	Scallop *(Chlamys nobilis)*	Chl n 1	38
	Abalone *(Haliotis midae, Haliotis discus, Haliotis rufescens)*	Hal m 2, Hal d 1, Hal r 1	36, 38, 119
	Turban shell *(Turbo cornutus)*	Tur c 1	81
	Common whelk *(Buccinum undatum)*	Buc u 1	99
	Fan shell *(Pinna atropurpurea)*	Pin a 1	109
	Brown garden snail *(Helix aspersa)*	Hel as 1	7
Arginine kinase	Tiger prawn *(Penaeus monodon)*	Pen m 2	210, 167
	King prawn *(Penaeus latisulcatus)*		167
	White shrimp *(Litopenaeus vannamei)*	Lit v 2	64
Myosin light chain	White shrimp *(Litopenaeus vannamei)*	Lit v 3	12
Sarcoplasmic calcium-binding protein	Tiger shrimp *(Penaeus monodon)*		179
	White shrimp *(Litopenaeus vannamei)*	Lit v 4	13

reacted to bigeye tuna collagen.[70] Furthermore, studies of allergens in red and golden snapper revealed a heat-stable high-molecular-weight protein believed to be collagen as a minor allergen in both snapper species.[164]

Fish allergy may result from allergy to protamine sulfate, a protein found in the sperm of salmon, trout, herring, and other species belonging to the families Salmonidae and Clupeidae. Protamine sulfate is a low-molecular-weight protein used as a heparin antagonist. Because of case reports of fish-allergic patients experiencing anaphylaxis after administration of protamine sulfate, extreme caution or use of alternative therapies in fish-allergic patients is advised by some experts.[41,94,158]

Allergic reactions, including anaphylaxis, have also been reported after ingestion of fish roe and caviar. In several case reports, the allergic individuals experienced a reaction after eating Beluga caviar, trout roe, or whitefish roe but had no allergy to fish or other types of roe.[58,120,156] In another case, a woman experienced an allergic reaction after consuming rainbow trout roe, and serum analysis demonstrated cross-reactivity with other types of fish roe.[120] A 118-kD protein, Hus h 1, has been identified as the culprit allergen in Beluga caviar allergy.[156] This is the hormone vitellogenin, found in fish eggs, and has also been proposed as the causative allergen in trout roe allergies.[58,156] A 33-kD alpha S1-casein–like allergen, a well-known major allergen in cow's milk, was identified as the culprit allergen in a subject who experienced anaphylactic shock after consuming kingfish caviar.[35] Although sea urchins fall into a different phylum from fish, it is worth mentioning sea urchin roe allergy, as several case reports have reported anaphylactic reactions following consumption of sea urchin roe.[75,162]

CRUSTACEAN ALLERGENS

The crustacea family includes shrimp, prawns, crabs, lobsters, crayfish, krill, and barnacles, and is a commonly reported cause of food allergy. The major allergen in crustacea has been identified as tropomyosin, an essential protein for muscle contraction found in vertebrates and invertebrates. Tropomyosin was originally identified as the major allergen in shrimp.[47,110,175] Subsequent studies have identified tropomyosin as the major allergen in other crustacean species, as well as in mollusk species. Although tropomyosins are major allergens in shellfish, arachnids (mites), and insects (cockroaches, midges), the tropomyosins of vertebrates such as cattle and chicken are considered nonallergenic, possibly because of their greater susceptibility to breakdown by digestive enzymes, as compared with shellfish, arachnid, and insect tropomyosins.[126] Invertebrate tropomyosins share a high (up to 100%) amino acid sequence homology with other invertebrates and a much lesser (50% to 60%) homology with vertebrate tropomyosins, supporting their role as the panallergen responsible for cross-reactivity across crustacea, insects, arachnids, and mollusks. This also helps explain the lack of allergenicity of vertebrate tropomyosins (see Cross-Reactivity section).[14,67,108]

