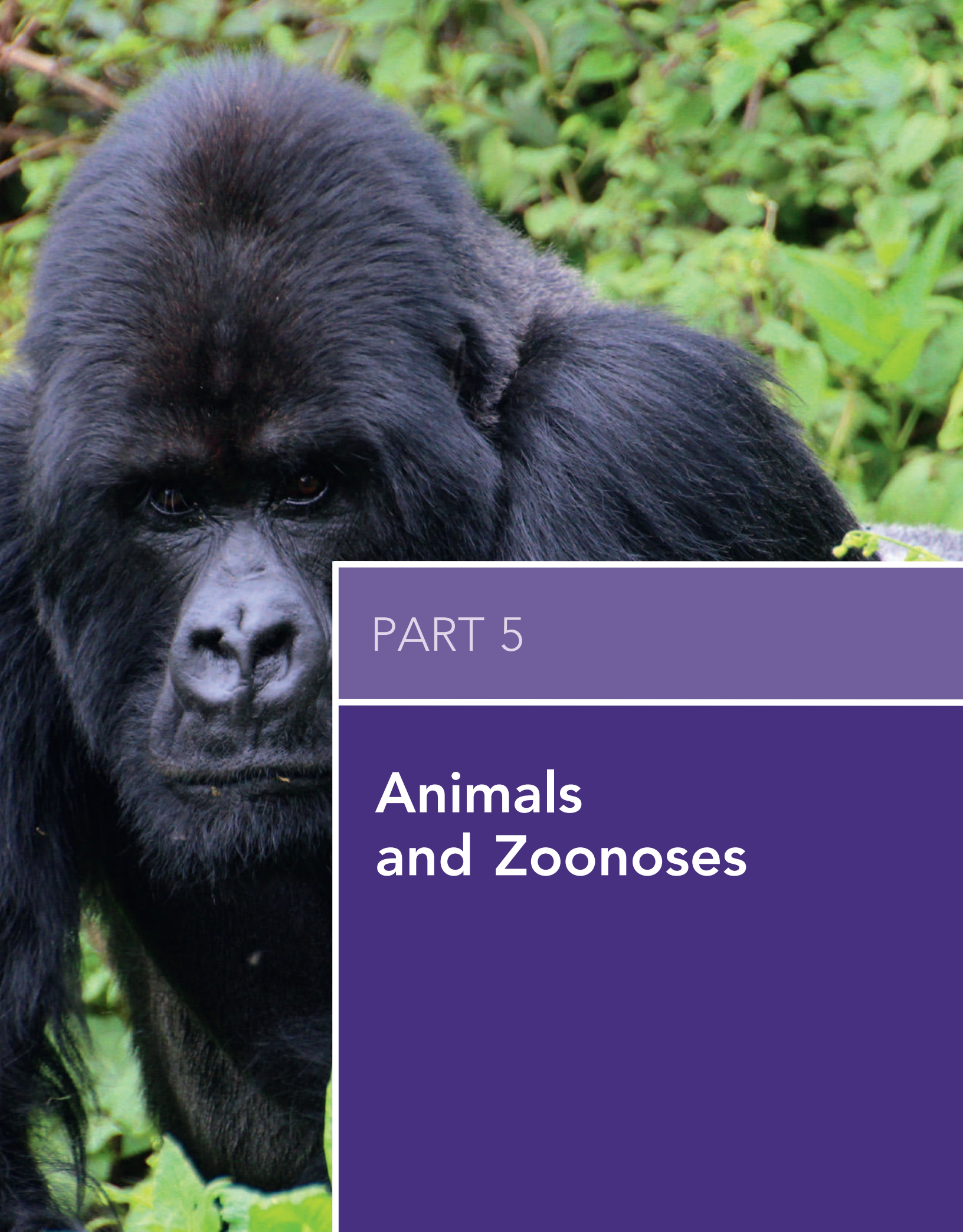

PART 5

Animals and Zoonoses

CHAPTER 30

Bites and Injuries Inflicted by Wild and Domestic Animals

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Wild and domestic animal bites are distinct from other injuries sustained by humans. Tearing, cutting, and crushing injuries may be combined with blunt trauma caused by falls or spinal injuries from thrashing. Animal bites may introduce environmental bacteria from numerous sources and cause local infection. Few traumatic lacerations are as regularly contaminated with as broad a variety of pathogens as are animal bites.

Care of patients presenting with animal bites and injuries requires considerations different from those of more routine traumatic events. Animal bites may transmit systemic diseases, many of which might cause substantial morbidity and mortality (zoonoses; see Chapter 34). Victims may develop posttraumatic sequelae from the encounter. Unfortunately, treatment decisions are often made without a strong scientific basis. Management recommendations for patients with wild animal injuries are often derived from a more robust experience with domestic animal attacks (i.e., dog and cat bites).

Domestic animal bites are common, and their incidence is rising.[48,246,367] Data for wild animal attacks are less robust, although the events themselves are often more dramatic and widely covered by the media. In the developed world, injuries from domestic animals have a much greater health and economic impact. Humans are not a preferred natural prey for any animal, and although some attacks are predatory, most attacks are caused by fear of humans (real or perceived), territoriality, protective instinct, or accident. Unfortunately, wild animal attacks are often sensationalized by the lay press. Media may represent animals as having anthropomorphic characteristics that do not accurately reflect their natural instinctive responses. This sometimes leads to misunderstanding animal behavior. Improperly informed readers are often misled into believing that wild animal attacks are both common and much less more likely to cause injury than attacks from their domestic counterparts.

As human settlements and populations continue to grow and encroach on nonurban territory, the incidence of human–wild animal encounters will increase. Thrill-seeking individuals may seek out animal encounters that historically would have been avoided. One hundred years ago, a wolf sighting in Yellowstone National Park would have been cause for alarm, yet today people travel there to see wolves in the wild and hope to approach them close enough to take pictures. Increased pressure of human proximity to animals increases the likelihood of an encounter resulting in a negative outcome (Figure 30-1).[45] It is important to note that animal-caused injuries are usually preventable. When experience allows humans to understand the typical behavior of a species, people can take proper precautions near potentially dangerous animals. For instance, when an animal attacks to defend itself or its territory, it is likely to cease this behavior when the person retreats and the perceived threat is diminished. Avoid animals with young offspring nearby or in the act of feeding. During a predatory attack, the intent of the animal is to kill and not allow its prey to escape. Understanding how to react in this situation decreases the potential for a disastrous outcome. This chapter interprets the present state of knowledge and makes logical and specific recommendations for these and other situations.

GENERAL EPIDEMIOLOGY

In the United States from 2001 to 2005, there were 472,760 reports by poison control centers of animal bites and stings, an average of 94,552 reports annually.[248] According to the 2012 *U.S. Pet Ownership and Demographics Sourcebook,* there were approximately 70 million pet dogs and 74.1 million pet cats in the United States.[14] There are 4.7 million dog bites per year in the United States. Cat bites are six times less likely to occur than dog bites. Medically attended dog bites are 3.2 times more common in children than in adults.[351]

Most recent studies derive data from U.S. emergency departments (EDs), which can play an integral role in maintaining animal bite surveillance.[56] Nationwide, data from the 2008 Healthcare Cost and Utilization Project revealed that there were 316,200 ED visits for dog bites, averaging 866 ED visits per day.[250] ED surveillance data from 2008 to 2010 analyzed records of 38,971 animal bite–related visits in North Carolina. By age 10 years, a child in North Carolina had a 1 in 50 risk of dog bite necessitating an ED visit. Incidence rates for dog bites were highest for children 14 years or younger. Rabies postexposure prophylaxis (PEP) was administered during 1664 of 38,971 (4.3%) of these visits.[346]

In Pennsylvania in 1995, county health officials reported 16,000 animal bites, 75% of which were dog related; the highest incidence of dog bites was among children younger than 5 years. Three-quarters of patients injured received wound treatment, and one-half received antimicrobials. Rabies PEP was prescribed for attacks by species as follows: 44% for cats, 30% for dogs, 7% for raccoons, 4% for bats, 2.5% for squirrels, 2.1% for groundhogs, 2% for foxes, and 8% for all other species.[288] Pittsburgh, Pennsylvania alone reported 790 dog bites, and an estimated 1388 went unreported; the annual incidence was 58.9 bites per 10,000 individuals.[93]

Dog bites constitute the majority of animal-related injuries to travelers. The distribution of injuries was examined using the GeoSentinel Surveillance Network between 1998 and 2005, recording cases from clinics across six continents. Of 279 reported injuries where the animal was identified, 51% were caused by dogs, 21% by monkeys, 8% by cats, and 1% by bats.[166] In India, where stray dogs cause 96% of rabies cases, the annual dog bite rate is 25.7 per 1000 individuals, and the victims most often are male.[4,99]

The annual incidence of cat bites in the United States is approximately 400,000.[372] Cats bite one in every 170 people each year, and 80% of these bites become infected.[180] Whereas dog bites tend to be more prevalent among children, surveillance data from North Carolina EDs found that the incidence rate for cat bites and scratches was highest among individuals over 79 years old. Lifetime risk of cat bite or scratch injury requiring an ED visit was 1 in 60 for the population studied.[346] Biting cats are typically stray females, and most human victims are female.

Of the approximately 30 million Americans who ride horses, 50,000 a year are treated for horse-related injuries in an ED. Dangers inherent to horses relate to speed and size. Some horses can gallop at speeds of up to 64.4 km/hr (40 miles/hr) and can kick with a force of up to 907 kg (1 ton). Bites and unintentional treadings (typically on feet) by horses also occur. A 2-year review of animal bites in Oslo, Norway, revealed that horses caused 2% of 1051 recorded bites; 53% of these horse bite victims were children.[122] In a study involving two trauma centers in Texas over a 7-year period, horses accounted for the majority (55%) of all large-animal–related trauma, injuring 79 patients.[304]

Monkey bites have gained increased attention. In 2011, a U.S. Army soldier died of a rabies infection while in Afghanistan. This

FIGURE 30-1 Yellowstone National Park visitors approach bull elk. *(Courtesy Luanne Freer, MD.)*

prompted a study to assess risk of animal bites for the military. Over just a 4-month period, 126 animal bites, 10 of which were monkey bites, were reported among deployed U.S. military. Monkey bites can also cause tetanus, herpesvirus B, and hepatitis B infections.[277]

The American Ferret Association estimates that 6 to 8 million domesticated ferrets reside in the United States. The Centers for Disease Control and Prevention (CDC) makes it clear that the 65 reported ferret bites in 10 years is a substantially lower number than those caused by dogs and cats (1 to 3 million)[27] (Table 30-1). In Arizona, 11 ferret bites were reported over 11 months; with the ferret population estimated at 4000 animals; the reported bite-to-ferret population ratio is approximately 0.3%.[393] The risk of attack by a ferret is greatest among infants and small children.

Internationally, animal bites and injuries pose a significant problem. A GeoSentinel review of injuries to travelers from 1998 to 2005 reported 320 animal-related injuries (1.8% of all reported injuries).[166] The review revealed that among travelers, women were more likely than men to be injured by animals. Men were more likely to be injured by dogs, and women by monkeys; children sustained animal injuries at a higher rate than they did any other travel-related injury. By geographic region, travelers were most likely to experience animal-related injuries in Southeast Asia, followed by Asia, Australia and New Zealand, Africa, Latin America, North America, and Europe.[166]

The South Mediterranean and the Middle East regions have experienced challenges with proliferation of stray dogs and cats associated with uncontrolled urban growth and numerous socioeconomic factors. With increasing numbers of animal vectors comes exposure to diseases that include rabies, toxoplasmosis, cystic echinococcosis, and visceral leishmaniasis. Canine leishmaniasis is also common in these countries.[306,357]

In India, stray animals are a major cause of morbidity. In one study, 64.7% of animal bites were by stray animals.[213] Dogs were the most common implicated animal (92%), then monkeys (3.2%), cats (1.8%), and foxes (0.4%). A 2003 survey conducted in India of 8500 households found an annual incidence rate of 1.7% for animal bites.[385]

In Sweden, 3 in 1000 (0.3%) citizens are injured by animals each year.[51] Domestic animals accounted for more than 90% of injuries. Moose alone accounted for 6% of wild animal–related injuries, and all other animals accounted for 4%. In this database, bites were not examined separately, and many injuries occurred during vehicular accidents with animals (e.g., the majority of injuries attributed to moose). In 1980, a survey of children ages 4 to 18 years estimated an incidence of more than 36 times the rate reported to health authorities. These figures are most likely based on the bites of domestic animals.[38]

TYPICAL VICTIM

No published reports characterize the typical wild animal attack victim. Two U.S. state health departments report that if all animal bites (including domestic) are considered, animal bites occur most often among male children between the ages of 5 and 9 years.[370,379] However, more than 90% of animal attacks in these states are caused by domestic animals, so this group may not accurately reflect the typical victim of a wild animal attack. In developing countries, many persons are exposed daily to biting animal species that are considered "exotic" in the developed world.

TABLE 30-1 Incidence (%) of Bites by Species in the United States as Reported in Seven Studies

	Study						
Species	**A**	**B**	**C**	**D**	**E**	**F**	**G**
Dog	89	91.6	78		75	60-90	80-85
Cat	4.6	4.5	16		20	5-20	10
Rodent	2.2	3	<1	65	2.5	2-3	
Monkey	0.1*	0.2	2.2	15	0.2		
Skunk		0.02	0.02	0.1			
Lagomorph	0.2	0.5			1		
Large mammal	0.03†	0.01‡	1.2	3§	0.5		
Reptile	0.1						
Bat		0.004	0.3	6	0.7		
Raccoon		0.08	1	3‖	0.5		
Human						2-3	
Other animal						<1	5-10¶

A: Marr J, Beck A, Lugo J: An epidemiologic study of the human bite, *Public Health Rep* 94:514, 1979.
B: Scarcella J: Management of bites, *Ohio State Med J* 65:25, 1969.
C: Sinclair CL, Zhou C: Descriptive epidemiology of animal bites in Indiana, 1990-1992: A rationale for intervention, *Public Health Rep* 110:64, 1995.
D: Kizer K: Epidemiologic and clinical aspects of animal bite injuries. *JACEP* 8:134, 1979.
E: Spence G: A review of animal bites in Delaware: 1989 to 1990, *Del Med J* 62:1425, 1990.
F: Up To Date: *Initial management of animal bites.* http://www.uptodate.com/online/content/topic.do?topicKey=.peds_env/5288&source=preview&anchor=H2#H2.
G: Answers.com: *Animal bite infections.* http://www.answers.com/topic/animal-bite-infections.
*Includes 21 monkeys, 4 raccoons, 3 ferrets, 1 weasel, 1 coatimundi, 1 skunk, and 1 goat.
†Includes 3 lions, 1 ocelot, 1 leopard, 1 polar bear, and 1 anteater.
‡Includes 1 goat, 1 ocelot, 1 jaguar, and 1 groundhog (which inflicted a bite on Groundhog Day).
§Includes 1 coyote.
‖Includes 1 kinkajou.
¶Includes rodents, rabbits, horses, raccoons, bats, skunks, and monkeys.

Persons in certain occupations (e.g., veterinary and animal control workers, laboratory workers) in developed countries are at greatest risk for animal bites. One study reported that 65% of veterinarians had sustained an animal-related injury during the preceding 12 months.[245] The U.S. Bureau of Labor Statistics reported that during a 5-year period, 186 occupational injury fatalities were caused by animal attacks, and that the majority involved cattle.[66] In one study of 102 animal control officers, the overall bite rate was 2 per 57 individuals per working day, which is 175 to 500 times the estimated rate for the general population. This study did not differentiate between wild and domestic animal bites.[37] The incidence of biting varies among species. In 2003, 93% of Wisconsin and Minnesota veterinarians were victims of dog or cat bites. Cattle and horses inflict the most injuries to veterinarians, with kicking, biting, and crushing being the top three mechanisms of injury.[137]

In every statistical series of bites, small numbers of exotic animals, including ocelots, jaguars, lions, leopards, polar bears, wolves, anteaters, and weasels, are represented. Bites from these animals occur as a result of exposure to wild and zoo animals and because of increasing popularity of keeping wild animals as pets. This practice, which typically involves exotic animals being kept illegally and without adequate training and understanding of animal care and behavior, all too often ends in tragedy. Statistics from the Exotic Animal Incidents Database recorded animal injuries and fatalities at accredited and nonaccredited zoos, circuses, and individual exotic pet owners in the United States from 1990 to 2012. There were 543 human injuries and 75 human deaths. Large felines were responsible for the most injuries (30%), followed by primates (24%), reptiles (19%), other (11%), elephants (10%), bears (5%), and marine (1%). Large felines were responsible for the most deaths (28%), followed by reptiles (25%), other (21%), elephants (19%), bears (5%), marine (2%), and primates (0%).[381]

Large felines are responsible for the majority of deaths from mammalian bites globally, specifically lions and tigers in Africa and Asia. By way of comparison, the World Health Organization (WHO) estimates that 5 million people per year are bitten and 125,000 killed by snakes, and that additional millions are killed by insect-borne diseases.[424] The people most at risk for snakebite live in rural, resource-poor settings and are employed in nonmechanical field occupations in Africa or Southeast Asia.[89]

In the United States, nearly 400 people are killed annually by animals (excluding zoonotic infections), with most deaths caused by bees, wasps/hornets, and traffic accidents involving deer. An average of 49 people die per year from anaphylaxis related to hymenopteran stings.[247] Deer-vehicle collisions account for nearly 200 deaths annually in the United States.[13]

CIRCUMSTANCES SURROUNDING AND PREVENTION OF ANIMAL BITES: ANIMAL BEHAVIOR

Analysis of human injuries caused by animals shows that these are predictable events with identifiable personal and environmental risk factors similar to those for diseases.[425] For example, family pets cause most bites, and the animals are usually provoked. Males experience 150% to 250% the rate of injuries compared with females at every age.[425] Table 30-2 lists U.S. animal-related fatalities by gender, 0 to 19 years old.[158] Injuries are frequently sustained while playing with the animal.[93] Most bites occur in summer months during the late afternoon. Children sustain a higher percentage of head and neck bites than do adults and are more likely to require medical attention.[152] Of all dog bites, 9% to 36% occur to the head and neck region, whereas this area is affected in 6% to 20% of persons who sustain cat bites.[152] Understanding patterns of animal bite injuries allows improved treatment and prevention.

Prevention of animal bites requires thorough knowledge of the patterns of behavior and personalities of the animals. A person who wants to avoid the bite of a particular species will often be able to gain expertise about that species' behavior only from those who work with it regularly. Detailed information about animal behavior and the attack patterns of animals is available on the Internet (Box 30-1).

BASIC PRINCIPLES FOR AVOIDING ANIMAL BITES

Domestic animals of any type rarely attack unless provoked, although unrestrained dogs are sometimes the exception. Physical attack is usually a last resort, but an animal will fight if it

TABLE 30-2 Selected Demographics for Animal-Related Fatalities in the United States from 1999 to 2007*

Type of Animal	Number of Deaths (percentage)	Annual Average Number of Deaths	Annual Death Rate per Million	Male (percentage)	Female (percentage)	Percentage 0 to 19 Years Old
Dog	250 (13.9%)	27.8	0.0955	137 (54.8%)	113 (45.2%)	48.8
Rat	3 (0.17%)	0.4	0.00115	3 (100.0%)	0 (0.0%)	0
Other mammal†	655 (36.3%)	72.9	0.250	504 (76.9%)	151 (23.1%)	15.0
Marine animal	10 (0.6%)	1.2	0.00382	9 (90.0%)	1 (10.0%)	30.0
Other nonvenomous insect or nonvertebrate	85 (4.7%)	9.4	0.0325	64 (75.3%)	21 (24.7%)	4.7
Crocodile or alligator	9 (0.5%)	1.0	0.00344	5 (55.6%)	4 (44.4%)	0
Other reptiles	77 (4.3%)	8.6	0.0294	38 (49.4%)	39 (50.6%)	1.3
Venomous snakes and lizards	59 (3.3%)	6.6	0.0225	47 (79.7%)	12 (20.3%)	13.6
Spiders	70 (3.9%)	7.8	0.0267	41 (58.6%)	29 (41.4%)	2.9
Scorpions	5 (0.3%)	0.6	0.0019	2 (40.0%)	3 (60.0%)	40.0
Hornets, wasps, and bees	509 (28.2%)	56.6	0.195	412 (80.9%)	97 (19.1%)	0.8
Centipedes and venomous millipedes	2 (0.1%)	0.2	0.000764	2 (100.0%)	0 (0.0%)	0
Other specified venomous arthropods	63 (3.5%)	7.1	0.0241	51 (81.0%)	12 (19.0%)	1.6
Venomous marine animals and plants	1 (0.1%)	0.2	0.000382	1 (100.0%)	0 (0.0%)	0
Unspecified venomous animal or plant	4 (0.2%)	0.4	0.00153	3 (75.0%)	1 (25.0%)	0
TOTAL	1802 (100%)	00.2	0.689	1319 (73.2%)	483 (26.8%)	13.6

From Forrester JA, Holstege CP, Forrester JD: Fatalities from venomous and nonvenomous animals in the United States (1999-2007). *Wilderness Environ Med* 23:146-152, 2012.

*Based on the Centers for Disease Control and Prevention (CDC) WONDER Database. This does not include fatalities related to vehicle-animal collisions or fatalities from riding animals.

†Other mammals includes cats, cows, horses, pigs, raccoons, and other hoofed livestock.

BOX 30-1 Animal Behavior and Attack Prevention Websites

Dog and cat bite prevention	http://www.cityoffortwayne.org/animal-bite-prevention.html
Dog bite prevention	http://www.petplace.com/dogs/preventing-dog-bites-things-to-do-before-you-get-a-dog/page1.aspx
Dog bite prevention and legal information	http://www.dogbitelaw.com
Moose attack prevention	http://www.survivaltopics.com/survival/survive-a-moose-attack/
Cougar attack prevention	http://www.arkanimals.com/dlg/cougar_attack.htm
Wolf behavior and human encounters	http://fwp.mt.gov/wildthings/wolf/human.html
Hunter education	http://www.hunter-ed.com/index.html
General animal attack information	http://www.articlesbase.com/health-and-safety-articles/how-to-avoid-animal-attack-injury-444613.html
Wild animal attack compilation	http://www.attack.igorilla.com

perceives threat. Reducing the risk of injury is often based on common sense and knowledge of animal behavior. For example, horses kick backward and with both rear feet, whereas cattle kick forward with only one foot. How a person reacts during a confrontation with an animal is also important. Nonpredatory species (e.g., cattle, deer) are very susceptible to human intimidation, whereas a direct stare at a canine or ape may be seen as a challenge.

Expert recommendations can reduce the chance of being attacked and bitten by a domestic animal (Box 30-2). For example, specific actions can be taken when an individual is threatened or under attack by a dog (Box 30-3). Dogs are guided by memory and instinct; fear and self-preservation are very strong instincts, so a perceived threat could lead to an attack. Territoriality is still ingrained in domestic dogs, even if humans provide for them. Protection of food can cause aggression, even in a docile dog. Any threat to a dog's mate, offspring, or owner may result in an attack. Personality changes may lead to aggression; causes include illness (e.g., distemper) and physiologic factors (e.g., a female in heat).

Like their domestic counterparts, wild animals rarely attack humans without provocation. Exceptions are large apex carnivores, which may be relatively unafraid of humans, and creatures infected with rabies. However, carnivores do not typically hunt humans as preferred prey. The animal's perception of provocation may not be readily apparent to the inexperienced individual. Patterns of behavior and attack differ by species.

When people attempt to capture or restrain wild animals, the resulting stress may cause even the most benign or "tame" animal to attack. When being captured or restrained for treatment of an injury, even typically docile animals may attack in self-defense, and can inflict a life-threatening injury (e.g., goring). Therefore, all situations that involve animal restraint and capture are considered high risk, and careful study of the species' behavior, the individual animal, and physical environment and available resources should precede actual attempts at restraint (see Chapter 37).

A large and lucrative market exists enabling individuals to raise wild animals as pets, particularly in the United States.[263] Not surprisingly, these animals will never be as predictable and nonaggressive as animals that have been domesticated for centuries. People habitually exposed to these nondomesticated animals sometimes demonstrate lack of common sense; consider the case of a pet Bengal tiger that attacked and killed its trainer, then did the same to its owner 6 weeks later.[25,133]

Most wild species have a strong sense of territoriality. Individuals, pairs, and larger groups establish a territory that ranges from square feet to miles and aggressively prevent any intrusion into that territory, particularly by members of their own species.

BOX 30-2 Advice for Avoiding the Bites and Attacks of Common Pets*

Dogs

Do not leave a young child alone with a dog.
Never approach or try to pet an unfamiliar dog, especially if it is tied up or confined.
Always ask the dog's owners if you can pet the dog.
Do not lean over a dog or pet it directly on the head.
Do not kiss a dog.
Avoid quick or sudden movements that may startle a dog.
Never pet or step over a sleeping dog.
Never try to take a bone or toy away from a dog (other than your own dog).
Know the appearance of an angry dog: barking, growling, snarling with teeth showing, ears laid flat, legs stiff, tail up, and hair on the back standing up.
Never step between two fighting dogs; if you need to separate them, use a bucket of water or a hose.
Do not approach a female dog that is nursing her pups.
Teach injury prevention advice to children from an early age.

Cats

Be aware that some cats do not like prolonged petting.
Know warning signs of an impending bite: twitching of the tail, restlessness, and "intention" bites (i.e., the cat moves to bite but does not bite).

Ferrets

Do not sell or adopt a ferret that is known to bite.
Do not push your fingers through the wires of a ferret cage.
Reach for a ferret from the side with the palm upward rather than from above.
Do not handle food and then handle young ferrets without first washing your hands.
Do not poke a ferret or pull on its tail or ears.
Never leave a ferret alone with a child or infant.
If a ferret bites and locks on very tightly, pour cold and fast-running water over its face.

*The prevention of bites and injuries from other animals is addressed in the appropriate sections of this chapter.

BOX 30-3 Suggested Actions If You Are Under Threat or Attacked By a Dog

- Stand totally still, and let the dog come to you.
- