10.4.2 Injuries, envenoming, poisoning, and allerg

10.4.2 Injuries, envenoming, poisoning, and allergic reactions caused by animals 1778

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1778 10.4.2 Injuries, envenoming, poisoning, and allergic reactions caused by animals David A. Warrell ESSENTIALS Mechanical injuries Attacks by wild and domesticated animals are increasing worldwide. They are best prevented by taking local advice about minimizing ex- posure. Injuries usually occur in places remote from medical care. They may involve extensive trauma, haemorrhagic shock, and a high risk of bacterial contamination. First aid consists of resuscitation, control of bleeding and perforating injuries, intravenous fluid re- placement, and rapid evacuation to hospital for emergency surgery and treatment of infection. Venomous snakes Bites by venomous snakes can cause death or permanent physical and mental morbidity. Snakebite is largely an occupational/environ- mental hazard of agricultural workers and their children in rural areas of the tropics. Bites are commonly inflicted on the lower limbs and could be prevented by wearing protective footwear, by using a light and prodding with a stick while walking at night, and by sleeping off the ground or under a mosquito net. Snake venoms are complex mixtures of toxic proteins causing ne- crosis, shock, haemostatic disturbances, paralysis, rhabdomyolysis, and acute kidney injury. Envenoming by Elapidae (cobras, kraits, mambas, coral snakes, Australian snakes, and sea snakes) can cause descending flaccid paralysis, starting with ptosis and progressing to respiratory paralysis. Some elapid venoms cause local necrosis, rhabdomyolysis, and haemostatic disturbances. Bites by Viperidae (vipers, adders, and pit vipers—rattlesnakes, moccasins, lanceheads) can cause severe local swelling, bruising, blistering, and necrosis together with shock, consumption coagulopathy, spontaneous systemic bleeding, acute kidney injury, and, with some species, neuromyotoxicity. First aid involves reassurance, immobilization of the whole pa- tient,

especially the bitten limb, rapid evacuation to the nearest hos- pital, and avoidance of dangerous traditional methods. When the necessary skills and equipment are available, pressure-pad immo- bilization should be applied immediately unless the possibility of a neurotoxic elapid bite can be excluded. In hospital, specific antivenom (hyperimmune equine or ovine immunoglobulins) is given if there is evidence of systemic or se- vere local envenoming. Polyspecific antivenoms cover envenoming by medically important snakes in the geographical area for which they are intended. Early anaphylactic or pyrogenic reactions and late serum sickness antivenom reactions are common but not predict- able by hypersensitivity tests. Incidence of severe early reactions is reduced by prophylactic low-dose subcutaneous adrenaline. After the initial dose of antivenom, the indication for repeated dosage is failure of restoration of blood coagulability after 6 h, or progression of other signs of envenoming. Assisted ventilation, renal dialysis, and cardiovascular support may be required. Necrotic tissue requires surgical debridement. Signs of compartment syndrome may be misleading and fasciotomy is almost never justified. Venomous fish Many fish of temperate and tropical seas can inflict dangerous stings—stingrays, catfish, weevers, scorpionfish, stonefish, and lionfish. Prevention is by wearing foot protection when wading and avoiding contact with tropical reef fish. Immediate agonizing pain is alleviated by immersing the stung limb in uncomfortably hot but not scalding water (less than 45°C). Erythematous swelling and necrosis may develop with the risk of infection by marine bacteria. Stingray spines can cause fatal penetrating injuries. Systemic envenoming is uncommon. Stonefish antivenom is available. Poisonous aquatic animals Ciguatera poisoning from eating tropical reef fish is prevalent in Pacific and Caribbean regions. Fish acquire polyether toxins from dinoflagellates. Acute gastroenteritis develops 1–6 h after ingestion, followed by neurotoxic and cardiovascular disturbances, notably persistent paraesthesiae and myalgias. Tetrodotoxin poisoning is attributable to the Japanese delicacy ‘fugu’ (puffer fish). Neurotoxic symptoms caused by this sodium channel blocker develop 10–45 min after ingestion. Fatal respiratory paralysis may ensue 2–6 h later. Scombroid poisoning results when bacterial decompos- ition of tuna and other dark-fleshed fish generates histamine. Anaphylactic-type symptoms develop within minutes to a few hours after ingestion. Paralytic shellfish poisoning is caused by eating bivalve molluscs contaminated with tetrahydropurine neurotoxins from dinofla- gellates whose mass blooming manifests as ‘red tide’. Neurotoxic symptoms appear within 30 min of ingestion, progressing to fatal respiratory paralysis within 12 h. Prevention is by not eating scaleless (tetrodotoxic) fish at any time, very large (ciguatera-toxic) reef fish, and shellfish when there is a red tide. Correct processing prevents scrombroid poisoning. Cooking does not destroy any of these toxins. Venomous marine invertebrates Cnidarians (jellyfish, stinging corals, sea anemones, and so on) have tentacles studded with stinging nematocysts. Lethal species are Indo-Australian box jellyfish, Irukandji, Portuguese man-o’- war (Physalia), and Chinese Stomolophus nomurai. Prevention is by observing warning notices on affected beaches, bathing in ‘stinger- resistant’ enclosures, or wearing protective clothing. Stings produce immediately painful irritant weals. Box jellyfish cause the most se- vere systemic symptoms: respiratory and cardiac arrest, generalized convulsions, and pulmonary oedema within minutes of the acci- dent. ‘Irukandji’ syndrome is distinctive: severe persisting musculo- skeletal pain, anxiety, trembling, headache, piloerection, sweating, tachycardia, hypertension, and pulmonary oedema starting about 30 min after stings by tiny cubomedusoids. Vinegar inactivates box jellyfish and Irukandji nematocysts. Hot water relieves the pain of Physalia and box jellyfish stings. Box jellyfish antivenom is available in Australia.

10.4.2 Injuries, envenoming, poisoning, and allergic reactions caused by animals 1779 Echinoderm (starfish and sea urchin) spines become embedded in waders' feet, sometimes penetrating bones and joints. Pain is re- lieved by hot water. Systemic envenoming is rare but there is a risk of marine bacterial infection. Molluscs—cone shells and small Australasian blue-ringed octo- puses can cause fatal envenoming. Venomous arthropods Hymenoptera—stings by bees (Apidae); wasps, yellow jackets, and hornet (Vespidae), and ants commonly cause allergic reactions, while rare mass attacks (e.g. by Africanized 'killer' bees) can result in fatal direct envenoming. People in whom systemic anaphylaxis has been provoked by a hymenopteran sting should always carry—and be competent to use—self-injectable adrenaline (epinephrine). Desensitization with purified venom should be considered if type I hypersensitivity is con- firmed by detecting venom-specific IgE. Massive envenoming by Apidae or Vespidae causes histamine toxicity, generalized rhabdo- myolysis, intravascular haemolysis, hypertension, pulmonary oe- dema, myocardial damage, bleeding, hepatic dysfunction, and acute kidney injury. Lepidoptera—stinging hairs of many species of moths and their caterpillars can excite cutaneous irritation and allergy, sometimes causing epidemics. In South America, caterpillars of atlas moths (Lonomia) cause many stings. Their venom contains antihaemostatic toxins causing spontaneous bleeding, polyarthralgia, and acute kidney injury. An antivenom is available in Brazil. Coleoptera—contact with 'Spanish fly' and 'Nairobi eye' beetles causes blistering. Scorpions—stings still cause numerous fatalities in North and South Africa, the Middle East, Mexico, Latin America, and India. Prevention is by excluding scorpions from homes. Severe local pain is the commonest symptom. Systemic symptoms vary ac- cording to the species of scorpion involved. 'Autonomic storm' is caused by massive release of acetylcholine and catecholamines by ion channel toxins. Cardiorespiratory effects include hyperten- sion, shock, tachy-, and bradyarrhythmias, electrocardiographic changes, and pulmonary oedema. Neurotoxic effects include er- ratic eye movements, fasciculation, and muscle spasms (pseudo- convulsions) causing respiratory distress. Pain is best controlled by digital block with local anaesthetic. Antivenom is available in some countries, but pharmacological treatment with prazosin and other vasodilators is preferred elsewhere. Spiders—bites are common in the Americas, Mediterranean, South Africa, and Australia but there are few fatalities. Only recluse spiders (Loxosceles) are reliably associated with necrotic araneism (arachnidism), but many innocent peridomestic species have been vilified. Local pain and swelling develop slowly, followed by the classic 'red-white-and- blue sign' and eventually an eschar, which sloughs leaving a necrotic ulcer. Systemic symptoms, including fever, rash, haemolysis, and acute kidney injury, are unusual. Bites by cosmopol- itan black and brown widow spiders, Latin American banana spiders, and Sydney funnel web spiders and their relatives, cause neurotoxic araneism. Immediate pain is followed by sweating with gooseflesh at the site of the bite. Systemic symptoms quickly evolve: headache, nausea, vomiting, profuse generalized sweating, fever, priapism, and painful muscle spasms, tremors, and rigidity that may cause respiratory distress or simulate an acute abdomen. Antivenoms widely used for Loxosceles and neurotoxic bites are of uncertain effectiveness. Ticks—mainly in North America and Australia, both ixodid (hard) and argasid (soft) ticks can inject a salivary neurotoxin during their blood meal, causing an ascending flaccid paralysis. The tick must be detached as soon as possible. Centipedes-cause painful stings in tropical countries, while toxic secretions of millipedes may be applied to skin, lips, and eyes by chil- dren who are handling or trying to eat them. Leeches Leeches have anticoagulant saliva. Land leeches infest rainforests and can invade clothing while aquatic leeches are swallowed in fresh water or they may penetrate body orifices of swimmers. Prevention is by applying repellents to skin, clothes, and footwear, by boiling or filtering drinking water and by avoiding affected waters. Clinical effects are local pain, itching, blood loss, secondary

infection, and phobia. Ingested aquatic leeches may obstruct pharynx, bronchi, or oesophagus. Use of medicinal leeches may be complicated by Aeromonas hydrophila infection. Mechanical injuries caused by animals Epidemiology Many species of wild animals have mauled and killed humans. Attacks by wild mammals are increasingly reported. Tigers, lions, leopards, and other big cats, hyenas, domestic dogs, jackals, wolves, bears, elephants, rhinos, hippopotamuses, buffaloes, bison, moose, elk, other large deer and antelopes, wild pigs, tapirs, chimpan- zees, baboons, ostriches, and cassowaries have killed people. The big cats, wolves, bears, elephants, hippopotamuses, and buffaloes are the most dangerous. Since 2000, about 60–80 confirmed un- provoked attacks by sharks with an average of 4.3 fatalities (case fatality c.8%) have been reported each year. Other fish, such as barracudas, moray, and conger eels, garfish, groupers, stingrays, and piranhas can inflict lethal injuries. Electric ‘eels’ Electrophorus electricus (Gymnotidae) (Fig. 10.4.2.1) of rivers and coastal waters in Florida and South American and marine torpedo rays (e.g. Torpedo spp., Torpediniformes) can impart stunning electric shocks but are unlikely to be lethal. Even the 5-cm Amazonian catfish (genus Vandellia, Trichomycteridae; Spanish ‘canero’; Portuguese ‘candirú’), the only vertebrate human ectoparasite, can traumatize humans by burrowing into their urethra, vagina, or anus, causing pain, bleeding, and obstruction. Crocodilians (alliga- tors, caimans, and crocodiles) kill, eat, and scavenge dead humans in Africa, Asia, and Oceania. In the United States of America, es- pecially Florida, alligators Alligator mississippiensis are responsible for a few deaths but in Africa, Nile crocodiles Crocodilus niloti- cus kill about 1000 people each year, and in South Asia, northern Australia, and New Guinea the saltwater crocodile C. porosus kills hundreds each year. Giant pythons very rarely kill humans in Africa (Python sebae), India (Python molurus), Indonesia (Python reticula- tus), Australia (Morelia amethistina), and South America (Eunectes murinus). Occasional human deaths have been attribute to attacks by Komodo dragons (Varanus komodoensis). To put these incidents into perspective, in the United States, collisions between vehicles

 and deer and injuries to horseback riders are much more common than attacks by wild animals. Bites by domestic dogs are common worldwide. In England and Wales, where the estimated dog population is 6 million, more than 200 000 bite victims attend hospital each year. In the United States, dogs are responsible for 80–90% of all animal bites. They bite about 4.7 million people each year (1.8% of the population), 800 000 of whom (0.3% of the population) require medical attention, and 12 are killed. Children are especially vulnerable. Other domestic animals that have caused severe injuries or deaths include camels, cattle, water buffalo, sheep, pigs, cats, and even ferrets. Prevention It is essential to obtain local advice about these environmental haz- ards. Where dangerous wild animals abound, wandering alone and unprotected between dusk and dawn incurs the highest risk of attacks. Staying in a vehicle and travelling in groups reduces risk. Pet dogs may attract large predators. In bear country, hikers should travel in groups, making plenty of noise. Bears should never be ap- proached (e.g. for photography), especially if there are cubs. Faced by a charging bear, avoid eye contact and do not attempt to hide, run away, or climb a tree. At a distance of 30 feet (c.10 m), a bear may be repelled by discharging a commercial pepper spray (10% capsicum oleoresin) towards its eyes. If attacked by a dog, avoid eye contact, shout, and fight back with sticks and stones. Young children should not be left alone with dogs, even family pets, and notoriously dangerous breeds should be banned. Elephants are dan- gerous whether wild or tamed. They should be treated with extreme respect or avoided, especially if they are in ‘musth’. Swimming or canoeing in hippo-infested waters or blocking their retreat to water is highly

dangerous. To prevent crocodilian attacks, keep well away from the water’s edge, do not bathe between dusk and dawn, and avoid canoeing in croc-infested waters. If attacked by a crocodilian on land, run; in the water, fight back, hitting the animal on its nose and eyes with any available weapon. To avoid shark attacks, never bathe in shark-infested waters, between sand bars and the deep ocean, where dead fish have been dumped, flocks of sea birds are feeding, or sewage is discharged. If attacked by a shark, fight back, hitting it on the nose and clawing at its eyes and gills. Chemical and electrical-field repellents and chain mail suits have been developed to protect divers. Clinical features Teeth, tusks, horns, claws, and spines gouge, tear, crush, avulse, and puncture soft tissues and break bones. Big cats, bears, pigs, pythons, crocodilians, and sharks will eat their victims. Bovines and elephants trample and kneel on the prostrate body. Body cavities may be punctured, resulting in pneumothorax, haemothorax, her- niation and strangulation of bowel, and rupture of liver and spleen. Horse and camel bites and kicks can fracture, dislocate, crush, and concuss. Wild and feral pigs, armed with lethal tusks, can inflict abdominal evisceration, pneumothorax and fractures and lacer- ations of tendons, arteries, and nerves. Giant pythons asphyxiate by constriction. Sharks amputate whole limbs, causing rapidly fatal haemorrhage. Garfish (needle fish) and sting rays can fatally im- pale. Infection is likely with all these traumas: rabies, tetanus, gas gangrene, cat scratch disease (Bartonella henselae), Pasteurella multocida, Capnocytophaga canimorsus, leptospires, Spirillum minus, Streptobacillus moniliformis, and aquatic organisms such as Vibrio vulnificus and Aeromonas hydrophila (see Section 8, Infectious diseases). Treatment Since wild animal attacks are most likely to happen in areas remote from medical care, delayed hospital treatment makes first aid espe- cially crucial for the survival of the victim. Fig. 10.4.2.1 Electric ‘eel’ Electrophorus electricus (Gymnotidae).

10.4.2 Injuries, envenoming, poisoning, and allergic reactions caused by animals 1781 First aid of severe injuries First, the patient and rescuers must be made safe from further danger and drowning. Bleeding is controlled by local pressure or tourniquets, perforating injuries are closed with pressure dress- ings, circulating volume repletion is started as soon as possible with intravenous fluids, and the casualty is evacuated promptly to hos- pital. Some regions have flying doctor services (e.g. AMREF in East Africa). All injuries inflicted by animals must be assumed to be in- fected by a range of organisms (see earlier paragraphs) and so it may be appropriate to start antibiotic treatment immediately. Medical treatment in the hospital Emergency surgery may be required. Blood loss should be replaced and attention given to local mechanical complications such as frac- tures, tension pneumothorax, damage to large blood vessels, per- foration of the bowel, and lacerations of other abdominal viscera. Thorough debridement or amputation of dead tissue may be re- quired with removal of foreign material, teeth, and so on, and irriga- tion and drainage. Except for wounds on the head and neck, which can be sutured immediately, primary suturing should be delayed for 48–72 h, after which further debridement, suturing, or covering with split-skin grafts should be considered. Wounds should be thoroughly cleaned with soap and water as soon as possible; suitable antiseptics include iodine and alcohol so- lutions. Prophylactic antimicrobials such as amoxicillin/clavulanic acid, doxycycline, or erythromycin have proved effective in dog- and cat-bite wounds and are indicated for multiple or severe wounds and bites on the face and hands. For other bites, use penicillin, an aminoglycoside and metronidazole and for marine or aquatic wounds, to cover unusual bacteria such as Vibrio and Aeromonas spp., doxycycline or co-trimoxazole or, in severe cases, a combin- ation of tetracycline with an aminoglycoside (e.g. gentamicin) and cefotaxime, or tetracycline with aminoglycoside and a fluoroquino- lone. Specific infections, such as tetanus, rabies, and Herpes simiae virus (from

monkey bites) must be considered and treated or pre- vented appropriately. Venomous animals For predation or defence, some animals inject venoms through fangs, chelicerae (venom jaws), stings, spines, hairs, nematocysts, and other specialized venom organs. ‘Spitting’ snakes, scorpions, and millipedes squirt venom on to absorbent mucous mem- branes. The flesh or skin of some animals contains poisons acquired through the food chain. Allergic reactions to injected venoms (e.g. of Hymenoptera and cnidarians) may cause more frequent and serious medical problems than their direct toxic effects. Venomous mammals Male duck-billed platypuses (Ornithorhynchus anatinus) have erectile venomous spurs on their hind limbs. These aquatic, egg- laying mammals of eastern Australia sting at least one person each year in Victoria, but only 17 cases have been reported since 1817. There is immediate, agonizing, persistent local pain, as well as pro- longed local swelling, chronic pain on movement, hyperaesthesia, wasting, inflammation, and regional lymphadenopathy. These ef- fects are not life-threatening in humans, but dogs have died of envenoming. In the absence of specific treatment, nonsteroidal anti-inflammatory agents (NSAIDs) or corticosteroids have proved effective. The venom contains a C-type natriuretic peptide (which causes mast-cell degranulation), nerve growth factor, several α- and β-defensin-like peptides, enzymes, and other peptides and proteins, including a sildenafil-like phosphodiesterase-5 inhibitor. Male ech- idnas, the other egg-laying mammal, possess a similar but smaller venom apparatus. Several species of Insectivora produce venomous saliva con- ducted into bite wounds by curved and sometimes grooved lower incisors. Venomous species include the Hispaniolan and Cuban so- lenodons (Solenodon paradoxus, S. (Apotogale) cubanus), northern water shrew Neomys fodiens, southern water shrew N. anomalus, and North American short-tailed shrew Blarina brevicauda. Their bites can kill rodents and lagomorphs, but in humans the effect is local pain, swelling, and inflammation. The saliva of vampire bats (Desmodontinae) contains permeability- increasing factors, a platelet inhibitor, draculin (an inhibitor of acti- vated factors X and IX), and a plasminogen activator which is being developed as a thrombolytic drug. The slow loris Nycticebus coucang (Primates; Lorisidae) possesses brachial glands whose secretion contains toxic protein very similar in structure to Fel d 1 cat allergen, which the lorises lick up and can inject when they bite. In humans, slow loris bites may be damaging, infective, or toxic, causing pain, swelling, and even anaphylaxis. Venomous snakes Fewer than 200 species of venomous snake (families Colubridae, Atractaspidinae, Elapidae, and Viperidae) have been responsible for severely envenoming humans, resulting in death or permanent disability. Since it may be difficult to distinguish venomous from nonvenomous species, unnecessary contact with all snakes should be avoided, and patients bitten by any species should be assessed carefully. Distribution The Antarctic; most islands of the western Mediterranean, Atlantic, Caribbean, and eastern Pacific (including Hawaii); Chile, Iceland, Ireland, Madagascar, New Caledonia, and New Zealand are free from venomous snakes. Elsewhere, venomous snakes are widely distributed up to altitudes of more than 4900 m in the Himalayas (Gloydius himalayanus), within the Arctic Circle (Vipera berus), in the Indian and Pacific oceans as far north as Siberia (Pelamis pla- tura/Hydrophis platurus), and in some freshwater lakes (Hydrophis semperi). Classification Medically important species have one or more pairs of enlarged teeth (fangs) in their upper jaws, containing a groove or closed channel through which they inject venom into their prey.

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1782 Colubridae The short, immobile fangs are at the back of the maxilla (Fig. 10.4.2.2). Most of the familiar snakes regarded as non- venomous (e.g. the British grass snake Natrix natrix helvetica and the smooth snake Coronella austriaca), belong to this large family. However, many colubrid species have

proved capable of causing at least local envenoming and some have caused severe envenoming or death, such as three African species—the boomslang Dispholidus typus and the vine, twig, bird, or tree snake or Voëlslang (Thelotornis kirtlandii and T. capensis); the Japanese yamakagashi Rhabdophis tigrinus; and the Southeast Asian red-necked keel- back R. subminiatus. (Fig. 10.4.2.2). Atractaspidinae (family Lamprophiidae) The African and Middle Eastern burrowing asps, stiletto snakes, or burrowing or mole vipers or adders strike sideways, impaling their victims on one of their two long front fangs, protruding through the partially closed mouth (Fig. 10.4.2.3). Four species, Atractaspis microlepidota, A. engaddensis, A. corpulenta and A. irregularis, have proved capable of killing humans. Elapidae This family includes cobras (Fig. 10.4.2.4), kraits, mambas, shield- nose snakes, coral snakes (Fig. 10.4.2.5), garter snakes, all the venomous Australasian snakes (Fig. 10.4.2.6), and sea snakes (Fig. 10.4.2.7). The short front fangs are immobile (10.4.2.4a and Fig. 10.4.2.7). Several African and Asian species (rinkhals and spitting cobras) can eject venom from the tips of their fangs (Fig. 10.4.2.3) as a fine spray for a distance of a few metres into the eyes of a perceived aggressor. Viperidae The front fangs are long, curved, and capable of a wide range of movement (Fig. 10.4.2.8). The subfamily Crotalinae comprises the American rattlesnakes (Fig. 10.4.2.9), moccasins, lance-headed vi- pers, and Asian pit vipers, which possess a heat-sensitive pit organ behind the nostril (Fig. 10.4.2.10). The Old World vipers and adders (subfamily Viperinae) lack this pit organ. Incidence of snakebite and medically important species Snakebite is a frequent medical emergency in rural areas of many tropical countries; its incidence is seriously underestimated by hospital returns, because many victims seek the help of trad- itional healers rather than western-style doctors. In Kilifi District, Kenya, where snakebites cause 6.7 deaths per 100 000 per year (0.7% of all deaths), 68% of the victims had sought treatment from (a) (b) Fig. 10.4.2.2 Back-fanged Colubroid snakes. (a) Back fangs of red-necked keelback (Rhabdophis subminiatus), a Southeast Asian colubrid snake (family Natricinae), capable of causing severe envenoming. (b) Baron’s green racer (Philodryas baroni), a South American colubrid snake (family Dispsadidae), capable of causing mild local envenoming. Copyright D. A. Warrell. Fig. 10.4.2.3 Slender burrowing asp Atractaspis aterrima, Nigeria, showing fang. Copyright D. A. Warrell.

 (a) (b) (c) Fig. 10.4.2.4 Common Indian cobra Naja naja: (a) short front fang, (b) and (c) showing defensive posture with open hood with ‘spectacle’ marking (specimen in Sri Lanka). Copyright D. A. Warrell. Fig. 10.4.2.5 Painted coral snake Micrurus corallinus, Brazil. Copyright D. A. Warrell. Fig. 10.4.2.6 Papua New Guinean taipan Oxyuranus scutellatus showing the distinctive dorsal red stripe. Copyright D. A. Warrell.

 traditional healers. In Africa, the saw-scaled or carpet viper Echis spp., puff adder Bitis arietans, and spitting cobras (Naja nigricollis, N. mossambica, and so on) are the species of greatest medical im- portance. In the Benue Valley of north-east Nigeria, E. ocellatus (Fig. 10.4.2.11) causes 500 bites per 100 000 population per year, with a 12% mortality. Vipers of the genus Echis, whose geo- graphical range extends through Africa north of the equator, the Middle East, and eastern Asia to India, are responsible for many bites and deaths. In India, the most important species are cobras Naja naja, N. kaouthia (Fig. 10.4.2.4), common krait Bungarus caeruleus, Russell’s viper Daboia russelii (Fig. 10.4.2.8), and the saw-scaled viper E. carinatus. A well-designed, nationwide study in India established that 46 000 people were killed by snakes in

2005. In children aged 5–14 years, snakebites caused 3% of all deaths. Among fatalities, 97% died in rural areas, only 23% of them in hospitals. In Bangladesh, a community-based study es- timated 600 000 bites and 6000 deaths each year. In Southeast Asia, the Malayan pit viper Calloselasma rhodostoma, D. siamen- sis, green pit vipers (e.g. Trimeresurus T. albolabris), and cobras N. kaouthia and N. siamensis cause most bites and deaths. In Myanmar, Russell's viper bite is a common cause of acute kidney injury and is responsible for most of the estimated 1000 snakebite deaths each year. In the United States of America, there are about 7000–8000 bites each year with about five deaths. Rattlesnakes, especially Crotalus adamanteus, C. atrox, C. horridus, C. oreganus, C. scutulatus, C. viridis and Sistrurus miliaris, are the most dan- gerous species. In Mexico there are about 27 000 bites each year. In Central and South America, medically important species include rattlesnakes (e.g. Crotalus simus, C. durissus) (Fig. 10.4.2.9) and the lance-headed vipers Bothrops atrox ('barba amarilla'), B. asper ('terciopelo'), B. bilineatus ('papagaio') and B. jararaca ('jararaca'). There are an estimated 4000 bites each year in Central America, fewer than 100 in the Caribbean, and 45 000 in South America. In the Amami and Ryukyu islands of Japan, the habu, Protobothrops flavoviridis, inflicted an average of 610 bites with 5.6 deaths per year during the 1960s. In the United Kingdom, the adder or viper Vipera berus is the only venomous species (Fig. 10.4.2.12). More than 100 people are bitten each year, but only 14 deaths have been reported since 1876, the last in 1975. Scandinavia has hundreds of adder bites each year, but very few deaths. V. aspis
causes most bites in France, while V. ammodytes is important in Eastern Europe. In Australia, there are about 1000 bites (4.76/100 000 popula- tion) and 2–5 deaths (0.1–0.2/100 000) per year. Recently, almost all fatalities have been attributed to brown snakes Pseudonaja spp. Other important species are tiger snakes (Notechis scuta- tus, and so on), taipan Oxyuranus scutellatus (Fig. 10.4.2.6), and death adders Acanthophis spp. There are several 100 deaths each year in New Guinea, mostly caused by taipans. The highest snakebite mortalities, up to 24% of all adult deaths, are recorded among hunter–gatherer tribes of Brazil (Kashinawa), Venezuela (Yanomamo), Ecuador (Waorani), Tanzania (Hadza), and Papua New Guinea. Epidemiology Most snakebites are inflicted on the lower limbs of farmers, plan- tation workers, herdsmen, and hunters in rural areas of tropical developing countries. The snake is usually trodden on at night or in undergrowth. Some species such as the Asian kraits Bungarus spp. and African spitting cobras N. nigricollis enter human dwell- ings at night in search of their natural prey and may bite people who roll over on to them while sleeping on the floor or in response to human odour or warmth. Snakes strike if inadvertently trodden upon or touched. In Europe, North America, and Australia, exotic venomous snakes are increasingly popular pets: their owners are sometimes bitten on their hands, especially when inebriated. In 120 9 8 7 6 5 4 3 2 1 0 110 100 90 80 70 60 50 40 30 20 10 0 Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec Average rainfall Study deaths (n = 562) Month Snakebite deaths in the study Average rainfall (in mm) Fig. 10.4.2.7 Monthly snakebite deaths in randomly selected study areas of India in 2005 (solid line) and average rainfall (dashed line), showing peak mortality during the monsoon. From Mohapatra B, et al. (2011). Snakebite mortality in India: a nationally representative mortality survey. PLoS Negl Trop Dis, 5(4), e1018.

1785 (a) (b) (c) Fig. 10.4.2.8 Eastern Russell's viper Daboia siamensis, Ban Mi, Thailand: (a) showing 'chain' pattern (scale in cm); (b) showing long, hinged front fangs (reserve fang on the left side) in dental sheath; (c) dissection of venom apparatus. Copyright D. A. Warrell. Fig. 10.4.2.9 South American tropical rattlesnake or cascabel Crotalus durissus cascavella. Specimen from Brazil. Copyright D. A. Warrell. Fig. 10.4.2.10 Southeast Asian white-lipped green pit viper

Trimeresurus (Trimeresurus) albolabris showing heat-sensitive pit organ between eye and nostril. Copyright D. A. Warrell.

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1786 the United States, 25% of bites result from snakes being attacked or handled. Serious bites by back-fanged (colubrid) snakes usu- ally occur under these circumstances. Seasonal peaks in the inci- dence of snakebite are associated with agricultural activities, such as ploughing before the annual rains in the West African Sahel and the rice harvest in Southeast Asia. In India, most snakebite deaths occur during the May to October monsoon season (Fig. 10.4.2.7). Other factors are fluctuations in the activity or population density of venomous snakes, severe flooding that concentrates the human and snake populations in decreasing areas of dry land (e.g. Bangladesh, Pakistan, India, Nepal, Myanmar, Vietnam, and Colombia) and clearing of primary forests during construction of new highways and irrigation and hydroelectric schemes (e.g. Brazil, Sri Lanka). Snakebite or injection of snake venom has been employed for sui- cide and homicide. Venom apparatus Venom glands of Elapidae and Viperidae are situated behind the eye, surrounded by compressor muscles (Fig. 10.4.2.8c). A venom duct leads to the base of the fang in which venom is conducted along a groove or through a closed canal. In Colubridae, or more broadly, Colubroid snakes, venom secreted by Duvernoy’s gland tracks down grooves in the anterior surfaces of fangs at the posterior end of the maxilla (Fig. 10.4.2.2). The average dry weight of venom injected at a strike is approximately for N. naja 60 mg, E. carinatus 13 mg, D. russelii 63 mg, and Daboia palaestinae 32 mg. The amount in- jected when a snakebites a human is highly variable. In a proportion of bites there is negligible envenoming (‘dry bites’): more than 50% of those bitten by Malayan pit vipers C. rhodostoma or Russell’s vi- pers; less than 10% bitten by Echis spp.; but more than 75% bitten by common brown snakes (Pseudonaja spp.) in Australia. The Palestine viper Daboia palaestinae expends only about one-tenth of the cap- acity of its venom gland at each consecutive strike, whereas Daboia siamensis exhausts more than three-quarters of its reservoir at the first strike. The popular belief that snakes are less dangerous after they have eaten is incorrect. Prevention of snakebite To reduce the risk of bites, snakes should never be disturbed, attacked, cornered, or handled, even if they are thought to be a harmless species or appear to be dead. Venomous species should never be kept as pets or as performing animals. In snake-infested areas, boots, socks, and long trousers should be worn for walks in undergrowth or deep sand, and gloves for exploring foliage. A light should always be carried at night together with a stick for prodding (a) (b) (c) Fig. 10.4.2.11 Saw-scaled or carpet vipers-genus Echis. (a) Echis ocellatus from West Africa. (Specimen from Nigeria). (b) Echis pyramidum from East Africa (specimen from Kenya). (c) Echis carinatus sochureki from the Middle East and South Asia (specimen from Oman). Copyright D. A. Warrell. Fig. 10.4.2.12 European adder or viper Vipera berus, the only venomous British snake (specimen from Wales). Copyright D. A. Warrell.

 the ground ahead. Lightweight boots that were resistant to Russell’s viper strikes were developed in Burma and proved acceptable to rice farmers for use during the high risk harvesting season. Collecting firewood; dislodging logs and boulders with bare hands; pushing sticks or fingers into burrows, holes, and crevices; climbing rocks and trees covered with dense foliage; and swimming in overgrown lakes and rivers are particularly hazardous activities. Unlit paths and gutters are especially dangerous after heavy rains. Sleeping on the ground carries a risk of nocturnal krait bites in South Asia and of spitting cobra bites in Africa, but well tucked-in mosquito nets are

protective. To prevent sea-snakebites, fishermen should not touch these animals when they are caught in nets or on lines. Swimmers and divers should not aggravate them and should avoid wading in the sea, especially in muddy estuaries, in sand, or near coral reefs. It is futile and ecologically undesirable to attempt to exterminate venomous snakes. Various substances toxic to snakes, such as in- secticides and methylbromide, have been used to keep human dwellings free of these animals. However, no effective yet harmless snake repellent has been discovered. Immunization against envenoming To be effective, high titres of a neutralizing antibody would have to be circulating at the time of the bite. This has been achieved in animals used for antivenom production but only by frequent im- munization, which would not be practicable even in the highest-risk human populations. An accelerated (anamnestic) secondary rise in antibody levels, stimulated by envenoming, would be too slow to pre- vent envenoming. An antirattlesnake vaccine for domestic dogs, of dubious efficacy, is marketed in the United States and pre-exposure immunization of farmers in Japan, against habu (Protobothrops flavoviridis) venom was ineffective. Properties of snake venoms More than 90% of the dry weight of venom consists of more than 100 different proteins: enzymes, nonenzymatic polypeptide toxins, and nontoxic proteins such as nerve growth factor. Enzymes consti- tute 80–90% of viperid and 25–70% of elapid venoms. They include digestive hydrolases, hyaluronidase, and activators or inactivators of physiological processes. Most venoms contain l-amino acid oxidase, phosphomono- and diesterases, 5′-nucleotidase, DNAase, NAD-nucleosidase, phospholipase A2, and peptidases. Elapid venoms also contain acetylcholine esterase, phospho- lipase B, and glycerophosphatase, while viperid venoms have metalloproteinases, endopeptidase, arginine ester hydrolase, kininogenase, as well as thrombin-like, factor X, and prothrombin- activating enzymes. Phospholipase A2 (lecithinase) is the most widespread and extensively studied of all venom enzymes. It damages mitochondria, red blood cells, leucocytes, platelets, per- ipheral nerve endings, skeletal muscle, vascular endothelium, and other membranes, produces presynaptic neurotoxic activity, opiate-like sedative effects, the autopharmacological release of histamine, and may be anticoagulant. The acetylcholinesterase found in most elapid venoms does not contribute to their neuro- toxicity. Hyaluronidase promotes the spread of venom through tissues. Proteolytic enzymes (metalloproteinases, endopeptidases, or hydrolases) are responsible for local changes in vascular permeability leading to oedema, blistering, and bruising, and to necrosis. Venom l-amino acid oxidases are homodimeric flavoenzymes that catalyse the oxidative deamination of an l- amino acid substrate to an α-keto acid, ammonia, and hydrogen peroxide. They are widely distributed in venoms of Viperidae and Elapidae. Their reported biological activities include induction of apoptosis, oedema, and haemolysis, antibacterial function, and platelet activation or inhibition. Polypeptide toxins (neurotoxins) Postsynaptic (α) neurotoxins such as α-bungarotoxin and cobrotoxin contain about 60–62 or 66–74 amino acids. They bind to acetyl- choline receptors at the motor endplate. Presynaptic (β) neuro- toxins, such as β-bungarotoxin, crotoxin, and taipoxin, contain about 120–140 amino acids and a phospholipase A subunit. These release acetylcholine at the nerve endings at neuromuscular junc- tions and then damage the endings, preventing further release of transmitter. Venom pharmacology The smaller neurotoxins of the Elapidae are rapidly absorbed into the bloodstream, whereas the larger phospholipase A2 presynaptic toxins and Viperidae toxins are taken up more slowly through the lymphatics. Venoms of the spitting cobras and rinkhals can be ab- sorbed through the intact cornea, causing systemic envenoming and even death in animals. Envenoming after ingestion of snake venom has not been reported in humans. Most venoms are concentrated and bound in the kidney, and some components are eliminated in the urine. Crotaline venoms are selectively bound in the lungs, con- centrated in the liver, and excreted in bile, while

polypeptide neuro- toxins, such as α-bungarotoxin, are tightly bound at neuromuscular junctions. Most venom components do not cross the intact blood– brain barrier and so central nervous system effects of venom toxins are controversial. Pathophysiology Swelling and bruising of the bitten limb result from increased vascular permeability induced by proteases, phospholipases, membrane-damaging metalloproteinases (haemorrhagins), and endogenous autacoids released by the venom, such as hista- mine, 5-hydroxytryptamine, and kinins. Venoms of some of the North American rattlesnakes and viperine species cause a gen- eralized increase in vascular permeability resulting in hypovol- aemia, haemoconcentration, hypoalbuminaemia, albuminuria, serous effusions, pulmonary oedema, and, in the case of Burmese D. siamensis, conjunctival and facial oedema (Fig. 10.4.2.13). Tissue necrosis near the site of the bite is caused by myotoxic and cytolytic factors: in some cases, ischaemia resulting from thrombosis, intracompartmental syndrome, or a tight tourni- quet may contribute. Causes of hypotension and shock include hypovolaemia, vasodilatation, and myocardial dysfunction. Some venoms release vasodilating autacoids such as histamine and ki- nins. Venom of the Brazilian jararaca B. jararaca was found to activate bradykinin and, through a bradykinin-potentiating pep- tide, to prolong its hypotensive effect by inactivating the peptidyl dipeptidase responsible both for destroying bradykinin and for converting angiotensin I to angiotensin II. This observation led

 1788 to the synthesis of angiotensin-converting enzyme (ACE) in- hibitors. Bradykinin-potentiating and ACE-inhibiting peptides have also been found in several other crotaline venoms (genera Bothrops and Agkistrodon). Four sarafotoxins have been isolated from the venom of the Israeli burrowing asp Atractaspis engad- densis (Fig. 10.4.2.3). They show 60% sequence homology with the endothelins, which are also 21-amino acid polypeptides. Sarafotoxins and endothelins are potent vasoconstrictors of cor- onary and other arteries, delay atrioventricular conduction, and are positively inotropic. Snake venoms can cause haemostatic defects in several different ways. Venom procoagulant enzymes, many of them serine pro- teases, activate the blood clotting cascade at various sites. Some Viperidae venoms contain thrombin-like fibrinogenases, which remove fibrinopeptides from fibrinogen directly. Others acti- vate endogenous plasminogen. Venoms may induce or inhibit platelet aggregation. Spontaneous systemic bleeding is caused by haemorrhagins, metalloendopeptidases, some with disintegrin- like and other domains, which damage vascular endothelium (Fig. 10.4.2.14). The combination of consumptive coagulopathy, thrombocytopenia, and vessel wall damage can result in mas- sively incontinent bleeding, a common cause of death after bites by Viperidae, Australasian Elapidae, and the few medically important Colubridae. Many venoms are haemolytic in vitro, but clinically significant intravascular haemolysis, apart from the microangiopathic haemolysis associated with disseminated intravascular coagulation described in victims of viperine and Australian brown snake Pseudonaja bites, is seen only after bites by D. russelii (Sri Lanka and India), and some Bothrops and colu- brid species. Acute renal tubular necrosis may be caused by severe hypotension, disseminated intravascular coagulation (D. russelii, D. siamensis), a direct nephrotoxic effect of the venom (D. siamen- sis), and myoglobinuria secondary to generalized rhabdomyolysis (sea snakes, D. russelii in Sri Lanka and India, and tropical rattle- snakes). Neurotoxic polypeptides and phospholipases block neuromuscular transmission causing death through bulbar or re- spiratory paralysis. Clinical features Fear, effects of treatment, and the venom contribute to the symp- toms and signs of snakebite. Even patients who are not envenomed may feel flushed, dizzy, and breathless, and may notice constriction of the chest, palpitations, sweating, and acroparaesthesiae. Tight tourniquets may produce swollen and

ischaemic limbs; local inci- sions at the site of the bite may cause bleeding and sensory loss and herbal medicines often induce vomiting. The earliest symptoms dir- ectly attributable to the bite are local pain and bleeding from the fang punctures, followed by pain, tenderness, swelling, and bruising extending up the limb, lymphangitis, and tender enlargement of re- gional lymph nodes. An anaphylaxis-like syndrome of early syncope, vomiting, colic, diarrhoea, angio-oedema, and wheezing may follow bites by European Vipera, Russell's vipers, Bothrops spp., Australian elapids, and Atractaspis engaddensis. Nausea and vomiting are common early symptom of systemic envenoming. Bites by Colubridae (back-fanged snakes) Severe envenoming causes repeated vomiting, colicky abdom- inal pain, headache, systemic bleeding with widespread ecchym- oses and the risk of intracerebral haemorrhage, incoagulable blood, intravascular haemolysis, and acute kidney injury. Local swelling and bruising may be the only results of envenoming. The first symptoms of envenoming may be delayed for 24–72 h after the bite. Bites by Atractaspidinae (burrowing asps or stiletto snakes) Local effects include pain, swelling, blistering, necrosis, and tender enlargement of local lymph nodes. Violent gastrointestinal symp- toms (nausea, vomiting, and diarrhoea), anaphylaxis (dyspnoea, respiratory failure), and electrocardiographic (ECG) changes (atrioventricular block, ST, T-wave changes) have been described in patients envenomed by A. engaddensis and A. microlepidota andersoni. Bites by Elapidae (cobras, kraits, mambas, African garter snakes, coral snakes, Australasian snakes, and sea snakes) Bites by kraits, mambas, coral snakes, and some cobras (e.g. N. haje, N. nivea, and N. philippinensis) produce minimal local effects, but the venoms of African spitting cobras (N. nigri- collis, N. mossambica, and so on) and Asian cobras (N. naja, N. kaouthia, N. sumatrana, and so on) cause tender local swelling,
Fig. 10.4.2.14 Haemorrhagin activity revealed clinically as gingival haemorrhage in a patient bitten by a saw-scaled or carpet viper Echis ocellatus in Nigeria. Copyright D. A. Warrell. Fig. 10.4.2.13 Gross bilateral conjunctival oedema (chemosis) in a Burmese rice farmer 48 h after being bitten by a Russell's viper (Daboia siamensis). Copyright D. A. Warrell.

 blistering, and superficial necrosis, which may be extensive (Fig. 10.4.2.15). 'Skip' lesions, separated by apparently normal areas of skin, may occur (Fig. 10.4.2.16). However, elapid venoms are best known for their neurotoxic effects. Early symptoms, be- fore there are objective neurological signs, include vomiting, 'heaviness' of the eyelids, blurred vision, paraesthesiae around the mouth, hyperacusis, headache, dizziness, vertigo, hypersalivation, congested conjunctivae, and 'gooseflesh'. Paralysis is first detect- able as ptosis and external ophthalmoplegia appearing as early as 15 min after the bite, but sometimes it is delayed for 10 h or even more than 24 h. Later the face, palate, jaws, tongue, vocal cords, neck muscles, and muscles of deglutition may become paralysed (Fig. 10.4.2.17). The pupils are dilated. Respiratory failure may be precipitated by airway obstruction at this stage, or later after paralysis of intercostal muscles and the diaphragm. Neurotoxic effects are completely reversible, either acutely in response to antivenom or anticholinesterases—for example, following bites by Asian cobras, some Latin American coral snakes Micrurus spp., and Australasian death adders Acanthophis spp.—or they may wear off spontaneously in 1 to 7 days. Excruciating pain and paraesthesiae radiating up the bitten limb have been described with bites by coral snakes (Micrurus tener and M. lemniscatus), explained by specific activation of acid-sensing ion channels by a venom toxin (MitTx). Severe, noncolicky, crescendo abdominal pain, attributable to the smooth muscle stimulating effects of an AVIT toxin, is often the most striking initial symptom in victims of krait bites (Bungarus caeruleus). Envenoming by terrestrial Australasian elapids produces four main groups of

symptoms: neurotoxicity (Fig. 10.4.2.18), haemo- static disturbances and, rarely, generalized rhabdomyolysis, and acute kidney injury. Painful regional lymph nodes are a useful sign of impending systemic envenoming, but local signs are usually mild, except after bites by the king brown or Mulga snake Pseudechis aus- tralis. Early symptoms include vomiting, headache, and syncopal attacks. Fig. 10.4.2.15 Extensive necrosis of skin and subcutaneous tissues in a Nigerian girl bitten nine days previously on the elbow by a black-necked or spitting cobra Naja nigricollis. Copyright D. A. Warrell. Fig. 10.4.2.16 Zimbabwean girl showing ‘skip lesions’ separated by areas of intact skin after envenoming by a Mozambique spitting cobra Naja mossambica. By courtesy of the late Revd Dr Robbie McCabe. Fig. 10.4.2.17 Neurotoxic envenoming. Ptosis, external ophthalmoplegia, and facial paralysis in a Sri Lankan patient envenomed by a common krait Bungarus caeruleus. Copyright D. A. Warrell.

 Patients ‘spat’ at by spitting elapids may develop venom ophthalmia. There is intense pain in the eye, blepharospasm, pal- pebral oedema, and leucorrhoea (Fig. 10.4.2.19a). Corneal ero- sions can be seen by slit-lamp or fluorescein examination in more than half of patients spat at by N. nigricollis. Rarely, venom is ab- sorbed into the anterior chamber causing hypopyon and anterior uveitis. Secondary infection of corneal abrasions may lead to per- manent blinding opacities or panophthalmitis (Fig. 10.4.2.19b). Bites by sea snakes and sea kraits Patients envenomed by sea snakes notice headache, a thick feeling of the tongue, thirst, sweating, and vomiting. Between 30 min and 3.5 h after the bite, there is generalized aching, stiffness, and ten- derness of the muscles. Trismus is common. Later there is gener- alized flaccid paralysis. Myoglobinuria appears 3–8 h after the bite. Myoglobin and potassium released from damaged skeletal muscles can cause acute kidney injury, while hyperkalaemia may precipi- tate cardiac arrest. Bites by Viperidae (vipers, adders, rattlesnakes, lance-headed vipers, moccasins, and pit vipers) Viper venoms usually produce more severe local effects than do those of other snakes. Swelling may become detectable within 15 min and usually by 2 hours, but is sometimes delayed for sev- eral hours. It spreads rapidly with bruising, sometimes involving the whole limb, adjacent trunk and, in children, the whole body (Fig. 10.4.2.25). There is associated pain and tenderness in regional lymph nodes, with bruising of overlying tissues and lymphangitic lines. Blistering, and necrosis may appear during the next few days (Fig. 10.4.2.20). Necrosis can be severe fol- lowing bites by some rattlesnakes, lance-headed vipers Bothrops spp., Asian pit vipers, and the large African Bitis species. When the envenomed tissue is contained in a tight fascial compartment such as the pulp space of digits or the anterior tibial compart- ment, ischaemia may result (Fig. 10.4.2.21). Absence of swelling 2 h after a viper bite suggests that there has been no envenoming. However, fatal envenoming by a few species can occur in the ab- sence of local signs (e.g. C. d. terrificus, C. scutulatus, and Burmese Russell’s viper). Haemostatic abnormalities are characteristic of envenoming by Viperidae. Persistent bleeding from fang punc- ture wounds, venepuncture, or injection sites, other new and par- tially healed wounds, and postpartum, indicates that the blood is incoagulable. Spontaneous systemic haemorrhage is most often detected in the gingival sulci. Epistaxis, haematemesis, cutaneous ecchymoses, haemoptysis, and subconjunctival, retroperitoneal, and intracranial haemorrhages (Fig. 10.4.2.22) are also seen. Patients envenomed by Burmese and Indian/SriLankan Russell’s vipers may suffer haemorrhagic infarction of the anterior pitu- itary, resulting in acute or chronic pituitary/adrenal insufficiency (Sheehan’s-like syndrome) (Fig. 10.4.2.23). Hypotension and shock are common in patients bitten by North American rattle- snakes (e.g. C. adamanteus, C. atrox, and C. scutulatus), Bothrops, Daboia, and Vipera species (e.g.

D. palaestinae and V. berus). The Fig. 10.4.2.18 Mozambique spitting cobra (Naja mossambica) in the act of ejecting venom from the tips of its fangs. Courtesy Dr David J. Williams. (a) (b) Fig. 10.4.2.19 Venom ophthalmia caused by the black-necked spitting cobra Naja nigricollis: (a) Acute venom ophthalmia showing intense painful inflammation and discharge. (b) Neglected cobra spit ophthalmia complicated by corneal erosion and pan ophthalmitis requiring enucleation to prevent sympathetic ophthalmia of the other eye. Copyright D. A. Warrell.

10.4.2 Injuries, envenoming, poisoning, and allergic reactions caused by animals 1791 central venous pressure is usually low and the pulse rate rapid, suggesting hypovolaemia resulting from extravasation of fluid into the bitten limb. Patients envenomed by Russell's vipers show evidence of generally increased vascular permeability. Direct myocardial involvement is suggested by an abnormal ECG or car- diac arrhythmia and reduced ejection fraction detected by echo-cardiography. Patients envenomed by some species of the genera Daboia, Vipera, Crotalus, Bothrops, and Australasian elapids may experience early transient and recurrent syncopal attacks, associ- ated with features of an autopharmacological or anaphylactic re- action, such as vomiting, sweating, colic, diarrhoea, shock, and angio-oedema. These symptoms may appear as early as 5 min or as late as many hours after the bite. Early collapse after bites by Australian brown snakes (Pseudonaja spp.) and tiger snakes (Notechis spp.) has been attributed to coronary and pulmonary thromboembolism but this seems unlikely. Acute kidney injury is a common mode of death in patients envenomed by Viperidae. Victims of Russell's viper may become oliguric within a few hours of the bite and complain of loin pain, suggesting renal ischaemia at a time when their plasma renin activity is high. Neurotoxicity, resembling that seen in patients bitten by Elapidae, is a feature of envenoming by a few species of Viperidae (e.g. C. d. terrificus, Gloydius spp., berg adder Bitis atropos and other small Bitis spe- cies, and Sri Lankan D. russelii) (Fig. 10.4.2.24). There is evidence of generalized rhabdomyolysis (Fig. 10.4.2.24), but progression to respiratory or generalized paralysis is unusual. Fig. 10.4.2.20 Swelling, blistering, and necrosis that required amputation in a Thai woman bitten on the hand four days earlier by a Malayan pit viper Calloselasma rhodostoma. There are widespread ecchymoses. Copyright D. A. Warrell. Fig. 10.4.2.21 Extensive necrosis of skin and muscle including the contents of the anterior tibial compartment in a patient bitten by a lancehead Bothrops marajoensis in Brazil 27 days earlier. Copyright D. A. Warrell. Fig. 10.4.2.22 CT scan showing intracranial haemorrhage in a child bitten by a common lancehead Bothrops atrox in Ecuador. The fluid level in the larger collection of blood indicates that the blood was incoagulable. Copyright D. A. Warrell. Fig. 10.4.2.23 Haemorrhagic infarction of the anterior pituitary in a Burmese patient who died after being bitten by a Russell's viper Daboia siamensis. By courtesy of Dr U Hla Mon, Yangon, Myanmar.

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1792 Envenoming by European vipers The common viper or adder V. berus (Fig. 10.4.2.12), the only venomous snake found in the United Kingdom, occurs in England, Wales, Scotland, and northern Europe, extending into the Arctic Circle and through Asia as far east as Sakhalin island and south to northern Korea. There are four other vipers that are widely distributed in mainland Europe: the nose-horned or sand viper V. ammodytes in the Balkans, Italy, Austria, and Romania; the asp viper V. aspis in France (south of Paris), Spain, Germany, Switzerland, and Italy; Lataste's viper V. latastei in Spain and Portugal, and Orsini's viper V. ursinii in southeastern France, central Italy, and Eastern Europe. The Montpellier snake Malpolon monspessulanus is a large back-fanged colubrid snake whose bite can cause transient mild local symptoms and rarely neurotoxicity. Clinical features of European

viper bite • Local envenoming: immediate sharp pain is followed by spreading pain, tenderness, and tender enlargement of regional lymph nodes within hours. Reddish lymphangitic lines and bruising appear, and the whole limb may become swollen and bruised within 24 h with involvement of the trunk and, in children, the whole body (Fig. 10.4.2.25). Intracompartmental syndromes and necrosis are rare. • Systemic envenoming: dramatic anaphylactic symptoms may appear between 5 min and many hours after the bite: nausea, retching, vomiting, abdominal colic, diarrhoea, incontinence of urine and faeces, sweating, fever, vasoconstriction, tachy- cardia, lightheadedness, shock with loss of consciousness, angio-oedema of the face, lips, gums, tongue, throat, and epi- glottis, urticaria, and bronchospasm. These symptoms may persist or fluctuate for as long as 48 h in the absence of treat- ment. Hypotension is a dangerous sign that usually develops within 2 h and may resolve spontaneously, persist, recur, or progress fatally. Clinical features of a bleeding diathesis are unusual, but bleeding from the gums and nose and into the lungs, gastrointestinal and genitourinary tracts, and serosal cavities and retroperitoneally can occur. The risk of bleeding is greatly increased by misguided treatment with heparin. Fatal haemothorax, massive haematemesis and melaena, haematuria, and intrauterine fetal death are rare tragedies. Acute kidney injury is not uncommon in children. Increased capillary per- meability is reflected by the local and sometimes generalized oedema, as well as the more focal angio-oedema that can lead to fatal occlusion of the upper airway, and pulmonary, and cere- bral oedema. Coma and seizures are attributable to hypoten- sion, cerebral oedema, hyponatraemia, hypoalbuminaemia, or hypoxaemia secondary to respiratory distress. Cardiac arrest, acute gastric dilatation, paralytic ileus, and acute pancreatitis are other reported complications. Classic mild neurotoxicity (ptosis, external ophthalmoplegia) has been reported after bites by several species of European Vipera, including V. aspis, V. berus, and V. ammodytes in certain geographical areas. • Laboratory findings: neutrophil leucocytosis is common. Serum creatine kinase (CK), transaminases, urea, and creatinine con- centrations may be raised, and bicarbonate may be reduced. Thrombocytopenia and mild coagulopathy; reflected by pro- longed prothrombin time, activated partial thromboplastin time, hypofibrinogenaemia, and raised fibrin degradation prod- ucts or D-dimer; is sometimes detected. Severe coagulopathy is uncommon. Electrocardiographic changes include tachy- and bradyarrhythmias, atrial fibrillation, flattening or inversion of T- waves, ST elevation or depression, second-degree heart block, and frank myocardial infarction. • Prognosis: most adder bites cause only trivial symptoms, but pa- tients must be assessed individually and deaths have occurred between 6 and 60 (average 34) h after the bite. Children may be severely envenomed: in a French series, there were three deaths in a group of seven children aged between 2.5 and 10 years. The dangers of adder bite should not be underestimated. The anti- venom treatment of adder bite is discussed in the following paragraphs. Laboratory investigations The peripheral neutrophil count may be raised to 20 000 cells/μl or more in severely envenomed patients. The blood film may show evidence of microangiopathic haemolysis. Initial Fig. 10.4.2.24 Brazilian girl bitten 24 h earlier by a tropical rattlesnake Crotalus durissus terrificus. She has bilateral ptosis, paralysis of the facial muscles, and gross myoglobinuria resulting from generalized rhabdomyolysis. Copyright D. A. Warrell. Fig. 10.4.2.25 Generalized swelling and bruising in a 4-year-old child bitten by a European adder Vipera berus in Sweden. Courtesy of Dr H Persson.

 haemocon- centration, resulting from extravasation of plasma (Crotalus species and Burmese D. siamensis), is followed by anaemia caused by bleeding or, more rarely, haemolysis. Thrombocytopenia is common following bites by pit vipers (e.g. Calloselasma rho- dostoma, Crotalus oreganus helleri)

and some Viperidae (e.g. Bitis arietans and Russell's vipers), but is unusual after bites by Echis species. 20-minute whole blood clotting test (20WBCT): this is a simple bedside test for venom-induced defibrinogenation or anticoagulation. A few millilitres of venous blood are placed in a new, clean, dry, glass vessel, left undisturbed for 20 min, and then tipped once to see if it has clotted or not. Positive 20WBCT (incoagulable blood) indicates systemic envenoming, either con- sumptive coagulopathy (plasma fibrinogen concentration below 0.5 g/litre) or effects of an anticogulant toxin (e.g. envenoming by Australian black snake, Pseudechis spp.). It may be diagnostic of a particular species (e.g. Echis spp. in Africa north of the equator). The only equipment required for the test is a new glass tube, but this may be difficult to find in modern hospitals where glass has been replaced by plastics. Glass is essential to contact-activate Hageman factor (factor XII) which initiates the 'intrinsic' coagulation pathway. Glass washed with soap or detergent may lose this property. A posi- tive 20WBCT had a positive predictive value of 89.7%, negative pre- dictive value of 93.5%, sensitivity of 92.9%, and specificity of 90.6% for plasma fibrinogen concentrations of less than 0.5 g/litre. Point of care INR coagulometers and D-dimer tests are not reliable in snake- envenomed patients. Laboratory tests of blood coagulation (prothrombin time, ac- tivated partial thromboplastin time, fibrinogen concentration) and fibrinolysis (fibrin/fibrinogen degradation products, D- dimer) are more sensitive but take much longer and are more demanding in equipment than the simple 20WBCT. Patients with generalized rhabdomyolysis show a steep rise in serum creatine kinase, myoglobin, and potassium levels. Black or brown urine suggests generalized rhabdomyolysis and/or intravascular haem- olysis; in both cases, positive urine sticks tests will not distinguish between blood, haemoglobin, and myoglobin. Concentrations of serum enzymes, such as CK and aspartate aminotransferase, are moderately raised in patients with severe local envenoming, due to muscle damage at the site of the bite. High concentra- tions (CK >2000 U/litre) suggest generalized rhabdomyolysis. Urine should be examined for blood/haemoglobin, myoglobin, and protein, and for microscopic haematuria and red cell casts. Electrocardiographic abnormalities such as sinus bradycardia, ST–T changes, various degrees of atrioventricular block, and hyperkalaemic changes may be seen. Immunodiagnosis Specific snake venom antigens have been detected in wound swabs, aspirates or biopsies, serum, urine, cerebrospinal fluid, and other body fluids. Venom antigenaemia can be quantitated using en- zyme immunoassay (EIA), providing the most accurate prognosis. Under ideal conditions, relatively high venom antigen concentra- tions (wound swabs or aspirates) may be detected quickly enough (15–30 min) to allow the selection of the appropriate monospe- cific antivenom. A commercial venom detection kit for Australian elapids is produced by Seqirus (formerly CSL), Melbourne. For retrospective diagnosis, including forensic cases, tissue around the fang punctures, wound and blister aspirate, serum, and urine should be stored for EIA immunodiagnosis. Polymerase chain re- action (PCR) to detect venom gland RNA or snake DNA in the bite wound are under development. Management of snakebite First aid The patient should be reassured and moved to the nearest hospital or dispensary as quickly, comfortably, and passively as possible. The whole patient should be immobilized, especially the bitten limb, using a splint or sling. Most traditional first aid methods are potentially harmful and should not be used. Local incisions and suction do not remove venom effectively and may introduce infection, damage tissues, and cause persistent bleeding. Vacuum extractors, potassium perman- ganate, and ice packs may potentiate local necrosis. Electric shocks are dangerous and have not been proved beneficial. Tourniquets and compression bands are potentially dangerous as they can cause gangrene, increased fibrinolysis, and bleeding in the occluded limb, peripheral nerve palsies, compartmental ischaemia, and intensifica- tion of local signs of envenoming. Pressure-immobilization (P-I) methods In animal studies, compressing

superficial veins and lymph- atics in the bitten limb delayed the spread of larger molecular weight toxins such as the presynaptic phospholipase A2 toxins of Australian elapid venoms. This delay might prevent development of life-threatening respiratory paralysis before the victim has had time to reach medical care. P-I is, therefore, indicated after bites by neurotoxic elapids but also, in cases of bites by unknown species, P-I should be applied immediately unless a bite by a neurotoxic elapid can, with confidence, be excluded. 1 Anker's (Monash) pressure-pad immobilization method (Fig. 10.4.2.26a). A pad of any available material, approximately 5 × 5 × 3 cm, is applied directly over the bite wound, at a pres- sure of about 70 mm Hg, and the limb is splinted. This delayed systemic envenoming, as assessed by measurements of venom antigenemia, in a preliminary field trial in Burmese Russell's viper bite victims. 2 Sutherland's original pressure-bandage immobilization method (Fig. 10.4.2.26b) involves bandaging the bitten limb with a series of long, 10-cm-wide elastic bandages, 'as firmly as for a sprained ankle' (about 55 mm Hg), starting distal to the bite site, continuing up to the groin or axilla and incorporating a splint. Although never subjected to formal clinical trials, the method was con- sidered effective, based on anecdotal reports of delayed systemic envenoming and rapid deterioration after release of the bandage, in some cases supported by measurements of venom antigenemia. However, in practice, the technique has proved difficult to apply, even in Australia, and it is demanding on equipment and training. External compression increases intracompartmental pressure and might accentuate the local effects of some necrotic snake venoms, but animal studies found little evidence that this was deleterious and confirmed the life-saving effects of lymphatic and venous compression.

 (a) (b)
Fig. 10.4.2.26 Pressure-immobilization methods. (a) Pressure-pad immobilization. A pad of whatever material is immediately available is placed directly over the bite wound and bound on very firmly with an inelastic bandage. The whole limb is then splinted to prevent movement at any of its joints. (b) Pressure-bandage immobilization. The bitten limb is firmly bound with long, wide (4 cm) elastic bandages, starting distal to the bite site and ending at the armpit or groin. A splint is incorporated. Courtesy of Dr David J Williams.

 Inhibition of the intrinsic lymphatic pump A study of lymphatic flow in human volunteers and in rats showed that nitric oxide (NO)–donating drugs, such as glyceryl trinitrate (GTN), applied topically to the bitten limb, substantially slowed lymphatic flow, despite movement of the limb. Topical application of NO-donating drugs might prove a useful adjunct to pressure-pad or pressure-bandage first-aid methods. Pursuing and killing the snake is not recommended, but if the snake has been killed, it should be taken with the patient to hospital. It must not be handled as even a severed head can inject venom. Patients being transported to hospital should lie on their left side in the recovery position to prevent aspiration of vomit. Persistent vomiting can be treated with chlorpromazine by intramuscular in- jection (25–50 mg in adults, 1 mg/kg in children; intravenous injec- tion risks hypotension), or chlorpromazine or prochlorperazine by intrarectal suppository. Syncope, shock, angio-oedema, and other autonomic symptoms can be treated with 0.1% adrenaline by intra- muscular injection (0.5 ml for adults, 0.01 ml/kg for children) and an antihistamine such as chlorphenamine maleate by intravenous injection (10 mg for adults, 0.2 mg/kg for children). Patients with incoagulable blood will develop haematomas after intramuscular and subcutaneous injections, and so the intravenous route should be used whenever possible except in the case of adrenaline. Respiratory distress and cyanosis should be treated by clearing the airway, giving

oxygen, and, if necessary, assisted ventilation. If the patient is uncon- scious and no femoral or carotid pulses can be detected, cardiopul- monary resuscitation must be started immediately. Hospital treatment Clinical assessment In most cases of snakebite, uncertainties about the species and the quantity and composition of venom injected can be resolved only by admitting the patient to hospital for at least 24 h of observation. Local swelling is usually detectable within 15 min of pit viper envenoming and within 2 h of envenoming by most other vipers, but may not de- velop in patients bitten by some vipers, colubrids, and elapids such as kraits, coral snakes, and sea snakes. Fang marks are sometimes invisible. Tender enlargement of regional lymph nodes draining the bitten area is an early sign of envenoming by Viperidae and some Elapidae, notably Australasian elapids. All the tooth sockets should be examined meticulously as this is usually the first site of spontan- eous bleeding: other common sites are the nose, conjunctiva, skin, and gastrointestinal tract. Persistent bleeding from venepuncture sites and other wounds implies incoagulable blood. Hypotension and shock are important signs of hypovolaemia, vasodilatation, or cardiotoxicity, seen particularly in patients bitten by North American rattlesnakes and some Viperinae (e.g. V. berus, Russell's vipers, D. palaestinae). Ptosis is the earliest sign of neurotoxic envenoming (Fig. 10.4.2.17). Respiratory muscle power should be assessed objectively and repeat- edly, for example, by measuring vital capacity. Trismus and general- ized myalgia with muscle tenderness suggest rhabdomyolysis (sea snakes). If a procoagulant venom is suspected, the coagulability of whole blood should be checked at the bedside using the 20WBCT. Antivenom treatment In managing cases of snakebite, the most important decision is whether or not to give antivenom, the only specific antidote for envenoming. There is abundant evidence that in patients with se- vere envenoming, the benefits of this treatment outweigh the risks of antivenom reactions (see following paragraphs). Antivenom has reduced the mortality of systemic envenoming by Echis ocellatus in Nigeria from 20% to 3% and by C. d. terrificus in Brazil from 74% to 12%. Antivenoms are effective in reversing hypotension caused by V. berus envenoming and coagulopathies caused by Bothrops species, Russell's vipers, C. rhodostoma, Trimeresurus T. albolabris, and Oxyuranus scutellatus. Antivenom, also known as antivenin, antivenene, antisnakebite serum, and anti-snakevenom (ASV) is the partially purified immunoglobulin (whole IgG, F(ab′)2, or Fab fragments) of horses or sheep that have been hyperimmunized with venom. Antivenoms are in short supply in sub-Saharan Africa and New Guinea; elsewhere, they are of variable efficacy and safety and are often used inappropriately. Indications for antivenom Antivenom is indicated if there are signs of systemic envenoming such as: • haemostatic abnormalities: spontaneous systemic bleeding, incoagulable blood, or thrombocytopenia • neurotoxicity: descending paralysis starting with ptosis and ex- ternal ophthalmoplegia • hypotension and shock, abnormal ECG, or other evidence of severe cardiovascular dysfunction • generalized rhabdomyolysis or massive intravascular haemolysis: black urine Supporting evidence of severe envenoming is a neutrophil leuco- cytosis, elevated serum enzymes such as CK and aminotransferases, haemoconcentration, severe anaemia, myoglobinuria, haemo- globinuria, methaemoglobinuria, hypoxaemia, and acidosis. In the absence of systemic envenoming, local swelling involving more than half the bitten limb, extensive blistering or bruising, bites on digits, and rapid progression of swelling are indications for anti-venom, especially in patients bitten by species whose venoms are known to cause local necrosis (e.g. Viperidae, Asian cobras, and African spitting cobras). Patients bitten by European Vipera spp. who show any evidence of envenoming should be admitted to hospital for observation for at least 24 h. Antivenom should be given whenever there is evidence of systemic envenoming (see earlier), even if its appearance is delayed for several days after the bite. Prediction of antivenom reactions Hypersensitivity testing by intradermal or subcutaneous injection or intraconjunctival instillation of

diluted antivenom was widely practised in the past. However, these tests delay the start of anti- venom treatment, are not without risk, and have no predictive value for early (anaphylactic) or late (serum sickness-type) antivenom reactions, because they are not usually the result of acquired IgE-mediated type I hypersensitivity Prevention of early antivenom reactions Prophylactic antihistamines (anti-H1 and anti-H2), corticosteroids, and adrenaline have been widely used, singly or in combination, without convincing evidence of effectiveness. However, premedica- tion of 1007 Sri Lankan snakebite victims with promethazine,

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1796 hydrocortisone, and adrenaline in a subcutaneous adult dose of 0.25 ml of 1:1000 was compared, each alone and in various com- binations. Compared with placebo, adrenaline significantly reduced severe reactions to antivenom by 43% (95% CI, 25–67) at 1 hour and by 38% (95% CI, 26–49) up to and at 48 hours after antivenom administration. Hydrocortisone and promethazine were ineffective, and addition of hydrocortisone negated the benefit of adrenaline. Routine prophylaxis with low-dose subcutaneous epinephrine (adult dose, 0.25 mg of 1: 1000 solution), given before starting anti- venom infusion, should now be generally recommended based on this convincing evidence. Contraindications to antivenom Atopic patients and those who have reacted previously to equine antiserum are at increased risk of developing severe antivenom re- actions. In such cases, antivenom should be given only if there is definite systemic envenoming. Reactions may be prevented or ameliorated by pretreatment with subcutaneous adrenaline (see earlier). There is no time for rapid desensitization. Selection and administration of antivenom Antivenom should be given only if its stated range of specificity in- cludes the species thought to be responsible for the bite. Whatever the stated expiry date on the ampoule, opaque solutions should be discarded, as precipitation of protein indicates loss of activity and an increased risk of reactions. However, expiry dates quoted on ampoules are often unnecessarily short, for commercial reasons; provided that the antivenom has been kept refrigerated and the so- lution is clear, a high proportion of its original activity is retained for 5 years or more. Monospecific (monovalent) antivenom is ideal if the biting species is known. Polyspecific (polyvalent) antivenoms are used in many countries because of the difficulty in identifying the species responsible for bites. Polyspecific and monospecific anti- venoms can be equally effective. Antivenoms may exhibit a range of paraspecific neutralizing activity. For example, the South African Vaccine Producer’s (formerly SAIMR) ‘polyvalent antivenom’, which is raised against the venoms of 10 species, has paraspecific activity against a further five species. It is almost never too late to give antivenom while signs of sys- temic envenoming persist, but, ideally, it should be given as soon as it is indicated. Antivenom has proved effective up to 2 days after sea snake bites and, in patients still defibrinogenated, weeks after bites by Viperidae. In contrast, local envenoming is probably not amenable unless antivenom is given within a few hours of the bite. The intravenous route is far more effective than intramuscular (Fig. 10.4.2.27). An infusion of antivenom diluted in approxi- mately 5 ml of isotonic fluid/kg body weight may be easier to con- trol than an intravenous ‘push’ injection of undiluted antivenom given at the rate of about 4 ml/min. However, there is no evidence that dilution, or slower administration of antivenom within the range 10–120 minutes, affects the incidence or severity of early antivenom reactions. Dose of antivenom Manufacturers’ recommendations are based on mouse protection tests and may be very misleading. Few clinical trials have been per- formed to establish appropriate initial doses, and in most coun- tries this is judged empirically. Many clinical severity grading and scoring systems are in use to guide choice of the initial dose of anti- venom but none has been tested for its prognostic significance. The patient’s condition may

deteriorate suddenly, making these rigid and unproven prescriptions unreliable. Many hospitals in the rural tropics give a standard dose of 1 to 2 ampoules to every patient who claims to have been bitten, irrespective of clinical severity. This practice squan- ders scarce, expensive antivenom, and exposes non-envenomed pa- tients to the risk of reactions. Some suggested initial doses are given in Table 10.4.2.1. Children must be given the same dose as adults. Response to antivenom Often, there is marked symptomatic improvement soon after anti- venom has been injected. In shocked patients, the blood pressure may rise and consciousness returns (C. rhodostoma, V. berus, Bitis arietans). Neurotoxic signs may improve within 30 min (Acanthophis spp., N. kaouthia), but the response usually take several hours. Spontaneous systemic bleeding usually stops within 15 to 30 min and blood coagulability is restored within a median time of 6 h after antivenom treatment, provided a neutralizing dose has been given. More antivenom should be given if severe signs of envenoming persist after 1 to 2 h, or if blood coagulability is not restored within about 6 h. Systemic envenoming may recur hours or days after an initially good response to antivenom. This is explained by the continuing absorption of venom from the injection site after clearance of antivenom from the bloodstream or redistribution of venom from the tissues into the vascular compartment. The apparent serum half-lives of antivenoms in envenomed patients range from 26 to 95 h. Envenomed patients should therefore be assessed daily for at least 3 or 4 days. Antivenom reactions Early (anaphylactic) reactions These reactions develop within 10 to 180 min of starting antivenom in between 3% and 84% of patients, depending on which antivenom is used. The inci- dence increases with dose and is lowest in antivenoms lacking 0.5 0.4 0.3 Fab antivenom (ul/ml) 0.2 0.1 0 0 1 3 6 12 24 48 Time after antivenom (hr) 1 VIAL Fab ANTIVENOM I.VI. COMPARED WITH 1 VIAL I.M.I. (9 PATIENTS VIA EACH ROUTE) Fab AV I.V. Fab AV I.M. Fig. 10.4.2.27 Serum therapeutic antivenom concentrations in two groups of patients with mild envenoming given the same dose of a Fab fragment antivenom by intramuscular or slow intravenous injection. Intramuscular administration resulted in delayed peak concentrations (at 24 h) sixfold less than by intravenous injection. Theakston RDG, Warrell DA, unpublished data.

Table 10.4.2.1 Guide to initial dosage of selected important antivenoms (key to abbreviations at foot of table) Species Latin name Common name Manufacturer, antivenom Initial dose (approximate) Acanthophis spp. Death adders CSL,a monospecific 1–3 vials Agkistrodon piscivorus, A. contortrix Copperhead and cottonmouth moccasins BTGg ‘CroFab’, Laboratorio Silanes (Mexico) Antivipmyn 4–6 vials Bitis arietans Puff adder SAVPb polyspecific, ICPc EchiTAb-plus-ICP 80 ml Bothrops asper Terciopelo ICPc polyvalent, Laboratorio Silanes (Mexico) Antivipmyn TRI 50–100 ml Bothrops atrox Common lancehead Butantan, FEDd Antibotropico 20 ml Bothrops (Bothriopsis) bilineatus Papagaio Butantan Antibotropico 20 ml Bothrops jararaca Jararaca Instituto Butantan, FEDd Antibotropico 20 ml Bothrops lanceolatus and B. caribbaeus Lesser Antillean fer de lance Sanofi-Pasteur BothroFav 2–6 vials Bungarus caeruleus Common krait Indian manufacturerse, polyvalent 100 ml Calloselasma (Agkistrodon) rhodostoma Malayan pit viper Thai Red Cross monovalent or haemato-polyvalent 100 ml Thai Government Pharmaceutical Organization monovalent 50 ml Cerastes spp. Desert (horned) vipers NAVPCf polyvalent 30–50 ml Vacsera AntiViper or polyvalent 30–50 ml Crotalus adamanteus Eastern diamondback rattlesnake BCGg ‘CroFab’, Laboratorio Silanes (Mexico) Antivipmyn 7–15 vials C. atrox Western diamondback rattlesnake BTGg ‘CroFab’, Laboratorio Silanes (Mexico) Antivipmyn 7–15 vials C. oreganus and C. viridis sspp. Western rattlesnakes BTGg ‘CroFab’ or Laboratorio Silanes (Mexico) Antivipmyn 7–15 vials C. simus and C. durissus sspp. Central and Southern American rattlesnakes ICPc or

Laboratorio Silanes polyvalent 5–15 vial Butantan, FEDd Anticrotalico, or Antibotropico-crotalico 5–20 vials Daboia (Vipera). Palaestinae Palestine viper Rogoff Medical Research Institute, Tel Aviv, Palestine, viper-monospecific 50–80 ml Daboia (Vipera) russelii Western Russell's viper Indian manufacturerse polyspecific 100 ml D. siamensis Eastern Russell's viper Thai Red Cross monovalent or haemato-polyvalent 50 ml Myanmar Pharmaceutical Factory monovalent 80 ml Dendroaspis spp. Mambas SAVPb Dendroaspis or polyvalent 50–100 ml Echis ocellatus, E. leucogaster, E. pyramidum (Africa) African saw-scaled or carpet vipers SAVPb Echis monovalent ICP, EchiTAb-plus-ICP, MicroPharm EchiTAb-G 20 ml, 3 vials, 1 vial Echis carinatus sspp. Asian saw-scaled viper Indian manufacturerse, polyvalent 50 ml Echis spp. Middle East Middle Eastern saw-scaled vipers NAVPCf Polyvalent Snake Antivenom Vacsera Polyvalent and Anti-Viper Venom Antiserum 50 ml Hydrophiinae Sea snakes CSLa sea snake antivenom 1–10 vials Lachesis spp. Bushmasters ICPc polyspecific, FEDd Antibotropico laquetico, Butantan Antiophidico 10–20 vials Micrurus spp. Central American and Brazilian coral snakes ICPc monovalent 1–5 vials Butantan Antielapidico 1–5 vials Naja kaouthia Monocellate Thai cobra Thai Red Cross cobra monovalent or neuro-polyvalent 100 ml N. naja Indian cobra Indian manufacturers,e polyvalent 100 ml N. nigricollis, N. mossambica, and so on African spitting cobras SAVPb polyvalent, ICPc EchiTAb-plus-ICP 100 ml Notechis scutatus Tiger snake CSL,a monospecific 1–3 vials (continued)

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1798 complement-activating aggregates. Fewer reactions occur when administration is by intramuscular rather than intravenous injec- tion. The symptoms are itching, urticaria, cough, nausea, vomiting, other autonomic manifestations, fever, and tachycardia. Up to 40% of patients with early reactions develop systemic anaphyl- axis: hypotension, bronchospasm, and angio-oedema. Deaths are rare, but individual cases, such as the asthmatic boy who died from anaphylactic shock after receiving Pasteur antivenom in England in 1957, have been widely publicized and have led to an unreason-able rejection of antivenom treatment. Early antivenom reactions are unlikely to be type I, IgE-mediated hypersensitivity reactions to equine serum protein. They result from complement activation by immune complexes or aggregates of IgG. Pyrogenic reactions Pyrogenic reactions result from contam- ination of the antivenom with endotoxin-like compounds. Fever, rigors, vasodilatation, and a fall in blood pressure develop 1 to 2 h after treatment. In children, febrile convulsions may be precipitated. Late serum sickness-type reactions Late reactions of serum sickness type may develop between 5 and 24 (mean 7) days after antivenom therapy. The incidence of these reactions and the speed of their de- velopment increases with the dose of antivenom. Clinical features include fever, itching, urticaria, arthralgia (sometimes involving the temporomandibular joint), lymphadenopathy, periarticular swell- ings, mononeuritis multiplex, albuminuria, and rarely, encephalop- athy. This is a classic immune complex disease. Treatment of antivenom reactions Adrenaline is the effective treatment for early reactions; 0.5 to 1.0 ml of 0.1% (1 in 1000, 1 mg/ml) is given by intramuscular injection into the lateral thigh to adults (children 0.01 ml/kg) at the first signs of a reaction. The dose may be repeated if the reaction is not controlled. Patients with profound hypotension, severe bronchospasm, or la- ryngeal oedema may be given adrenaline by slow intravenous in- jection (0.5 mg diluted in 20 ml of isotonic saline over 10–15 min). For bronchospasm, a β2 agonist such as salbutamol should be given by inhaler or nebulizer, together with oxygen. A histamine anti-H1 blocker, such as chlorphenamine maleate (10 mg for adults; 0.2 mg/ kg for children) can be given by intravenous injection to combat the effects of histamine release during the reaction, but this is less urgent. Pyrogenic reactions are treated by physically cooling the patient and giving antipyretics. Late reactions respond to an oral

antihistamine such as chlorphenamine (2 mg every 6 h for adults; 0.25 mg/kg per day in divided doses for children) or to oral prednis- olone (5 mg every 6 h for 5 to 7 days for adults; 0.7 mg/kg per day in divided doses for children). Supportive treatment Neurotoxic envenoming Bulbar and respiratory paralysis may lead to death from aspiration, airway obstruction, or respiratory failure. A clear airway must be maintained and, if bulbar muscle weakness results in pooling of secretions, or respiratory distress develops, a cuffed endotracheal tube, laryngeal mask airwayor i-gel supraglottal airway should be inserted or a tracheostomy performed. Provided they are ad- equately ventilated, patients with neurotoxic envenoming remain fully conscious with intact sensation and can respond to spoken questions by flexing a finger or toe. Lifting their paralysed eyelids so that they can see is very reassuring. Patients have been effectively ventilated manually (by Ambu bag or anaesthetic bag), as in the 1952 poliomyelitis epidemic in Copenhagen, for 30 days and have recovered after 10 weeks of mechanical ventilation. Although artifi- cial ventilation was first suggested for neurotoxic envenoming more than 100 years ago, patients continue to die because they are denied this simple procedure. Anticholinesterases have a variable but potentially useful ef- fect in patients with neurotoxic envenoming, especially when postsynaptic neurotoxins are involved. However, recent media claims that intranasal neostigmine might provide a universal first- aid method for snakebite victims are unsubstantiated, misleading, and fanciful. The ‘Tensilon test’ should be performed in all cases of severe neurotoxic envenoming, as with suspected myasthenia gravis. Atropine sulphate (0.6 mg for adults; 50 µg/kg for children) or glycopyrronium is given by intravenous injection followed by edrophonium chloride (Tensilon) by slow intravenous injection in an adult dose of 10 mg, or 0.25 mg/kg for children or neostigmine bromide or methylsulphate (Prostigmin) by intramuscular injec- tion (0.02 mg/kg for adults, 0.04 mg/kg for children). The ‘ice test’ is a possible alternative to the Tensilon test. In myasthenia gravis, application of an ice-filled plastic glove to one eye for 2 minutes results in improvement in ptosis on that side, due to inhibition of anticholinesterase. Patients who respond convincingly can be maintained on neostigmine methylsulphate, 0.5 to 2.5 mg every Species Latin name Common name Manufacturer, antivenom Initial dose (approximate) Oxyuranus scutellatus Australian and New Papuan Taipan CSL,a monospecific 1–6 vials Pseudonaja textilis Eastern brown snake CSL,a monospecific 1–3 vials Trimeresurus (Trimeresurus) albolabris, T. (T.) macrops White-lipped and large-eyed green pit viper Thai Red Cross monovalent or haemato-polyvalent 100 ml Vipera berus and other European Vipera European adder and other vipers MicroPharm ‘ViperaTAb’, Sanofi-Pasteur ViperFav 100–200 mg, 4 ml a CSL, Commonwealth Serum Laboratories, Australia; b SAVP, South African Vaccine Producers (formerly SAIMR: South African Institute for Medical Research); c ICP, Instituto Clodomiro Picado, Costa Rica; dFED, Fundação Ezequiel Dias, Brazil; eIndian manufacturers (Vins, Bharat, Premium Serums and Vaccines, and so on); f NAVCP, National Antivenom and Vaccine Production Center, KSA; g BTG (formerly Protherics). Table 10.4.2.1 Continued

 1 to 3 h up to 10 mg/24 h maximum for adults or 0.01 to 0.04 mg/kg every 2 to 4 h for children by intramuscular, intravenous, or sub- cutaneous injection. Hypotension and shock If the central venous pressure is low or there is other clinical evidence of hypovolaemia, isotonic saline should be infused. If there is evidence of increased capillary permeability (e.g. facial and conjunctival oedema, serous effusions, haemoconcentration, hypoalbuminaemia, and so on) it may be safer in the long term to rely on a selective vasoconstrictor such as dopamine (starting dose 2.5–5 µg/kg per min by intravenous infusion). Delayed hypotension that develops about 1 week after bites by

Burmese D. siamensis is a consequence of acute pituitary-adrenal insufficiency (Sheehan's-like syndrome) responds to intravenous hydrocortisone. Oliguria and acute kidney injury Urine output, serum creatinine, urea, and electrolytes should be measured each day in patients with severe envenoming, and in those bitten by species known to cause acute kidney injury (e.g. Russell's vipers, hump-nosed pit viper (Hypnale hypnale), C.d. terrificus, Bothrops spp., sea snakes). If urine output drops below 400 ml in 24 h, urethral and central venous catheters should be inserted. If urine flow fails to increase after cautious rehydration, patient should be placed on strict fluid balance. Dopamine (2.5 µg/kg per min by intravenous infusion) has proved effective in some patients bitten by Russell's vipers, although its use has been largely abandoned by nephrologists. Renal replacement therapy (peritoneal or haemo- dialysis or haemofiltration) will usually be required. In Rangoon, Burma, the mortality of acute kidney injury following D. siamensis envenoming has been reduced to less than 30% by using peritoneal dialysis, usually for only 72 h. Local infection at the site of the bite After bites by some species (e.g. Bothrops spp., C. rhodostoma), local infections caused by unusual bacteria derived from the snake's venom or fangs develop in 10% or more cases. A booster dose of tetanus toxoid should be given, but prophylactic antibiotics are not indicated unless the wound has been incised or tampered with in any way or if there is necrosis with the associated risk of Clostridium tetani and other anaerobes. If a local abscess develops, it should be drained and the pus cultured. Penicillin, chloram- phenicol, or erythromycin are usually effective. An aminoglycoside such as gentamicin should be given for 48 h if there is evidence of local necrosis. Management of local envenoming Bullae are best left intact. The bitten limb should be nursed in the most comfortable position but not elevated excessively as this in- creases the risk of intracompartmental ischaemia. Once definite signs of necrosis have appeared (blackened anaesthetic area with putrid odour or signs of sloughing), surgical debridement, imme- diate split-skin grafting, and broad-spectrum antibiotic cover are indicated. Intracompartmental syndrome and fasciotomy Swelling of envenomed tissues within tight fascial compartments such as the digital pulp spaces and anterior tibial compartment may cause ischaemia that adds to the risk of venom-induced ne- crosis. This may explain why digital bites are so often necrotic. The classic signs of 'compartment syndrome' are excessive pain, weak- ness and tenderness of the compartmental muscles, and pain when they are passively stretched, hypoaesthesia of skin supplied by nerves running through the compartment, and obvious tenseness of the compartment. Misleadingly, these signs are frequently pre- sent in snakebitten limbs in which intracompartmental pressures are normal. Recent studies in the United States failed to demon- strate any benefit of fasciotomy in snakebite victims. In any case, fasciotomy is absolutely contraindicated until blood coagulability has been fully restored (by adequate doses of antivenom followed by clotting factors). Surgery must be justified by demonstrating that intracompartmental pressure is consistently raised to less than 30 mm Hg below mean arterial pressure, or it exceeds 45 mm Hg in adults or 30 mm Hg in children, when measured directly with a Stryker transducer. Haemostatic disturbances Once specific antivenom has been given to neutralize venom pro- coagulants, restoration of coagulability and platelet function may be accelerated by giving (reliably screened) fresh whole blood, fresh frozen plasma, cryoprecipitates (containing fibrinogen, factor VIII, fibronectin, and some factors V and XIII), or platelet concentrates. Heparin has been used to treat a variety of snakebites, usually with disastrous results. Heparin did not prove beneficial in patients envenomed by Echis ocellatus. Other drugs Corticosteroids, antifibrinolytic agents (aprotinin and ε-aminocaproic acid), antihistamines, trypsin, and a variety of traditional herbal rem- edies have all been used, but none has proved effective and most are potentially harmful. Treatment of snake venom ophthalmia caused

by spitting cobras and rinkhals First-aid treatment involves urgent decontamination of the affected eye(s) using large volumes of water or any other available bland fluid (even urine!). A single topical administration of local anaesthetic drops such as 0.4% oxybuprocaine hydrochloride, 4% lidocaine hydrochloride, or tetracaine hydrochloride drops cures the agonizing pain. Adrenaline (0.1%) drops are also effective. Corneal abrasions must be excluded by fluorescein staining and/ or slit-lamp examination. A prophylactic topical antibiotic such as tetracycline, chloramphenicol, soframycin, ciprofloxacin, or gatifloxacin should be instilled. Posterior synechiae, ciliary spasm, and discomfort are prevented with 2% atropine, scopol- amine, or homatropine. In case of allergic keratoconjunctivitis in someone previously spat at, topical antihistamines are used. Topical or intravenous antivenom and topical corticosteroids are contraindicated. Interval between bite and death Exceptionally, patients may die 'within a few minutes' (reputedly after a bite by the king cobra Ophiophagus hannah) or as long as 41 days (Echis carinatus) after snakebite. However, most deaths occur about 8 h after cobra bites (N. naja), 18 h after krait bites (Bungarus caeruleus), 16 h after North American rattlesnake bites

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1800 (Crotalus spp.), 3 days after Russell's viper bites, and 5 days after Echis bites. Venomous lizards Two species of venomous lizard (genus Heloderma) have proved capable of envenoming humans. Venom from submandibular glands pools in labial gutters in the lower jaw and is conducted along grooves in the lower teeth. The Gila monster H. suspec- tum (Fig. 10.4.2.28), which is striped with a short thick tail and grows to 55 cm in length, occurs in the south-western United States and adjacent areas of Mexico. The Mexican beaded lizard or escorpión H. horridum, which is spotted with a relatively long thin tail and reaches 1 m in length, is found in western Mexico south to Guatemala. Heloderma venoms contain lethal glycopro- tein toxins, Gila, and horridum toxins, phospholipase A2, and 5 bioactive peptides of great interest, including helospectin (a vaso- active intestinal peptide analogue) and exendins-3 and -4, which are glucagon-like peptide-1 (GLP-1) homologues that stimulate insulin secretion and inhibit glucagon secretion. A synthetic homologue of exendin-4, exenatide, is a high affinity GLP-1 re- ceptor agonist which has been developed for treatment of type 2 diabetes mellitus. Bites are rare and are usually inflicted on the fingers, hands, and forearms of inebriated young men who are handling or trying to catch the lizards. The lizard hangs on with its powerful jaws and is difficulty to disengage. Expert opinion currently favours levering the jaws apart with a screw driver, run- ning the cold tap over the attached lizard, placing its four feet on the ground or introducing some alcohol into its mouth. There is immediate severe throbbing or burning local pain that radiates up the limb with tender swelling and regional lymphadenopathy. Systemic symptoms include weakness, dizziness, tachycardia, hypotension, syncope, angio-oedema, sweating, rigors, tinnitus, nausea, and vomiting. There may be leucocytosis, coagulopathy, electrocardiographic changes, myocardial infarction, and acute kidney injury. No fatal cases have reliably been reported. Specific antivenom is not generally available. A powerful analgesic may be required. Hypotension should be treated with fluids, adrenaline, or a pressor agent such as dopamine. Recently, venomous salivary secretion have been demonstrated in other groups of lizards such as iguanas (Iguanidae), glass/alli- gator lizards (Anguidae), and monitors (Varanidae), notably the Komodo dragon Varanus komodoensis that has been responsible for human fatalities that were attributed to trauma of infection of the bite wounds. Poisonous amphibians and birds Poisonous amphibians The moist skin of amphibians such as frogs, toads, newts, and sala- manders is an accessory respiratory organ, which is protected from microorganisms by highly toxic secretions containing amines, peptides, proteins, steroids, and

alkaloids. Some compounds are synthesized de novo, while others are sequestered from prey such as ants, beetles, and millipedes. The bitter flavour and lethal effects of these secretions and the vivid warning colouration of many spe- cies defend them against predators. The skin of ‘poison-dart’ frogs (Dendrobatidae) of Central and South America secrete lipophilic alkaloids such as batrachotoxins (Phyllobates spp.), which activate sodium channels; histrionico toxins (Dendrobates histrionicus) (Fig. 10.4.2.29), which block nicotinic receptors; pumiliotoxins (D. pumilio), which affect sodium channels; and epibatidine (Epipedobates tricolor), a powerful analgesic and nicotinic receptor Fig. 10.4.2.28 Gila monster Heloderma suspectum. Copyright D. A. Warrell. Fig. 10.4.2.29 Poison frog Dendrobates histrionicus (Dendrobatidae) Bahia Solauo, Colombia. Its skin secretion contains potent nicotinic receptor antagonists, histrionicotoxins. Copyright D. A. Warrell.

10.4.2 Injuries, envenoming, poisoning, and allergic reactions caused by animals 1801 agonist. Two Colombian tribes, the Embará and Noanamá Chocó, use the skin poisons of three species of Phyllobates to coat the tips of their blow-gun darts. Some toads can squirt from their parotid glands venom containing bufadienolides which affect membrane Na+, K+-ATPase. When licked or put in the mouth by dogs or chil- dren, or when ingested as Chinese traditional medicines such as Kyushin, Yixin Wan, or the topical aphrodisiac Ch’an-Su, the poi- sons can cause fatal digoxin-like poisoning. Symptoms include hypersalivation, cyanosis, cardiac arrhythmias, and generalized convulsions. Antidigoxin antibodies (‘Digibind’, ‘DigiTAb’) have some therapeutic effect. The skin of three species of newts, genus Taricha, from the western United States, contains tarichatoxins identical to tetro- dotoxin, which also occurs in some toads, frogs, fish, crustaceans, and octopuses (see following paragraphs). Tetrodotoxin can be absorbed through the gastric mucosa, explaining the death of a man who swallowed a 20-cm long Oregon rough-skinned newt Taricha granulosa. He developed paraesthesia of the lips, pro- gressing to more generalized numbness and weakness, and had a cardiopulmonary arrest about 2 h after swallowing the newt. Poisonous birds The feathers, skin, and breast muscles of five species of pitohui or thickhead, passerine birds from New Guinea (genus Pitohui; Pachycephalidae) and the blue-capped ifrita or ifrit (Ifrita kow- aldi; Cinclosomatidae) contain homobatrachotoxin, a potent steroidal alkaloid that activates sodium channels and was ori- ginally isolated from the skin of South American poison-dart frogs (Phyllobates—see earlier paragraphs). The birds may ac- quire the poison by eating melyrid beetles (Choresine spp.). Poisonous pitohuis have an unpleasant peppery odour, and their skin has a bitter flavour. Contact with their feathers causes numbness and burning of the tongue, lip or skin wounds, and sneezing. This may be a protective mechanism, and the striking ‘warning’ colouration of the hooded pitohui (P. dichrous) (Fig. 10.4.2.30) may be the subject of Müllerian mimicry by less poisonous species. Venomous fish About 200 species of fish inhabiting temperate and tropical seas possess a defensive venom-injecting apparatus that can inflict dangerous stings, but more than 1200 species are now thought to be venomous. Fatal stings have been reported from cartilagenous fish (class Chondrichthyes), such as sharks and dogfish (order Squaliformes) and stingrays and mantas (order Rajiformes), and from bony fish (superclass Osteichthyes), such as ray-finned fish (class Actinopterygii) of the orders Siluriformes (catfish), Perciformes (families Trachinidae (weever fish), Uranoscopidae (stargazers or stone-lifters), and others) and Scorpaeniformes (scorpion fish, stonefish, lion fish Synanceja/Synanceia spp.) (Fig. 10.4.2.31). Two species of lion fish have been introduced into the Atlantic ocean and now occupy the SE coast of the United States and the Caribbean, posing an ecological threat to the region. The Indo-Pacific region and other tropical waters have the richest venomous fish fauna, but dangerous species such as sharks, chimaeras, and weevers also occur in temperate northern waters, and several large rivers in South American,

West Africa, and Southeast Asia are inhabited by freshwater stingrays Potamotrygon spp. (Fig. 10.4.2.32). Venom glands are embedded in grooves in the spines or, in the case of stingrays, lie beneath a membrane covering the long barbed precaudal spine. Incidence and epidemiology Weever fish are common around the coast of the British Isles, especially off Cornwall. Hundreds of stings occur in some years, with a peak incidence in August and September. It has been estimated that there are 1500 stings by rays and 300 stings by scorpion fish in the United States each year. Stings by venomous freshwater rays (Potamotrygon hystrix, P. motoro) are common in the Amazon region of Brazil. Ornate, but aggressive and venomous members of the genera Pterois and Dendrochirus (lion, zebra, tiger, turkey, or red fire fish) (Fig. 10.4.2.31), which are popular aquarium pets, often sting their owners on the fingers. Most fish stings are inflicted on the soles of the feet of people wading near the shore Fig. 10.4.2.30 Hooded pitohui Pitohui dichrous. Varararta National Park near Port Moresby, Papua New Guinea. By courtesy of Dr Ian Burrows. Fig. 10.4.2.31 Lion fish Pterois volitans (Scorpionidae). Copyright D. A. Warrell.

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1802 or in the vicinity of coral reefs. Venomous fish are effectively cam- ouflaged (Synanceja spp.) or lie partly covered by sand. Stingrays lash their tails at the intruding limb and usually impale the ankle (Fig. 10.4.2.33). Fatal fish stings are very rarely reported. Prevention Fish stings can be prevented by employing a shuffling gait when wading, by avoiding handling living or dead fish, and by keeping clear of fish in the water, especially in the vicinity of tropical reefs. Footwear protects against most species except stingrays. Venom composition The instability of most fish venoms at normal ambient temperat- ures has made them difficult to study. Stingray and weeverfish venoms contain peptides, enzymes, and a variety of vasoactive compounds such as kinins, 5-hydroxytryptamine, histamine, and catecholamines. Pharmacological effects include local necrosis, direct actions on cardiac, skeletal, and smooth muscle, resulting in ECG changes, hypotension, paralysis, and central nervous system depression. Clinical features Immediate sharp, agonizing pain is the dominant symptom. Hot, erythematous swelling extends up the stung limb and may per- sist with pain for several days and be complicated by necrosis (Fig. 10.4.2.33) and secondary infection by marine Vibrio spp. (such as V. vulnificus), freshwater species (such as Aeromonas hydrophila), and other unusual bacteria, particularly if the spine remains embedded in the wound. Stingray spines, which are up to 30 cm long, can cause severe lacerating injuries, especially to the lower legs, but if the victim inadvertently lies on the ray or falls on to it, the spine may penetrate the thoracic or abdominal cavities with fatal results. Systemic effects are uncommon after weever stings (Trachinidae), but people stung by rays or Scorpaenidae (scorpion- and stonefish) may develop nausea, vomiting, signs of autonomic nervous system stimulation; such as diarrhoea, sweating, and hypersalivation; car- diac arrhythmias, hypotension, respiratory distress, neurological signs, and generalized convulsions. Patients have died within 1 h of being stung by Synanceja verrucosa. Treatment Pain is alleviated by immersing the stung limb in water, which is uncomfortably hot yet not scalding (<45°C; the 50°C recommended by some authorities will cause a full thickness scald!). Temperature can be assessed with the unstung limb. Addition of magnesium sul- phate is unnecessary. Injection of a local anaesthetic is less effective even when applied as a ring block in the case of stung digits, but a local nerve block with 0.5% of plain bupivacaine is effective. The venomous spine (which may be barbed), fragments of membrane, and other foreign material should be removed as soon as possible. Systemic effects must be treated symptomatically. An adequate airway should be established, and cardiopulmonary resuscitation may be needed. Severe hypotension may respond to adrenaline, bradycardia to atropine. Seqirus (formerly CSL) in

Australia manu- facture an antivenom specific for Synanceja trachynis, S. verrucosa, and S. horridus. This has paraspecific activity against the venoms of the North American scorpion fish (Scorpaena guttata) and some other members of the Scorpaenidae. One ampoule (2 ml or 2000 units) is given intravenously for each two puncture marks found at the site of the sting. The dose is increased for patients with se- vere symptoms. Antibiotic treatment for secondary infections should take into account the range of possible marine pathogens. Doxycycline or co-trimoxazole covers Vibrio and Aeromonas spp. Poisoning by ingestion of aquatic animals Acute gastrointestinal symptoms ('food poisoning') after eating sea- food are usually caused by bacterial or viral infections such as Vibrio parahaemolyticus (crustaceans, especially shrimps), V. cholerae (crabs and molluscs), non-O group 1 V. cholerae (oysters), V. vulnifi- cus (oysters), Aeromonas hydrophila (frozen oysters), Plesiomonas shigelloides (oysters, mussels, mackerel, cuttlefish), Shigella spp. Fig. 10.4.2.32 Fresh water stingray Potamotrygon sp. Copyright D. A. Warrell. Fig. 10.4.2.33 Necrotic and secondarily infected wound at the site of a sting by a freshwater ray Potamotrygon hystrix in a Brazilian patient. By courtesy of Dr João Luiz Costa Cardoso.

10.4.2 Injuries, envenoming, poisoning, and allergic reactions caused by animals 1803 (molluscs), Campylobacter jejuni (clams), Salmonella typhi (mol- luscs), hepatitis A virus (molluscs, especially clams, and oysters), Norwalk virus (clams and oysters), and astro- and calici- viruses (cockles and other molluscs). Botulism has been caused by eating smoked fish and canned salmon; and in Japan and elsewhere, fish and molluscs became contaminated with methyl mercury from in- dustrial waste, causing severe neurological damage and fetal abnor- malities ('Minamata disease'). Natural toxins acquired in the food chain, originally from bac- teria can contaminate the tissues of a variety of fish, shellfish (bivalve molluscs) and other marine animals, giving rise to the several dis- tinctive syndromes of seafood poisoning. Ciguatera fish poisoning Symptoms develop between 1 and 6 h (extreme range, min to 30 h) after eating fish such as groupers, snappers, parrot fish, mackerel, moray eels, barracudas, and jacks. These are warm-water shore or reef fish. The global incidence is thought to exceed 50 000 cases per year. Up to 2% of the population may be affected each year (e.g. in Kiribati, Tokelau, and Tuvalu in the Pacific region) with a case fatality of 0.1%. The toxins responsible are polyethers such as ciguatoxin (activates Na^+ channels), maitotoxin (activates Ca^{2+} channels), and scaritoxin, ultimately derived along the food chain from benthic dinoflagellates such as Gambierdiscus toxicus. They are concentrated in the liver, viscera, and gonads, especially of large carnivorous fish. The increasing market for exotic fish from the Caribbean and else- where has led to cases of ciguatera in the United Kingdom. Acute gastrointestinal symptoms—nausea, vomiting, diarrhoea, abdominal pain and cramps, and a metallic taste in the mouth— are followed by neurological symptoms—paraesthesiae around the mouth and extremities, reversed hot-cold sensation (dysesthesia), increased salivation, dilatation of the pupils, strabismus, ptosis, weakness, and ataxia, usually resolve within a few hours, but paraes- thesiae and myalgia may persist for a week, or even months. Pruritus of the soles and palms and rashes may occur. Cardiovascular fea- tures include braycardia, hypotension, and hypovolemia. Similar symptoms (chelonitoxication) may follow ingestion of marine tur- tles in the Indo-Pacific area, with a much higher case fatality. Tetrodotoxin poisoning Scaleless fish, such as porcupine, sun, puffer, and toad fish (order Tetraodonitiformes) may become highly poisonous at certain seasons, such as May to June, the spawning season in Japan. Tetrodotoxin, an aminoperhydroquinazoline, is one of the most potent nonprotein toxins known. It produces neurotoxic and cardiotoxic effects by blocking voltage-gated sodium ion chan- nels. It is found concentrated in the ovaries, viscera, and skin of tetraodontiform fish; in the skin of newts (genus

Taricha), frogs, and toads (genera Colostethus, Atelopus, Bracycephalus), and salamanders; in the saliva of octopuses; in the digestive glands of several species of gastropod molluscs; in a starfish, flatworm Planorbis spp., and nemertine worms in Japan; and is produced by some bacteria (Pseudomonas, Pseudoalteromonas, Vibrio spp., and so on). Puffer fish ('fugu') is particularly popular in Japan where, des- pite stringent regulations, there are still cases of tetrodotoxin poi- soning, with about four deaths each year. Nausea and abdominal pain occur but usually no vomiting or diarrhoea, or there may be no gastrointestinal symptoms. Neurotoxic symptoms character- ized by rapid onset, within 10–45 minutes, of weakness, dizziness, paraesthesiae of the lips, tongue, throat and, later, the limbs. Pallor, sweating, and increased salivation may be present. Tachycardia, hypotension, difficulty breathing, and flaccid ascending paralysis may lead to respiratory paralysis; death usually occurs 2–6 hours after eating the fish. Usually, consciousness is retained throughout, although victims may appear comatose. Development of fixed di- lated pupils and brain stem areflexia suggests brain death, but com- plete recovery is possible with mechanical ventilation. Freshwater puffer fish poisoning in northern Thailand has been attributed to saxitoxin. Histamine-like syndrome (scombrotoxic poisoning) The dark red flesh of scrombroid fish (tuna, mackerel, bonito, skip- jack) and of canned nonscrombroid fish (sardines, pilchards) may be decomposed by the action of bacteria, such as Proteus morgani and Klebsiella pneumoniae, which decarboxylate muscle histidine into saurine, histamine, cadaverine, and other unidentified toxins: 100 g of spoiled fish may contain almost 1 g of histamine. Histamine ab- sorbed from the gut is normally broken down by N-methyl trans- ferase and diamine oxidase (histaminase), but if the histamine concentration is very high, or the patient is taking a diamine oxi- dase inhibitor such as isoniazid (as antituberculosis chemotherapy), scombrotoxic poisoning may result. Toxic fish may produce a tin- gling or smarting sensation in the mouth when eaten. Within min- utes or up to a few hours after ingestion, flushing, burning, sweating, urticaria, and pruritis may develop with headache, abdominal colic, nausea, vomiting, diarrhoea, bronchial asthma, giddiness, and hypotension. Poisoning by ingesting carp gallbladder In parts of East Asia, the raw bile and gallbladder of various spe- cies of freshwater carp (e.g. the grass carp Ctenopharyngodon idel- lus, 'plaa yeesok' Probarbus jullienii) are believed to have medicinal properties. Patients in China, Taiwan, Hong Kong, Japan, Thailand, and elsewhere have developed acute abdominal pain, vomiting, and watery diarrhoea 2 to 18 h after drinking the raw bile or eating the raw gallbladder of these fish. One patient developed flushing and dizziness. Hepatic and renal damage may develop, progressing to oliguric or nonoliguric acute kidney injury (acute tubular necrosis). The hepatonephrotoxin has not been identified, but is heat stable and may be derived from the carp's diet. Paralytic shellfish poisoning Five main clinical syndromes of shellfish poisoning are recognized. Many of the causal toxins, derived from dinoflagellates and diatom algae, have been identified but no specific antidotes have been discovered. Diarrhoeal shellfish poisoning: Symptoms indistinguish- able from acute infective gastroenteritis evolve usually within 30 minutes to 12 hours of eating the contaminated shellfish— diarrhoea, nausea, vomiting, and abdominal colic with recovery over a few days. The toxins responsible include okadaic acid and other dinophysis toxins, pectenotoxins, and yessotoxins, many of which are protein phosphatase inhibitors. They occur in mus- sels, cockles, scallops, oysters, whelks, and green crabs in Japan, Europe, and Africa.

 Neurotoxic shellfish poisoning: Milder gastrointestinal and neurotoxic symptoms without paralysis develop 1–3 hours after ingestion of molluscs contaminated by brevetoxins from Karenia brevis (formerly known

as Gymnodinium breve or G. brevis) dino- flagellates which can also cause ‘red tides’. Neurotoxic symptoms, reminiscent of ciguatera fish poisoning, include paraesthesiae, cold allodynia (pain or hyperaesthesia on touching cold objects), my- algia, vertigo, and ataxia. In the United Kingdom there have been several outbreaks of neurotoxic red-whelk (Neptunea antiqua) poi- soning attributable to tetramine. Paralytic shellfish poisoning: Bivalve molluscs, such as mussels, clams, oysters, cockles, and scallops (and also xanthid, coconut, and horseshoe crabs) may acquire tetrahydropurine neurotoxins such as saxitoxin and gonyautoxins from dinoflagellates (Alexandrium spp., Pyrodinium bahamense var. compressum and Gymnodinium catena- tum). These may be sufficiently abundant between latitudes 30 ºN and 30 ºS during the warmer months of May to October to produce a ‘red tide’. The dangerous season is signalled by the deaths of large numbers of fish and sea birds. Symptoms develop within 30 min of ingestion. Descending paralysis may progress to fatal respiratory paralysis within 12 h in 8% of cases. Amnesic shellfish poisoning: Develops after ingestion of mussels and other molluscs contaminated with domoic acid from diatoms (Pseudonitzschia spp.). Gastroenteritis starts within 24 h of exposure and, in in about half the cases, neurotoxic symptoms develop within 48 h. Severe headache and short-term memory loss are common. Amnesia is sometimes permanent. Severe symptoms include agi- tation, seizures, coma, profuse respiratory secretions, circulatory instability, and death. Elderly patients and those with underlying illnesses were most vulnerable. Azaspricid poisoning: Acute gastrointestinal symptoms develop within 6–18 hours of Ingestion and last up to 5 days. Diagnosis and treatment of seafood poisoning The differential diagnosis includes bacterial and viral food poi- soning and allergic reactions. No specific treatments or antidotes are available, but gastrointes- tinal contents should be eliminated by emetics and purges if this can be achieved safely and within 1 to 2 h of ingestion. Activated char- coal adsorbs saxitoxin and other shellfish toxins. Atropine is said to improve gastrointestinal symptoms and sinus bradycardia in patients with gastrointestinal and neurotoxic poisoning. Calcium gluconate may relieve mild neuromuscular symptoms. Oximes and anticholinesterases appear ineffective in ciguatera and tetrodo- toxin poisoning, respectively. Mannitol has been advocated for early treatment of ciguatera poisoning. In cases of paralytic poisoning, endotracheal intubation and mechanical ventilation and cardiac re- suscitation have proved life-saving. The symptoms of scrombrotoxic poisoning can be alleviated with antihistamines and bronchodilators. Prevention of poisoning by ingestion of aquatic animals Ciguatera toxin, tetrodotoxin, scombrotoxins, and most other marine toxins are heat stable, so cooking does not prevent poi- soning. Some toxins are fairly water soluble and may be leached out by soaking. Therefore, water in which fish are cooked should not be drunk. In tropical areas, the flesh of fish should be separ- ated as soon as possible from the head, skin, intestines, gonads, and other viscera, in which toxins are concentrated. All scaleless fish should be regarded as potentially tetrodotoxic, and very large fish carry an increased risk of being ciguatera toxic. Moray eels and parrot fish (Scaridae) should never be eaten because of the high risk of unusually rapid and severe ciguatera and scaritoxic fish poi- soning. Scrombroid poisoning can be prevented by eating fish fresh or by freezing fish as soon as possible after they are caught. Shellfish should not be eaten during the dangerous seasons and when there are red tides. Venomous marine invertebrates Cnidarians (Coelenterata) These include jellyfish, cubomedusoids, sea wasps, Portuguese-men- o’- war, or bluebottles, hydroids, stinging corals, and sea anemones. Their tentacles are armed with millions of nematocysts (stinging capsules). When triggered by contact or chemicals, stinging hairs are everted at enormous acceleration and force, penetrating the skin as far as the epidermo- dermal junction and producing lines of painful irritant weals. Cnidarian venoms contain peptides and other vasoactive substances such as 5-hydroxyhistamine, histamine, pros- taglandins, and

kinins, which cause immediate excruciating pain, inflammation, and urticaria. Epidemiology The most dangerous species, the box jellyfish, cubomedusoid, sea wasp, or indringa Chironex fleckeri of northern Australia, has caused more than 70 deaths since 1883. Most stings occur in December and January. Chiropsalmus quadrumanus and C. quadrigatus have caused fatal jellyfish stings in the Indo-Pacific region. Portuguese men-o'-war (Physalia spp.), Chinese jellyfish (Stomolophus nomu- rai) and tiny cubomedusoids (Carukia barnesi) responsible for many 'Irukandji stings' in northern Queensland, Florida, and Guadeloupe in the Caribbean, have also caused fatalities. Pelagia noctiluca may swarm in vast numbers off the northern Adriatic coast, stinging many swimmers. The North American sea nettle (Chrysaora quin- quecirrha) is widely distributed throughout the Atlantic and Indo- Pacific oceans and is especially abundant in Chesapeake Bay on the Maryland coast. There are millions of stings each year but no fatalities Prevention Bathers, especially children, should keep out of the sea at times of the year when dangerous cnidarians are prevalent, especially when warning notices are displayed; or they should bathe in 'stinger-resistant' enclosures, although these do not exclude Irukandji. Wetsuits or Lycra garments, nylon stockings, and other clothing will protect against nematocyst stings. Clinical features Immediate severe pain is the commonest symptom. Nematocyst stings may leave a diagnostic pattern on the skin: C. fleckeri produces wide, striated brownish-purple weals (Fig. 10.4.2.34), whereas Carukia barnesi causes a transient erythematous macule, and the Portuguese man-o'-war (genus Physalia) produces chains of oval weals surrounded by erythema. Chirodropids (genera Chironex and Chiropsalmus) cause the most severe systemic symptoms— respiratory arrest, generalized convulsions, pulmonary oedema,

 and cardiac arrest within minutes of the accident. Other systemic effects include cough, nausea, vomiting, abdominal colic, diar- rhoea, rigors, severe musculoskeletal pains, and profuse sweating. 'Irukandji syndrome' consists of severe musculoskeletal pain, anx- iety, trembling, headache, piloerection, sweating, tachycardia, hypertension, and pulmonary oedema starting about 30 min after a sting by C. barnesi (and by other species of tiny cubomedusoids) and persisting for hours. Physalia species can also cause severe sys- temic envenoming, including intravascular haemolysis, peripheral gangrene, and acute kidney injury. Treatment Victims of box jellyfish stings may die within minutes and so first aid is urgent. The victim is taken out of the water to prevent drowning, adherent tentacles are washed off with sea water or removed by shaving the skin and hot water is applied to relieve pain as for fish stings (see earlier). Undischarged nematocysts in adherent tentacles should be inhibited. For Chironex and other cubozoans, including Irukandji, commercial vinegar or 3–10% aqueous acetic acid may inhibit further nematocysts discharge, although this has become controversial, but is not recommended for stings by Physalia or Stomolophus. For Chrysaora stings, baking soda and water (50% w/ v) is used. In vitro, several popular remedies, such as alcohol (in sun lotion), ammonia, acetic acid, and meat tenderizer, caused massive discharge of Chrysaora quinquecirrha and Physalia physalis tent- acles. However, 5–15% lignocaine hydrochloride prevented dis- charge and relieved the pain of Chiropsalmus quadrumanus and Chrysaora quinquecirrha stings, in proportion to the concentra- tion applied. Pressure-immobilization with a crepe bandage may increase the amount of venom injected and is not recommended. Cardiopulmonary resuscitation has proved life-saving in several Australian patients stung by C. fleckeri who became cyanosed, co- matose, and pulseless. A specific 'sea wasp' antivenom for C. fleckeri is manufactured in Australia but its efficacy is being questioned. Treatment with verapamil is not recommended. Starfish and sea urchins (Echinodermata) These animals are

protected by hard exoskeletons with numerous long, sharp projecting spines (Fig. 10.4.2.35) and grapples (globiferous pedicellariae), which can release venom and a violet- coloured liquid when embedded in the skin. Severe pain and local swelling may result, and sometimes systemic effects such as syn- cope, numbness, generalized paralysis, aphonia, respiratory dis- tress, cardiac arrhythmias, and even death. Embedded fragments of spines may penetrate bones and joints and lead to secondary infection and chronic granulomas. Treatment Hot water (see earlier paragraphs) may relieve the pain. Skin penetrated by the spines, usually the soles of the feet, should be softened with 2% salicylic acid ointment or acetone. An attempt should then be made to squeeze out the spines or removed them surgically but this may prove difficult. No antivenoms are avail- able. There is a risk of marine bacterial infections (see earlier paragraphs). Cone shells and octopuses (Mollusca) The 500 species of cone shells (genus Conus) are carnivorous marine snails that harpoon their prey (fish, polychaete worms, and other molluscs), implanting a radular tooth charged with venom containing a mixture of small (10–30 amino acid) peptide toxins (Fig. 10.4.2.36), conotoxins, that block acetylcholine recep- tors and voltage-sensitive calcium and sodium ion channels. Cone shells are attractive and valuable collectors' items, but col- lectors may be stung. Symptoms of envenoming include nausea, vomiting, paraesthesia, and numbness of the lips and site of sting, numbness, dizziness, ptosis, diplopia, dysarthria, dyspnoea, and loss of consciousness. In a series of 35 cases mostly stung by Conus geographus reported in Japan (1896–1996), 10 died within 2 to 5 h of the sting. Several species of small octopus found in the Australian and West Pacific region (blue-ringed octopuses, Hapalochlaena spp.) Fig. 10.4.2.35 Black long-spined sea urchin Diadema setosum (Diadematidae) with spines 35 cm long, Madang, Papua New Guinea. Copyright D. A. Warrell. Fig. 10.4.2.34 Extensive weals from contact with the stinging tentacles of the box jellyfish Chironex fleckeri in an Australian stung in Darwin. By courtesy of Drs B. Currie and P. Nitschke.

 (Fig. 10.4.2.37) inject salivary tetrodotoxin when they bite swimmers with their powerful beaks. Bites are painful and cause local bleeding, swelling, and inflammation. Severe neurotoxic symptoms, and even fatal generalized paralysis, may develop within 15 min of the bite. Treatment No antivenoms are available. Cardiopulmonary resuscitation and mechanical ventilation may be required. Venomous arthropods Bees, wasps, yellowjackets, hornets,
and ants (Hymenoptera) The most frequent and severe hymenoptera stings are inflicted by members of the families Apidae (honey bees Apis mellifera, A. cerania, A. dorsata, and so on, and bumble bees Bombus spp.), Vespidae (wasps, yellow jackets, white-faced 'hornets', paper wasps genera Vespula, Dolichovespula, Polistes, and true hornets genus Vespa) (Fig. 10.4.2.38), and Formicidae (American fire ants genus Solenopsis, Australian bull or bulldog ants genus Myrmecia). Allergic reactions to single stings from hymenoptera are common, whereas envenoming resulting from many stings is rare. Venom allergens in- clude phospholipases A, hyaluronidase, acid phosphomonoesterases, and polypeptide neurotoxins such as apamin and melittin (A. mel- lifera). Nonallergenic compounds include vasoactive amines, such as histamine, 5-hydroxytryptamine, catecholamines and kinins, cholinesterase (in the venom of Vespula germanica), pheromones, 2-methylpiperidine alkaloids (in venoms Solenopsis), and anti- inflammatory peptides from honey bee venom. Epidemiology Each year, fewer than five people die from identified hymenopteran sting anaphylaxis in England and Wales, 2–3 per year in Australia, and 40–50 in the United States. The incidence of systemic reactions to stings by hymenoptera has been reported as 0.4 to 0.8% in chil- dren. In one adult population in the United States, the prevalence of systemic allergic sting

reactions was found to be 4%; 20% of this population showed evidence of venom hypersensitivity (skin tests or radioallergosorbent test, RAST). In the United Kingdom, most patients allergic to bee venom are beekeepers or their relatives. Since the escape of swarms of African honey bees A. m. scutellata in Brazil, in 1957, this aggressive strain has spread throughout Latin America and north as far as Las Vegas in the United States. About 30 deaths from mass attacks by these bees have been reported each year. Two species of fire ants, Solenopsis richteri and S. invicta, were imported into the United States from South America in 1918 and have now spread to 13 southern states where an estimated 2.5 million people are stung each month. The incidence of systemic allergic re- actions is about 4 per 100 000 population per year, and there have Fig. 10.4.2.37 Southern/lesser blue-ringed octopus Hapalochlaena maculosa, Point York, Southern Australia. Copyright D. A. Warrell. Fig. 10.4.2.38 Stinger of European wasp Vespula vulgaris. Copyright D. A. Warrell. (a) (b) Fig. 10.4.2.36 Cone shell Conus bullatus harpooning and then ingesting a small fish. Copyright D. A. Warrell.

 been fatalities. In Tasmania and southern Australia, the jack jumper ant Myrmecia pilosula causes 90% of all ant stings. About 2–3% of the population are hypersensitive, and there have been deaths from anaphylaxis. Prevention Patients who have a history of systemic anaphylaxis following a sting and who have evidence of hypersensitivity to the venom of the same family of hymenoptera (venom-specific IgE detect- able in the serum or a positive skin test) should be considered for desensitization with purified venoms. This treatment proved significantly more effective than placebo or the previously used whole-body extracts of hymenoptera in preventing anaphylactic reactions to sting challenge. Desensitization usually involves weekly visits to hospital for at least 8 weeks for the administra- tion of gradually increasing doses of venom. When protection has been demonstrated by the patient's ability to tolerate 100 µg of venom (equivalent to two stings) they are ready for maintenance therapy, usually 100 µg of venom every 4–8 weeks. A period of 2–5 years of maintenance desensitization is recommended, after which more than 90% of subjects will remain protected against systemic reactions after stopping treatment. Desensitization is complicated by systemic reactions in 5–15% of patients and by local reactions in 50%. Wasps are attracted by sweet things and meat in kitchens, green- grocers' shops, orchards, vineyards, brightly coloured floral pat- terns, and perfumes. Hornets are attracted by light. Some hornets (e.g. Asian Vespa mandarina) are so aggressive that their nests must be eradicated before the area can be farmed. The risk of mass attacks by apids and vespids can be reduced by vigilance. Observing increasing numbers of vespids can lead to discovery and destruction of their nests. Attacks on farm animals and a ten- dency for bees to pursue apiarists walking away from the hives are signs of an increasingly aggressive colony, prompting replacement of the queens. Clinical features Toxic effects In nonsensitized people, a sting, which, in the case of Vespidae and Apidae, introduces about 50 µg of venom, will rapidly produce a hot, red, painful swelling and weal a few centimetres in diameter, which persists for no more than a few hours. These effects are dangerous only if the airway is obstructed, following stings on the tongue. As few as 30 stings can cause fatal systemic envenoming in children, but children and adults have survived more than 1 000 stings by A. mellifera. Symptoms suggest histamine toxicity—vasodilatation, hypotension, vomiting, diarrhoea, throbbing headache, coma, and bronchoconstriction. In Latin America, victims of mass attacks by A. m. scutellata develop generalized rhabdomyolysis (grossly ele- vated serum CK, aminotransferases, and myoglobin), intravascular haemolysis, hypercatecholaminaemia (hypertension, pulmonary oedema, myocardial damage), bleeding, hepatic dysfunction, and acute

kidney injury. In nonsensitized individuals, stings from Solenopsis and Myrmecia spp. produce pain, itching, swelling, and erythema around a central weal, which last a few hours, and later vesicles or pustules. In an unsensitized patient, an estimated 10 000 S. invicta stings caused no systemic envenoming. Allergic effects: Systemic anaphylaxis Clinical suspicion of dangerous venom hypersensitivity arises when systemic symptoms follow a sting. Systemic symptoms in- clude tingling scalp; itching, initially of the palms, soles, axillae, and perineum, becoming generalized; flushing; dizziness; syncope; wheezing; abdominal colic (uterine colic in women), violent diar- rhoea, incontinence of urine and faeces; tachycardia and visual dis- turbances; all developing within a few minutes of the sting. Over the next 15–20 min, urticaria, angio-oedema of the lips, gums, and tongue, a generalized redness of the skin with swelling, oedema of the glottis, profound hypotension, and coma may develop. The median time to first cardiac arrest is 10–20 min after the sting but deaths have occurred after only 2 min. A few patients develop serum sickness a week or more after the sting. Some patients with sting allergy have other evidence of an atopic disposition. Reactions are enhanced by β-blockers. Severe local reactions to stings: a separate subset of patients who become allergic to hymenoptera venoms develop delayed and some- times massive and persistent local swelling hours or days after the sting without showing any systemic features of anaphylaxis. Such reactions, which may be progressively more severe after successive stings, do not predict increased risk of anaphylaxis. Diagnosis of anaphylaxis and venom hypersensitivity Detection of a raised mast-cell tryptase concentration is useful in confirming the diagnosis of anaphylaxis and excluding panic attacks and other causes of collapse. Serum/plasma concentrations peak 0.5–1.5 h after the attack, but persist for 6–8 h. Type I hyper- sensitivity is confirmed by detecting venom-specific (Vespidae, Apidae, Formicidae) IgE in the serum using RAST or by prick-skin tests. Among hymenoptera venoms, there is strong cross reactivity between bumble bee and honey bee venoms and between wasp, yellow-jacket, and true hornet venoms, but not between venoms of Apidae and Vespidae. Patients who have suffered a systemic re- action have a 50–60% risk of a reaction to their next sting. Local reactions, even massive ones involving persistent swelling of the whole stung limb, in the absence of systemic symptoms, do not pre- dict a systemic reaction following subsequent stings. Children who have generalized urticaria after a sting have only a 10% chance of a systemic reaction when restung. Hypersensitivity to venom may be lost spontaneously in some children and young adults but this is unpredictable and unreliable. In some countries, live insect-sting challenge is used to assess hypersensitivity and response to im- munotherapy. The RAST test can be used for a post-mortem diag- nosis of hymenoptera sting anaphylaxis. Treatment The barbed stings of Apidae remain embedded at the site of the sting and continue to inject venom, so they should be removed immedi- ately by any means possible. Vespids can withdraw their stings and sting repeatedly. Wasp stings may become infected because some species feed on rotting meat. Domestic meat tenderizer (papain) di- luted roughly 1:5 with tap water is said to produce immediate relief of pain. Ice packs and aspirin are also effective. Systemic but not topical antihistamines can be used for more severe local reactions. Massive local reactions may require aspirin, nonsteroidal anti-inflammatory agents, or even corticosteroids.

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1808 Systemic anaphylaxis First, the patient must be laid down and kept flat, ideally in the re- covery position. Immediate cardiopulmonary resuscitation may be needed. Adrenaline should be given as soon as possible: 0.1% (1:1000) (0.5–1 ml for adults; 0.01 mg/kg for children) given by intramuscular injection into the anterolateral thigh, or, if the patient is unconscious or pulseless, diluted 1:100 000, by slow intravenous injection. In rare cases, blood pressure fails to respond to even re- peated

doses of adrenaline and fluid resuscitation. These patients should be given cardiopulmonary resuscitation, selective bron- chodilators such as salbutamol, pressor agents such as dopamine, and intravenous histamine H1 blockers such as chlorphenamine maleate (10 mg for adults; 0.2 mg/kg for children). Corticosteroids probably have no effect in acute anaphylaxis, but may prevent re- lapses a few hours later. Patients who know that they are hypersen- sitive should wear an identifying tag or bracelet (such as provided by Medic-Alert or Medi-Tag in Britain) as they may be discovered unconscious after being stung. They should be trained to give them- selves adrenaline using an 'EpiPen' or similar apparatus, but a high proportion of those who carry these kits are unable to use them effectively through lack of training. Shock and upper- or lower- airway obstruction are the main modes of death following insect- sting anaphylaxis. Severe envenoming from multiple stings by hymenoptera should be treated with adrenaline, intravenous antihistamines (doses as mentioned earlier), and corticosteroids. Intensive care is essential. Intravenous fluids may protect the kidneys from the damaging ef- fects of myoglobinuria and haemoglobinaemia ('pigment neph- ropathy'), as in patients with the crush syndrome. Experimental antivenoms have been produced but are not yet commercially avail- able. Exchange transfusion or plasmapheresis might be considered to remove venom in severe cases. Renal dialysis is often needed. Butterflies and moths (Lepidoptera) The stinging hairs of some species of adult moths can cause con- tact dermatitis and urticaria ('lepidopterism'), while caterpillars can produce local or even systemic effects ('erucism'). Venomous lepidoptera are found in all parts of the world, but most cases of lepidopterism are reported from Middle and Southern America. Severe cutaneous urticating eruptions can be caused by cater- pillars of oak processionary moths Thaumetopoea processionea (Thaumetopoeidae) in central/southern Europe and of the genus Megalopyge (Megalopygidae—called 'puss caterpillars' in the southern United States) and by adult female moths of the genus Hylesia (Saturniidae), which have barbed setae ('flechettes') on their abdomens (Fig. 10.4.2.39). Epidemics of stings by these moths have been described, especially from coastal areas of Brazil, Mexico, Peru, and Venezuela. In Brazil, Colombia, Guyana, Paraguay, Peru, and Venezuela, caterpillars of atlas or emperor moths (Lonomia obliqua, L. achelous; Saturniidae) cause thousands of stings each year. A tourist died of Lonomia envenoming died a few days after returning to Canada from Peru where she had trodden on some of these caterpillars. Venom injected through their bristles con- tains fibrinolytic (factor XIII activator); anticoagulant; procoagu- lant (activators of prothrombin, factor X, factor V), kallikrein-like, metalloproteinase, and phospholipase A2 activities resulting in defibrinogenation and spontaneous bleeding. The case fatality of about 2% is usually attributable to cerebral haemorrhage. Symptoms include local burning, erythema, swelling, inflammation, head- ache, nausea, vomiting, malaise, bleeding from nose, gums, gut, genitourinary tract, and partly healed scars, polyarthralgia, and acute renal failure. Laboratory findings in envenomed patients are decreased plasma fibrinogen, factor V, factor XIII, and plasminogen concentrations, as well as increased fibrin/fibrinogen degradation products and fibrinolytic activity but a normal platelet count. An effective antivenom ('Soro antilonômico') is produced by Instituto Butantan, São Paulo, Brazil. Beetles (Coleoptera) The most notorious vesicating beetle is 'Spanish fly' Lytta vesicato- ria (Meloidae—blister beetles) whose venom contains cantharidin, which causes blistering 2–3 h after application to the skin. 'Nairobi eye' and similar blistering conditions in Australia and Southeast Asia are caused by Paederus (Staphylinidae) species 5–10 mm in length (Fig. 10.4.2.40). The typical skin lesions (dermatitis linearis), whose appearance may be delayed 12–96 h after contact, consist of erythema, itching, and blistering caused by inadvertently crushing and smearing the beetle. Systemic symptoms such as fever, arth- ralgia, and vomiting may arise in severe cases. The active principle Fig. 10.4.2.39

Lesions caused by urticating abdominal hairs of female moths Hylesia spp. in Brazil. Copyright D. A. Warrell. Fig. 10.4.2.40 Vesicating beetle Paederus crebripunctatus (Staphylinidae) responsible for causing ‘Nairobi eye’. Courtesy of Dr John Paul.

10.4.2 Injuries, envenoming, poisoning, and allergic reactions caused by animals 1809 pederin is the most complex nonproteinaceous insect toxin known. Treatment is palliative. The toxin is easily spread to other sites such as the eye by fingers. Scorpions (Scorpiones, Buthidae, Hemiscorpiidae) Species capable of inflicting fatal stings occur in North Africa and the Middle East (Androctonus, Buthus, Hemiscorpius (Fig. 10.4.2.41), Leiurus spp.) South Africa (Parabuthus spp.); India, Sri Lanka, and Nepal (Hottentotta (formerly Mesobuthus) tamulus); North, Central and South America, Trinidad and Tobago (Centruroides (Fig. 10.4.2.42), Tityus (Fig. 10.4.2.43) spp.). Scorpion toxins target Na+, K+, Ca2+, and Cl- ion channels causing direct effects and the re- lease of neurotransmitters such as acetylcholine and catecholamines. Epidemiology In Mexico, 250 000 stings with 70 deaths are reported each year, attributed to Centruroides limpidus, C. noxius, C. suffusus, and so on. Brazil recorded 91 000 scorpion stings and 121 deaths in 2016, more for snake-bites. In Khuzestan Province, Iran, 25 000 stings (Hemiscorpius lepturus, Androctonus spp., and Buthus spp.) are treated each year and are the fourth major cause of death. Algeria and Tunisia report tens of thousands of stings and hundreds of deaths. In the United States 15 000 stings, mainly by Centruroides exilicauda (Fig. 10.4.2.42) are reported in Arizona each year but deaths are rare. In Brazil, the important species are Tityus serru- latus (Fig. 10.4.2.43) and other Tityus spp. In 2005, among 36 558 reported stings, there were only 50 deaths (case fatality 0.14%). In India, many people are stung by the red scorpion Hottentotta (for- merly Mesobuthus) tamulus with fatalities in adults and children. Prevention Scorpions can be excluded from houses by incorporating a row of ceramic tiles into the base of the outside wall, making the doorsteps at least 20 cm high, and using residual insecticides, such as carba- mate or organophosphate sprays or dusts indoors. Clinical features Intense local pain is the commonest symptom. There may be slight local oedema and tender enlargement of regional lymph nodes, but stings by Hemiscorpius lepturus (Iran, Iraq, Pakistan, and Yemen) are relatively painless. Systemic symptoms usually develop within minutes but may be delayed for as much as 24 h. They vary, ac- cording to the species of scorpion involved. Most scorpion venoms stimulate the release of acetylcholine and catecholamines, often re- sulting in initial cholinergic and later adrenergic symptoms. Early symptoms include vomiting, profuse sweating, piloerection, alter- nating brady- and tachycardia, abdominal colic, diarrhoea, loss of sphincter control, and priapism. Later, severe life-threatening car- diorespiratory effects may appear: hypertension, shock, tachy- and bradyarrhythmias, ECG changes, and pulmonary oedema with or without evidence of myocardial dysfunction. Severe cardiovascular complications are particularly associated with stings by Androctonus Fig. 10.4.2.41 Hemiscorpius lepturus (Hemiscorpiidae), Iran. Courtesy of Dr M. Radmanesh. Fig. 10.4.2.42 Arizona bark scorpion Centruroides (Sculpturatus) exilicauda. Copyright D. A. Warrell. Fig. 10.4.2.43 Brazilian yellow scorpion Tityus serrulatus, São Paulo, Brazil. Scale in cm. Copyright D. A. Warrell.

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1810 spp., Leiurus quinquestriatus, Hottentotta tamulus, and Tityus spp. (Fig. 10.4.2.44). Neurotoxic effects such as erratic eye movements, fasciculation, and muscle spasms, which can be misinterpreted as tonic-clonic convulsive movements, and respiratory distress are a particular feature of stings by Centruroides (sculpturatus) exilicauda in Arizona. Parabuthus transvaalicus envenoming in southern Africa is more likely to cause ptosis and dysphagia with death from respiratory paralysis.

Hemiplegia and other neurological lesions have been attributed to fibrin deposition resulting from dissem- inated intravascular coagulation, for example, after stings by Nebo hierichonticus in the Middle East. Hypercatecholaminaemia could explain hyperglycaemia and glycosuria but in the case of stings by the black scorpion of Trinidad (Tityus trinitatis) there is severe abdominal pain with nausea, vomiting, and haematemesis, hyperglycaemia, and biochemical evi- dence of acute pancreatitis attributable to simultaneous spasm of the sphincter of Oddi and pancreatic exocrine hypersecretion. In Iran and Iraq, stings by Hemiscorpius lepturus (Hemiscorpiidae) produce a unique clinical syndrome. The sting is painless but macular erythema, pupura, and bullae develop at the site with induration in 39% of cases, swelling and necrosis that requires surgery in 20% of cases (Fig. 10.4.2.45). Systemic symptoms include dry mouth, thirst, dizziness, nausea, vomiting, fever, cardiac arrhythmias, ST depres- sion on ECG, hypoglycaemia, confusion and convulsions, leucocyt- osis, thrombocytopenia, coagulopathy, haemolytic anaemia with haemoglobinuria, proteinuria, and acute kidney injury. Twenty per cent (20%) of paediatric cases required dialysis. Early treatment with Rhazi Institute antivenom proved effective. Treatment Pain responds to local infiltration or ring block with local anaes- thetic. Parenteral opiate analgesics, such as pethidine or morphine, may be required, but are said to be dangerous in victims of C. exil- icauda (sculpturatus). Antivenom is recommended. In a recent trial in children stung by C. sculpturatus in Arizona, antivenom treatment was associated with more rapid resolution of symptoms and less requirement for midazolam sedation than placebo. In India, two studies found that addition of a new antivenom raised against H. tamulus concanensis venom produced more rapid recovery than prazosin alone. Antivenom should be administered intravenously as soon as possible in patients with systemic envenoming and in young children stung by dangerous species, even before the development of these symptoms. For patients with cardiovascular symptoms (hypertension, bradycardia, and early pulmonary oedema), vasodilators such as the α1-blocker prazosin are recommended. Patients who develop left ventricular failure despite early prazosin therapy benefit from dobutamine. The use of atropine (except in cases of life-threatening sinus bradycardia), cardiac glyco- sides and β-blockers is not recommended. Spiders (Araneae) All but one family of this enormous order are venomous, but only about 20 species have proved dangerous to humans. Many others have been wrongly accused of inflicting harmful bites. Spiders bite with a pair of small fangs, the chelicerae, to which the venom glands are connected. Medically important genera include Loxosceles, causing necrotic araneism, and Latrodectus, Phoneutria, Atrax, Hadronyche, and Missulena spp., causing neurotoxic araneism. Epidemiology Spider bites are common in some parts of the world but there are now few fatalities. In Brazil in 2016 there were 29 000 spider bites with 22 fatalities. In Central and South America, Loxosceles spp. such as L. laeta and L. gaucho (Fig. 10.4.2.46) are widely distributed and cause many bites. In Chile, the case fatality of loxoscelism ranges from 1 to 17%. In the southern and south-central United States, the brown recluse spider L. reclusa caused at least 200 bites and six deaths during the last century. Bites by L. rufescens have been re- ported in the Mediterranean region, North Africa, and Israel. Most bites from Loxosceles spp. occur in bedrooms while people are asleep or dressing. Fig. 10.4.2.44 Twenty-six-day-old child stung on right axilla by a Brazilian yellow scorpion (Tityus serrulatus) in urban São Paulo: showing agitation and pulmonary oedema. Copyright D. A. Warrell. (a) (b) Fig. 10.4.2.45 (a) Local swelling, blistering, and ‘purpuric plaque’ caused by the sting of Hemiscorpius lepturus in Iran. (b) Progressing to necrosis with granulation tissue. Courtesy of Dr M Radmanesh.

 Black and brown widow spiders are cosmopolitan in distribu- tion. Latrodectus tredecemguttatus (sometimes

referred to, loosely, as ‘tarantula’) lives in fields in Mediterranean countries and has been responsible for epidemics of bites. The Australian redback spider (L. hasselti) (Fig. 10.4.2.47) causes up to 340 bites each year in Australia; 20 deaths have been reported. It has colonized parts of Japan, New Zealand, UAE, and New Caledonia. In the United States, L. mactans was responsible for 63 deaths between 1950 and 1959. Several species of Latrodectus occur in Latin America (Fig. 10.4.2.48). Wandering, armed, or banana spiders Phoneutria spp. (Fig. 10.4.2.49), cause bites and a few deaths in Latin American coun- tries. They have been imported into temperate countries in bunches of bananas, causing a few bites and deaths. Highly dangerous funnel web spiders Atrax spp. are restricted to south-eastern Australia and Tasmania. The Sydney funnel web spider (A. robustus) is found only within a 160-mile (256-km) ra- dius of Sydney. The aggressive males caused at least 13 deaths be- tween 1927 and 1980. Members of the related genera Hadronyche and Missulena may be equally dangerous. In England, mild neurotoxic araneism has been described after bites by Steatoda nobilis and S. grossa (Theridiidae) and the wood- louse spider Dysdera crocata. Necrotic araneism Skin lesions, varying in severity from mild localized erythema and blis- tering to extensive granulomas and tissue necrosis, have been falsely attributed to a large variety of familiar peridomestic species, such as the Australian white-tailed spider Lampona cylindrata, North American hobo spider Tegenaria agrestis, European and South American wolf spiders Lycosa spp. (including the Italian ‘tarantula’ L. terentula), and cosmopolitan sac spiders Cheiracanthium spp. However, only mem- bers of the genus Loxosceles have proved capable of causing ‘necrotic Fig. 10.4.2.46 South American recluse spider Loxosceles laeta, Brazil. Copyright D. A. Warrell. Fig. 10.4.2.47 Australian redback spider Latrodectus hasselti, Adelaide, showing the dorsal red hourglass marking. Copyright D. A. Warrell. Fig. 10.4.2.48 Curaçao black widow spider Latrodectus curacaviensis, Brazil. Copyright D. A. Warrell. Fig. 10.4.2.49 Brazilian armed, wandering, or banana spider Phoneutria nigriventer. Copyright D. A. Warrell.

arachnidism/araneism’. Venom sphingomyelinase D is implicated in the pathogenesis of dermonecrosis. Neutrophils adhere to the endo- thelium of cutaneous capillaries and degranulate. The bite itself is usually painless and unnoticed. Burning develops over several hours at the site of the bite, with swelling and development of a character- istic macular lesion, the red-white-and-blue sign (Fig. 10.4.2.50) showing areas of red vasodilatation, white vasoconstriction, and blue prenecrotic cyanosis. A blackened eschar develops, which sloughs in a few weeks, leaving a full thickness necrotic ulcer. Sometimes an entire limb or area of the face is involved. Facial bites cause much swelling. Some 13% of cases have systemic symptoms such as fever, headaches, scarlatiniform rash (Fig. 10.4.2.51), jaundice, methaemoglobinaemia, and haemoglobinuria resulting from intravascular haemolysis. Renal failure may ensue. The average case fatality is about 5%. Neurotoxic araneism The bite is very painful immediately, but local signs are minimal (L. mactans) or moderate (L. hasselti). After about 30 min, there is painful regional lymphadenopathy, then headache, nausea, vomiting, and local sweating with piloerection (‘gooseflesh’, ‘goose bumps’), a sign highly suggestive of neurotoxic araneism (Fig. 10.4.2.52). Envenoming by L. mactans and L. tredecemguttatus, causes profuse generalized sweating and fever with painful muscle spasms, tremors, and rigidity. This may be sufficiently severe to embarrass respiration. The classic ‘facies latrodectismica’ is an agonized grimace, caused by facial spasm and trismus, associated with swollen eyelids, congested conjunctivae, flushing, and sweating (Fig. 10.4.2.53). Abdominal rigidity may simulate an acute abdomen and prompt laparotomy. Fig. 10.4.2.50 ‘Red-white-and-blue’ sign developing 18 h after a bite by the Brazilian

recluse spider Loxosceles gaucho. Copyright D. A. Warrell. Fig. 10.4.2.51 Blanching generalized scarlatiniform rash appearing 3 days after a bite above the left hip by a Brazilian recluse spider Loxosceles gaucho. By courtesy of Dr João Luiz Costa Cardoso. Fig. 10.4.2.52 Intense local sweating and piloerection at the site of a Brazilian banana spider bite Phoneutria nigriventer 30 min earlier. Copyright D. A. Warrell. Fig. 10.4.2.53 ‘Facies latrodectismica’ with profuse sweating and painful muscle spasms, persisting 24 h after a bite by Latrodectus mactans (‘viuda negra’, black widow) near Cusco, Peru. Copyright D. A. Warrell.

10.4.2 Injuries, envenoming, poisoning, and allergic reactions caused by animals 1813 Other features include tachycardia, hypertension, restlessness, irrit- ability, psychosis, priapism, and rhabdomyolysis. A localized or dif- fuse rash may appear several days later. Envenoming by Phoneutria and Atrax spp. produces similar features. Treatment First aid In Australia, pressure-immobilization (see Fig. 10.4.2.26) is recom- mended for bites by A. robustus and Hadronyche species. Specific treatment Antivenoms for envenoming by Latrodectus spp. are made in Australia, Mexico, South Africa, Brazil, and some other South American coun- tries; for Atrax spp. in Australia; for Loxosceles spp. in Argentina, Brazil, and Peru; and for Phoneutria spp. in Brazil. Despite decades of use, there is no decisive evidence for the efficacy of Loxosceles antivenoms, but neurotoxic araneism is more obviously responsive to antivenom. Supportive treatment Oral dapsone (100 mg twice daily) is said to reduce the extent of necrotic lesions by inhibiting neutrophil degranulation and calcium gluconate (10 ml of a 10% solution, given by slow intravenous in- jection) is said to relieve the pain of muscle spasms caused by the venom of Latrodectus spp. rapidly and more effectively than muscle relaxants such as diazepam or methocarbamol. Evidence for the efficacy of these drugs is lacking. Antihistamines, corticosteroids, α-blockers, and atropine have also been advocated. For necrotic araneism caused by Loxosceles spp., early surgical debridement, corticosteroids, antihistamines, and hyperbaric oxygen all have their advocates, but there is no basis for recommending their use. Ticks (Acari) Taxonomy and epidemiology Ticks, with mites, form the order Acari of the class Arachnida. Adult females of about 34 species of hard tick (family Ixodidae) and imma- ture specimens of nine species of soft ticks (family Argasidae) have been implicated in human tick paralysis. The tick’s saliva contains a neurotoxin, which causes presynaptic neuromuscular block and decreased nerve-conduction velocity. The tick embeds itself in the skin with its barbed hypostome introducing the salivary toxin while it engorges with blood. Although tick paralysis has been reported from all continents, including Europe, most cases occur in western North America (Dermacentor andersoni), eastern United States (D. variabilis), and eastern Australia from north Queensland to Victoria (Ixodes holocyclus—known as the bush-, scrub-, paralysis-, or dog-tick). In British Columbia there were 305 cases with a 10% case fatality be- tween 1900 and 1968. About 120 cases have been reported in the United States, and in New South Wales there were at least 20 deaths between 1900 and 1945. Clinical features Ticks are picked up in the countryside or from domestic animals, particularly dogs, in the home. Aalmost all fatal cases are children. After the tick has been attached for about 5 or 6 days a progressive ascending lower motor neurone paralysis develops with paraesthe- siae. Often a child, who may have been irritable for the previous 24 h, falls on getting out of bed first thing in the morning and is found to be weak or ataxic. Paralysis increases over the next few days: death results from bulbar and respiratory paralysis and aspiration of stomach contents. Vomiting is a feature of the more acute course of Ixodes holocyclus envenoming. This clinical picture has often been misinterpreted as poliomyel- itis. Other neurological conditions, including Guillain–Barré syn- drome, paralytic rabies, Eaton–Lambert syndrome, myasthenia gravis, or

botulism, may also be suspected. Diagnosis and cure depends on finding the tick, which is likely to be concealed in a crevice, orifice, or hairy area of the body. The scalp is the commonest place. Fatal tick paralysis has been caused by a tick attached to the tympanic membrane. Treatment The tick must be discovered and detached without being squeezed. It can be painted with ether, chloroform, paraffin, petrol, or turpen- tine, or prised out between the partially separated tips of a pair of small, curved forceps. Following removal of the tick there is usu- ally a rapid and complete recovery; but in Australia, patients have died even after the tick had been detached. The antivenoms, raised in dogs and rabbits in Australia, are no longer produced. Centipedes and millipedes (subphylum Myriapoda) Centipedes (class Chilopoda) Epimorph centipedes have 15–191 pairs of legs and move rapidly and distractedly. They occur in most parts of the world including the Arctic Circle. The largest, Scolopendra gigantea of South America, can grow to more than 30 cm in length. Many species can inflict painful stings through a pair of modified claws (forcipules) on the postcephalic segment (Fig. 10.4.2.54). More than 3000 stings are (a) (b) Fig. 10.4.2.54 (a) Thai centipede (Scolopendra dehaani) (b) showing venom ‘claws’ or forcipules which are modified limbs. Copyright D. A. Warrell.

 reported each year in Brazil. Venoms contain serotonin, histamine, lipids, polysaccharides, proteases, and peptides that are neurotoxic to insects. Stings cause intense radiating pain, swelling, inflamma- tion, erythema, and lymphangitis, and sometimes local necrosis. Systemic effects such as vomiting, sweating, headache, cardiac ar- rhythmias, myocardial ischaemia, rhabdomyolysis, proteinuria, acute renal failure, and convulsions are extremely rare. The risk of mortality was probably greatly exaggerated in the older literature. Hypersensitivity may have played a role in these reactions. Reports of documented fatalities remain elusive but are said to occur on some Indian Ocean islands. The most important genus is Scolopendra which is distributed throughout tropical countries. Local treatment is the same as for scorpion stings. No antivenom is available. Millipedes (class Diplopida) Millipedes are widely distributed. They may exceed 35 cm in length, have hundreds of legs (not a thousand, despite their name), move sluggishly, and tend to coil into a ball. Most species possess glands in each of their body segments which secrete, and in some cases squirt out, irritant liquids for defence. These contain hydrogen cyanide and a variety of aldehydes, esters, phenols, and quinonoids. Members of at least eight genera of millipedes have proved injurious to humans, including Rhinocricus (Caribbean), Spirobolus (Tanzania and Papua New Guinea), Spirostreptus and Iulus (Indonesia), and Polyceroconas (Salpidobolus) (Papua New Guinea). Children are at risk when they handle or try to eat these large arthropods. When venom is squirted into the eye, intense conjunctivitis results, and there may be corneal ulceration and, allegedly, blindness. Skin lesions initially stain brown (‘mahogany stains’) or purple, blister after a few days, and then peel (Fig. 10.4.2.55). They have been mistaken for signs of child abuse. First aid is generous irrigation with water. Eye injuries should be treated as for snake venom ophthalmia (see earlier in this chapter). Leeches (phylum Annelida, class Hirudinea) Leeches are bloodsucking, hermaphroditic, egg-laying annelids, which have elongated annulated bodies. They attach themselves to leaves, rocks, or the host by a posterior sucker. To feed, the leech applies its anterior sucker containing the mouth armed with three radially arranged jaws which make a Y-shaped incision. Blood is sucked out by the action of the muscular pharynx. To prevent blood clotting, the saliva contains a histamine-like vasodilator and anticoagulants, such as: hirudin from the medicinal leech Hirudo medicinalis, which inhibits thrombin and factor IXa; hementin from Haementeria ghilianii, which is directly fibrinolytic; and hementerin from H. depressa (= H. lutzi), a

plasminogen activator. Other en- zymes include esterases, antitrypsin, antiplasmin, and antielastase. Recombinant hirudin is now produced as a therapeutic anticoagu- lant. The medicinal leech is still used by plastic surgeons to reduce haematomas under skin grafts; the wound may become infected with Aeromonas hydrophila, which lives symbiotically in the leech's gut. Two groups of leeches cause human morbidity and even mortality in tropical countries. Land leeches Species of the genera Haemadipsa and Phyrobdella are 1–8 cm long. They infest, often in enormous numbers, the damp leaf litter and low vegetation of rainforests, choosing game trails and watering places. By standing on the posterior sucker and waving the anterior sucker, they can sense their prey with amazing efficiency. They drop on to the prey or pursue it with a looping or lashing motion. Leeches usually attach themselves to the lower legs or ankles and are adept at penetrating clothing, even long trousers tucked into socks and lace-up boots. The bite is usually painless and infested individuals may not realize what has happened until they hear a squelching sound, notice that their feet are warm and wet, and see blood welling over the tops of their boots. Land leeches ingest about 1 ml of blood in 1 h and then drop off, but the wound continues to bleed for some time and forms a fragile clot. Aquatic leeches These species may be swallowed by individuals who drink stagnant water or even mountain stream water, or they may attack bathers, entering the mouth, nostrils, eyes, vulva, vagina, urethra, or anus. Hirudo medicinalis can ingest 5–15 ml of blood, increasing its initial weight up to 10 times. The enormous brightly coloured buffalo leech Hirudinaria manillensis of Southeast Asia, is up to 16 cm long and can ingest 1 ml of blood in 10 min. Limnatis nilotica occurs around (a) (b) Fig. 10.4.2.55 Skin and mucosal lesions (a) caused by application of giant Papua New Guinea millipede (b) (Spirobolus vogesi). Copyright Dr Bernie Hudson.

 the Mediterranean, Middle East, and North Africa. Myxobdella af- ricana occurs in East Africa. Dinobdella ferox (5 cm long) is found in Asia. Some aquatic leeches are very slow feeders and may remain attached for days or even weeks. L. nilotica and D. ferox have been implicated in 'halzoun'. However, in Lebanon, leech infestation con- tracted from spring water ('alack') is distinguished from 'halzoun' following ingestion of raw offal (see Section 7 Infectious Diseases). Prevention Leech intrusion can be reduced by impregnating clothing, especially the bottoms of trousers and socks, with repellents such as dibutyl phthalate and diethyl toluamide and applying them to the skin and the inside and outside of footwear. If these compounds are not avail- able, invasion of footwear during jungle walks can be prevented, ra- ther messily, by rolling a rope of tobacco in the tops of the socks and keeping the feet well soaked with water or using an aqueous ex- tract of tobacco leaves. Women's pantyhose are said to prevent leech attachment, but may be damaged by DEET-containing repellents. Effective leech-proof light cotton socks are available commercially. Children should be discouraged from bathing in leech-infested waters and all drinking water should be boiled or filtered. Clinical features The main effect is blood loss, but other symptoms include pain caused by the bite, secondary infection, a residual itching, and phobia. Ingested aquatic leeches usually attach to the pharynx but may penetrate the bronchi or oesophagus. H. manillensis entering via the anus can reach the rectosigmoid junction of the bowel causing perforation and periton- itis. Patients with a leech in the pharynx often have a feeling of movement at the back of the throat with cough, hoarseness, stridor, breathlessness, epistaxis, haemoptysis, and haematemesis. Fatal upper airway obstruc- tion may result. The leech Limnatis nilotica is no longer thought to be a cause of 'halzoun' (Lebanon) or 'marrara' (Sudan) (see Chapter 8.13 on pentastomiasis) but aquatic leech infestation could be a differential diag- nosis of those dramatic

syndromes of pharyngeal obstruction. Bleeding may persist for up to a week after the leech has dropped off. In rural Thailand, vaginal bleeding in girls who have swum in ponds or canals is often attributable to infestation by aquatic leeches. Sexual abuse may be wrongly inferred if this diagnosis is not considered. Transmission of rinderpest and other viruses, leptospirosis, and Trypanosoma cruzi has been suggested but not proved. Secondary infection of medicinal leech bites by Aeromonas hydrophila has been described. Treatment Leeches are best scraped off with a fingernail. Traditional methods such as applying a grain of salt, a lighted match or a cigarette, alcohol, turpentine, or vinegar make the leech regurgitate into the wound, creating a risk of infection. Local bleeding can be stopped by applying a styptic, such as silver nitrate or a firm dressing. Aquatic leeches that have penetrated the respiratory, upper gastro- intestinal, genitourinary tracts, or rectum must be removed by endoscope. Spraying with 30% cocaine, 10% tartaric acid, or di- lute (1:10 000) adrenaline makes the leech detach from the naso- pharynx, larynx, trachea, or oesophagus, while irrigation with a concentrated salt solution may be effective in the genitourinary tract and rectum. Leeches should not be pulled off so roughly that the mouth parts are left in the wound as this will lead to a chronic infection. Antimicrobial treatment of secondary bacterial infec- tions (e.g. of Aeromonas hydrophila with cefuroxime or a quin- olone) may be required. FURTHER READING Mechanical injuries caused by animals Auerbach PS (ed) (2016). Wilderness medicine, 7th edition. Mosby Elsevier, Philadelphia, PA. Packer C, et al. (2011). Fear of darkness, the full moon and the noc- turnal ecology of African lions. Plos One, 6, e22285. Spotte S (2002). Candirú: life and legend of the bloodsucking catfish. Creative Arts Books Company, Berkeley, CA. Woodroffe R, Thirgood S, Rabinowitz A (eds) (2005). People and wildlife: conflict or coexistence? Cambridge University Press, Cambridge. Websites Polar bears: http://kho.unis.no/doc/Polar_bears_Svalbard.pdf Shark attacks: http://www.flmnh.ufl.edu/fish/Sharks/ISAF/ISAF.htm Venomous mammals Madani G, Nekaris KA (2014). Anaphylactic shock following the bite of a wild Kayan slow loris (Nycticebus kayan): implications for slow loris conservation. J Venom Anim Toxins Incl Trop Dis, 20, 43. Whittington CM, et al. (2008). Defensins and the convergent evolution of platypus and reptile venom genes. Genome Res, 18, 986–94. Venomous snakes de Silva HA, et al. (2011). Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: a randomised, double-blind, placebo- controlled trial. PLoS Med, 8, e1000435. Gutiérrez JM, et al. (2017). Snakebite envenoming. Nat Rev Dis Primers, 3, 17063. Meier J, White J (eds) (1995). Handbook of clinical toxicology of animal venoms and poisons. CRC Press, Boca Raton, FL. Mohapatra B, et al. (2011). Snakebite mortality in India: a nationally representative mortality survey. PLoS Negl Trop Dis, 5, e1018. Sutherland SK, Tibballs J (2001). Australian animal toxins: the crea- tures, their toxins and care of the poisoned patient, 2nd edition. Oxford University Press, Melbourne. Warrell DA (2004). Epidemiology, clinical features and management of snakebites in Central and South America. In: Campbell J, Lamar WW, Greene H (eds) Venomous reptiles of the Americas, 2nd edition, pp. 709–61. Cornell University Press, Ithaca, NY. Warrell DA (2010). Snake bite. Lancet, 375, 77–88. Weinstein SA, et al. (eds) (2011). 'Venomous' bites from non-venomous snakes: a critical analysis of risk and management of 'colubrid' snake bites. Elsevier, London. White J (2013). A clinician's guide to Australian venomous bites and stings. CSL, Parkville. Websites Antivenoms World Health Organization (WHO) 2018 Guidelines: http:// www.who. int/bloodproducts/snake_antivenoms/snakeantivenomguide/en/ Envenoming worldwide http://www.toxinology.com/ http://www.vapaguide.info/ Snakebite in South and South East Asia (WHO SEARO 2016 Guidelines), 2nd edition: http://apps.who.int/iris/handle/10665/249547 Snakebite in Africa (WHO AFRO 2010

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