Convincing evidence for the role of tropomyosin as a major shrimp allergen originated with studies by Daul and coworkers.[47] Using the brown shrimp *(Penaeus aztecus)* model, a 36-kD tropomyosin protein named Pen a 1 was identified and shown to react with the sera of 82% of shrimp-allergic individuals.[47] Similar tropomyosins were also identified as the major allergens in other shrimp species, including Pen i 1 in Indian white shrimp *(Penaeus indicus),* Met e 1 in sand shrimp *(Metapenaeus ensis),* and Par f 1 in Neptune rose shrimp *(Parapenaeus fissurus).*[110,114,175] A study of the black tiger prawn *(Penaeus monodon)* and king prawn *(Penaeus latisulcatus)* identified several major antigens in both species, with one thought to represent tropomyosin and another arginine kinase.[167] Studies of other crustacea have identified tropomyosin as the major allergen in American and Chinese spiny lobsters *(Homarus americanus* and *Panulirus stimpsoni),* designated Hom a 1 and Pan s 1, respectively, and red crab *(Charybdis feriatus),* named Cha f 1.[106,107] Two major IgE-binding proteins of 35- to 37-kD and 97-kD were demonstrated in extracts of lobster in pooled sera from subjects with respiratory symptoms caused by Norwegian lobster *(Nephrops norvegicus).*[206] The 35- to 37-kD allergen likely represented tropomyosin, but made up only 0.02% to 1% of the total protein. The 97-kD allergen made up 7% to 15% of the total protein, suggesting the presence of another major allergen in addition to tropomyosin in Norwegian lobster.

Tropomyosin proteins have also been identified as the major allergens in two species of krill, designated Eup s 1 in *Euphausia superba* and Eup p 1 in *Euphausia pacifica,* with the krill tropomyosins showing high IgE-binding epitope sequence homology to shrimp tropomyosin Pen a 1.[140] Tropomyosins were found to be the major allergens in gammaridean and caprellid amphipods.[135] Amphipods can be accidentally collected with seaweed during seaweed harvest and therefore become part of nori (dried laver) sheets used in sushi making and as condiments in other foods, raising concerns about the safety of nori sheets in individuals with shellfish allergies. Finally, tropomyosins have been identified as major allergens in two species of barnacle, Bal r 1 in the Acorn barnacle *(Balanus rostratus)* and Cap m 1 in the Goose barnacle *(Capitulum mitella).*[186] These tropomyosins shared higher sequence identity with mollusk tropomyosins compared with other crustacean tropomyosins, suggesting that barnacle tropomyosin is evolutionally more closely related to the molluscan tropomyosin family.[186]

In addition to tropomyosins, other major allergens have been identified and characterized in crustacea, particularly shrimp. A 356–amino acid protein designated Pen m 2 has been found in tiger shrimp *(P. monodon).* This protein showed homology to arginine kinase from other crustacea and was found to react with serum IgE from shrimp-allergic individuals.[210] A similar 40-kD protein was isolated from white Pacific shrimp *(Litopenaeus vannamei)* and identified as arginine kinase.[64] Designated Lit v 2, this new protein was recognized by IgE in serum from shrimp-allergic individuals and had 96% identity to Pen m 2.[64] Arginine kinase has also been identified as a major allergen in king prawns.[167] Another new shrimp allergen, a myosin light-chain protein in white Pacific shrimp, is named Lit v 3.[12] Lit v 3 demonstrated IgE binding in 55% of white Pacific shrimp-allergic individuals.[12] A 20-kD allergen was purified from the abdominal muscle of black tiger shrimp and identified as a sarcoplasmic calcium-binding protein (SCP).[179] Of sera from 16 crustacea-allergic individuals, eight reacted to SCP, whereas 13 reacted to tropomyosin, supporting SCP as a crustacean allergen.[179] An SCP in white Pacific shrimp (*L. vannamei*), named Lit v 4, has been identified as a major allergen, particularly in the pediatric population.[13]

MOLLUSK ALLERGENS

Molluscan shellfish allergy has been ascribed to nearly all of the commonly consumed types of mollusks, including terrestrial and marine snails, whelk, limpet, and abalone among the gastropods; oyster, clam, scallop, mussel, and cockle among the bivalves; and squid, octopus, and cuttlefish among the cephalopods. Tropomyosins appear to be the major allergens in mollusks, and specific tropomyosin allergens have been characterized in all classes of mollusks.[191]

In the cephalopod class, the tropomyosin Tod p 1 was found to be the major allergen in the Pacific flying squid *(Todarodes pacificus).*[129] In studies on the common octopus *(Octopus vulgaris),* the tropomyosin protein Oct v 1 was designated as the major octopus allergen, including identification of several IgE-binding epitopes with sequence similarities to IgE-binding epitopes of other molluscan shellfish and crustacea.[83] Amino acid sequence analysis demonstrates 64% homology between Oct v 1 and shrimp tropomyosin Pen a 1, and 63% homology between Tod p 1 and Pen a 1.[191]

In the bivalve class of mollusks, tropomyosin allergens have been characterized in the Pacific oyster *(Cassostrea gigas),* razor clam *(Ensis macha),* mussel *(Perna viridis),* and scallop *(Chlamys nobilis).*[38,82,87] Cra g 1 and Cra g 2 were isolated from the oyster, with Cra g 1 having 76% sequence homology with mussel tropomyosin, 74% with abalone tropomyosin, and 58% with *M. ensis* (shrimp) tropomyosin.[82] Studies on razor clam allergens isolated three major allergens between 30 and 45 kD in size that

demonstrated IgE binding with serum from a razor clam–allergic patient. One allergen, designated Ens m 1, is likely clam tropomyosin.[87] Other studies identified tropomyosin as the major allergen in the scallop, designated Chl n 1, and the mussel, named Per v 1, and confirmed their reactivity to IgE antibodies from shellfish-allergic subjects.[38]

Among the gastropods, tropomyosins have been demonstrated to be major allergens in the abalone (Hal m 2, Hal d 1, Hal r 1), turban shell (Tur c 1), common whelk (Buc u 1), and fan shell (Pin a 1).[36,38,81,99,109,119] There are at least two major allergens in the abalone, *Haliotis midae*.[119] The first, a 38-kD IgE-binding protein designated Hal m 2, is likely tropomyosin.[119] Another study identified tropomyosin as the major allergen of *Turbo cornutus,* a horned turban mollusk and popular food item in Japan. The major allergen, named Tur c 1, was found to be 35 kD in size and identified as tropomyosin, but it was found to have an IgE-binding epitope dissimilar to those in oyster and shrimp tropomyosins.[81] Studies identifying the major allergens in common whelk revealed three IgE-binding proteins. One, with a molecular weight of 40 kD, was presumed to be tropomyosin (Buc u 1).[99] A study of snail tropomyosin found that brown garden snail *(Helix aspersa)* tropomyosin, named Hel as 1, shared high homology with other edible mollusk tropomyosins (69% to 84% identity). However, tropomyosin reacted with only 18% of the sera from snail-allergic patients, suggesting that tropomyosin may be only a minor allergen in snails.[7]

In addition to tropomyosins, many studies have identified nontropomyosin allergens in numerous mollusk species, including snails, whelk, pen shell, fan shell, abalone, and limpet in the gastropod family; oyster, scallop, and razor clam in the bivalves; and squid, octopus, and cuttlefish in the cephalopod family.[191] Most of these nontropomyosin allergens remain to be identified, although research suggests that some of them may be hemocyanin, myosin heavy chain, and amylase.[191]

CROSS-REACTIVITY

Cross-reactivity may be defined as "the recognition of distinct antigens by the same IgE antibody, demonstrable by in vivo and in vitro tests, which clinically manifests as reactions caused by antigens that are homologous to different species."[205] Individuals may demonstrate sensitization by positive allergy testing to multiple species of fish and/or shellfish without demonstrating overt symptoms after consumption of that particular seafood, although the clinical significance of this observation is unclear. As discussed previously, the major allergens responsible for allergies due to fish and shellfish are parvalbumins and tropomyosins, respectively. The homology of the epitopes of these proteins across different types of seafood is thought to produce cross-reactivity.

When looking at cross-reactivity within the class of bony fish, it is estimated that approximately 50% of individuals allergic to a particular fish species will be allergic to another fish species.[195] Among crustacea, cross-reactivity appears to be even higher, with approximately 75% of individuals allergic to a crustacean species being allergic to another type of crustacea, likely because of the greater degree of similarity among tropomyosins compared with parvalbumins.[195] Both clinical and serologic cross-reactivity among fish and shellfish have been well documented. However, some studies have produced conflicting results, suggesting that the mechanisms of cross-reactivity and responsible allergens have not been completely elucidated. Furthermore, most studies have only looked at in vitro and serologic cross-reactivity, with few studies testing for actual clinical cross-reactivity.

Although some degree of cross-reactivity is common, species-specific allergies have been reported to sole, swordfish, tuna, and shrimp.[6,85,93,133] In studies on monospecific fish allergies, subjects with allergies to multiple fish species showed IgE binding to 12- to 13-kD bands (parvalbumins), whereas monosensitive subjects showed IgE binding to unique bands at 40 kD in tuna,[85] 25 kD in swordfish,[93] and 6 to 7 kD and 40 kD in tropical sole.[6] Such monospecific reactions are thought to be secondary to IgE antibodies to minor, species-specific antigens rather than to the major allergenic proteins, parvalbumins and tropomyosins.

It is noteworthy that because different antigens are responsible for causing allergic reactions to fish and shellfish, cross-reactivity between fish and shellfish does not occur. Allergy to both fish and shellfish in a single individual may occur, but it is not due to cross-reactivity. Nonetheless, in the American telephone survey previously discussed, it was estimated that 10% of individuals with a seafood allergy have an allergy to both fish and shellfish,[180] perhaps reflecting an atopic predisposition in this population.

FISH CROSS-REACTIVITY

Both serologic and clinical cross-reactivity across different fish species have been demonstrated and are hypothesized to be secondary to the major fish allergen parvalbumin. In adults with clinical sensitivity to cod, positive skin prick reactions were reported to mackerel, herring, and plaice, and sera from the same individuals demonstrated IgE binding to a protein in the 11- to 14-kD region of mackerel, herring, and plaice extracts, likely representing parvalbumin.[72] Mackerel, herring, and plaice inhibited codfish immunoassays and demonstrated at least the presence of serologic cross-reactivity to different fish species.[72] Cross-reactivity among IgE epitopes for six different fish species, including cod, tuna, salmon, perch, carp, and eel, was demonstrated by IgE-immunoblot inhibition experiments.[27] In another study, when sera from fish-allergic individuals were incubated with recombinant carp parvalbumin, IgE-reactivity to cod, tuna, and salmon was lost, suggesting the presence of common epitopes across these fish species.[189] In a study of children with codfish allergy, skin testing was most frequently positive with eel (85%), bass, dentex, sole, and tuna (55%), whereas it was least frequently seen with dogfish (10%).[48] This suggests the presence of common epitopes, but also supports the presence of significant variation within these common epitopes. Cross-reactivity across nine commonly consumed fish in Norway was studied. Cod, salmon, pollock, herring, and wolffish had the most potent cross-reactive allergens, whereas halibut, tuna, flounder, and mackerel were the least allergenic, suggesting that cross-reactivity among IgE epitopes is highest in the setting of close phylogenetic relationships between fish species.[198]

Other studies have demonstrated similar variable cross-reactivity among different fish species. In one case study, a 4-year-old boy experienced anaphylactic reactions on contact with many different types of fish, including cod, tuna, salmon, trout, and eel, among others.[115] In other studies of individuals with fish allergy confirmed by skin test and immunoassay reactivity, the majority of subjects reacted to only one type of fish, whereas a much smaller proportion of individuals reacted to two or more species of fish on oral challenge.[20,73] These studies demonstrate that while clinically significant cross-reactivity exists, it varies across allergic individuals, and that sensitization as indicated by positive allergy testing cannot always predict clinically significant allergic reactions. Similarly, up to 40% of patients sensitized to fish (positive allergy testing) do not present with symptoms on consumption of other fish species,[195] supporting the observation that subclinical sensitization is not always predictive of clinical hypersensitivity.

As a whole, the fish parvalbumins share amino acid homologies ranging from 60% to 80%, which both supports the role of parvalbumin as a major fish allergen and helps to account for the variable clinical cross-reactivity seen in fish-allergic individuals.[118] Variable clinical cross-reactivity and monospecific fish allergies can also be explained by the presence of nonparvalbumin and species-specific fish allergens. Thus, it seems that parvalbumin is a panallergen in most or all fish species, whereas some species contain additional species-specific allergens.[192]

Cross-reactivity with nonfish parvalbumins may exist. One case report documented a patient who experienced anaphylaxis following consumption of frog legs, with subsequent protein microsequencing implicating the alpha isoform of frog parvalbumin as the causative allergen.[76] Subsequent studies have demonstrated in vitro cross-reactivity between frog and fish beta-parvalbumins, suggesting that parvalbumins may be a new family of cross-reactive allergens.[77]

SHELLFISH CROSS-REACTIVITY

Cross-reactivity among shellfish is more extensive than fish cross-reactivity. It is due to the panallergen tropomyosin, which has significant sequence homology throughout crustacea and mollusks, as well as in other invertebrates, such as arachnids and insects.[160] In the American telephone survey discussed previously, 38% of individuals reported an allergy to more than one type of crustacea, 49% had an allergy to more than one type of mollusk, and 14% reported an allergy to both crustacea and mollusks.[180] Studies have demonstrated marked homology between shrimp, crab, and lobster tropomyosins, as well as likely cross-reactivity between shrimp and crab, and shrimp and lobster as evidenced by IgE inhibition assays.[106,107] In addition, studies on krill have used immunoblot to demonstrate in vitro cross-reactivity between krill, shrimp, lobster, and crab tropomyosin.[140] A study found that 81% of atopic shrimp-allergic individuals demonstrated cross-reactivity to crab, crayfish, and lobster by SPT.[46] Cross-reactivity has been demonstrated among shrimp, crab, crayfish, and lobster by positive skin testing.[203]

Studies of cross-reactivity among mollusks using laboratory analysis and SPT have demonstrated cross-reactivity among abalone, snail, white mussel, black mussel, oyster, and squid.[119] Laboratory methods have been used to demonstrate cross-reactivity of abalone, scallop, and mussel tropomyosins.[38] These studies establish subclinical cross-reactivity, but because oral challenges were not performed, the clinical significance of these observations remains to be investigated.

In addition to cross-reactivity within the crustacea and mollusk phyla, cross-reactivity between crustacea and mollusks has been widely reported. Inhibition experiments were used to demonstrate cross-reactivity between oyster and crustacean, and between squid and shrimp.[30,103] One group of researchers was able to demonstrate in vitro cross-reactivity between squid and shrimp tropomyosin allergens, but not between squid and octopus or squid and other mollusks.[129] In a study of patients with a history of shrimp anaphylaxis, 100% of patients' sera reacted with tropomyosins from 13 different crustacea and mollusks, although because oral challenges were not conducted, the clinical importance is uncertain.[108]

Shellfish cross-reactivity has been reported in circumstances of occupational seafood allergy and food-dependent, exercise-induced anaphylaxis. In one case, a seafood restaurant worker presented with occupational asthma and urticaria after contact with shrimp and scallops, with laboratory analysis confirming cross-reactivity between shrimp and scallops.[66] A 14-year-old girl with a recurrent history of oral swelling and discomfort after ingesting shrimp, crab, squid, and octopus presented with similar symptoms after scallop ingestion followed by intensive exercise.[211] Laboratory investigation demonstrated that her serum IgE reacted to multiple types of crustacean and mollusk tropomyosins, with the level of IgE-reactivity and species-specific IgE scores correlating directly with the degree of sequence homology between each seafood tropomyosin and shrimp tropomyosin. In the case of scallops, the patient's scallop-specific IgE score was not as high as for shrimp and other shellfish, consistent with the lesser homology in the amino acid sequence of scallop tropomyosin with shrimp tropomyosin and consistent with the observation that other immunologic mechanisms, specifically food-dependent, exercise-induced anaphylaxis, was necessary for clinical reactivity.[211]

SHELLFISH CROSS-REACTIVITY WITH INSECTS AND ARACHNIDS

Invertebrate tropomyosin is also found in nonmarine allergenic organisms, including cockroaches, dust mites, and other insects and arachnids, and has been demonstrated to be a major allergen in dust mites and cockroaches via inhalational exposure.[2,9,172] Between shrimp and fruit fly, shrimp and cockroach, and shrimp and house-dust mite, tropomyosin sequence identities share 87%, 90%, and 89% homologies, respectively, supporting the role of tropomyosin as an invertebrate panallergen.[160] A growing body of evidence suggests that this highly conserved tropomyosin protein is responsible for causing cross-reactivity between shellfish and inedible arthropoda and insects.[43,57,108,122,207] For example, inhibition experiments demonstrated cross-reactivity between shrimp and nonbiting midges (chironomids).[57] In other studies, cross-reactivity was demonstrated between crustacean, chironomid, and cockroach tropomyosins.[207] Immunoblot and inhibition studies demonstrated in vitro cross-reactivity between Atlantic shrimp and German cockroaches.[43] Sera from shrimp-allergic subjects demonstrated IgE reactivity against grasshopper, cockroach, and fruit fly tropomyosins.[108] Tropomyosin IgE from shrimp-allergic individuals demonstrated cross-reactivity to mite, cockroach, and lobster tropomyosins.[14] In a study of five patients with barnacle allergy, two patients demonstrated in vitro cross-reactivity to house-dust mites, although the responsible cross-reactive allergen was not identified.[121]

Skin prick studies demonstrated cross-reactivity between shellfish and other arachnids and insects. For example, there are significant correlations between positive SPT with chironomid extract and various crustacea.[57] In a study of patients attending an allergy clinic in Hong Kong, Wu and colleagues found that 90% of patients with shellfish allergy demonstrated house-dust mite cross-reactivity by SPT.[208] In one unique study, Orthodox Jews with dust mite/cockroach hypersensitivity were found to have positive SPTs and IgE reactivity to shrimp. Because they had never been exposed to shellfish due to religious dietary prohibitions, it is hypothesized that sensitization to shrimp tropomyosin occurred via cross-reactivity to house-dust mite or cockroach tropomyosin.[59]

The previously discussed studies support the presence of in vitro and serologic cross-reactivity between shellfish and nonmarine allergenic organisms. Accumulating data suggest that this cross-reactivity also has important clinical implications. In one study, a series of individuals developed both laboratory and clinical evidence of shrimp allergy over the course of immunotherapy for house-dust mite allergy, suggesting that dust mite allergen served as the sensitizing agent in causing the shrimp allergy.[202] In a series of patients with asthma induced by snail consumption, house-dust mite sensitization was likely the causal event, although tropomyosin was thought to play only a minor role as a cross-reactive allergen.[201] Clinical cross-reactivity was demonstrated in a study in which asthmatic subjects sensitized to house-dust mite showed laboratory and clinical allergy to limpets.[15]

FUTURE DIRECTIONS

The current standard of care for managing seafood allergies is avoidance diets and provision of a self-injectable epinephrine device. Much research is under way to develop new strategies for treating and preventing seafood allergies. Some of the therapeutic modalities currently under investigation include sublingual and oral immunotherapy, anti-IgE therapy, peptide immunotherapy, traditional Chinese medicine, DNA immunization, and development of hypoallergenic seafood for human consumption.[28,55]

Although traditional allergen-specific immunotherapy was discovered nearly a century ago and has been used successfully in the treatment of peanut allergy, it is currently not recommended because of an unacceptably high incidence of dangerous systemic allergic reactions during the treatment course.[144,150] Additionally, there appears to be a potential for developing hypersensitivity to cross-reacting food allergens, such as shrimp, as described in subjects undergoing house-dust mite immunotherapy.[202] Given the high incidence of adverse reactions using traditional immunotherapy, alternatives are currently under investigation and promising new methods are being developed. For example, sublingual immunotherapy, originally developed to treat allergic rhinoconjunctivitis and asthma, was used successfully and safely to treat hazelnut food allergy in hazelnut-allergic patients.[56] Studies looking at the efficacy of specific oral tolerance induction or oral immunotherapy in inducing desensitization to food allergens have yielded promising results, although the long-term effects of such therapy have not been rigorously investigated.[26,28,124,147,155] In one study including patients with fish allergy, a standardized oral immunotherapy protocol induced

desensitization, as evidenced by conversion from skin test positive to skin test negative, following treatment in 78% of subjects who completed the oral immunotherapy protocol.[155]

Another promising modality currently in clinical trials is recombinant humanized monoclonal anti-IgE antibodies. These IgG antibodies directed against the IgE molecule bind to freely circulating IgE, creating antigen-antibody complexes that are then cleared from the circulation. Use of anti-IgE appears to decrease levels of circulating free IgE, inhibit early- and late-phase responses to allergens, suppress inflammation, and improve control of allergic diseases.[55,127] A clinical trial using anti-IgE in the treatment of peanut allergy found that a large number of patients had a significant decrease in clinical symptoms in response to peanut challenge following treatment.[111]

Peptide immunotherapy is a therapy currently under investigation that uses peptide fragments containing reactive epitopes rather than the complete protein allergen, the hypothesis being that these peptide fragments are immunogenic but are theoretically unable to cross-link IgE molecules, activate mast cells, and cause clinical allergic symptoms.[25,28] Use of these peptide fragments for immunotherapy would thus render T cells unresponsive to subsequent allergen exposure without causing dangerous systemic allergic reactions during the course of therapy. Thus far, clinical studies using peptide immunotherapy for bee venom sensitivity and cat allergy have demonstrated promising results, with subjects experiencing a significant decrease in allergic symptoms after allergen exposure following therapy.[25,137,148,149,190] Studies using peanut allergen peptides suggest that peptide immunotherapy may have a future role in treatment of food allergies, including seafood allergy.[65,79]

Traditional Chinese medicine and use of herbal remedies have gained attention as potential modalities for treating allergic diseases, including food allergies. In studies on peanut allergy using murine models, the food allergy herbal formula-1 and the simplified food allergy herbal formula-2 significantly reduced IgE levels and blocked anaphylactic reactions to peanuts for up to 5 weeks following therapy.[112,184] Although Chinese herbal remedies hold promise and have shown efficacy in murine models, human studies are only currently under way, and the active ingredients and mechanism of action of these remedies remain to be delineated.[181]

A new approach for treatment of food allergy is DNA immunization.[183] With this strategy, a plasmid DNA (pDNA) vector encoding a specific food allergenic protein would be injected subcutaneously or delivered orally. The pDNA sequence would be taken up by APCs, the DNA transcribed and translated, and the allergenic protein then presented on the surface of the APC as an endogenously produced protein. This endogenous protein would induce a Th1 response (rather than Th2 as occurs in allergic disease) with suppression of allergen-specific IgE production, thus producing desensitization to the specific food allergen.[28,166] Although promising in murine models, allergen DNA immunization is likely years away from practical use.

Genetic alteration of epitopes on food allergens to suppress their allergenicity is currently under investigation as a method for producing safer allergens for immunotherapy. Hypoallergenic foods could be developed for consumption by individuals with food allergies. For example, studies on shrimp tropomyosin (Pen a 1) have demonstrated that substitution of critical amino acids in Pen a 1 epitopes results in significant reduction of IgE binding while still preserving immunogenicity.[102] Such a mutated molecule could be used safely and effectively for immunotherapy without the risk of allergic reaction during treatment, or the mutant could be incorporated into the genome to create a hypoallergenic organism.[102] A recombinant hypoallergenic carp parvalbumin mutant has been constructed that has 95% reduced IgE reactivity and diminished allergenicity as demonstrated by in vitro assays and in vivo SPT, but retains immunogenicity, making it a candidate for immunotherapy.[187] Studies using genetic transformation technology to modify the allergic structure in shrimp are under way,[37,159] with the eventual goal of producing nonallergenic transgenic seafood that is safe for consumption by individuals with seafood allergy.

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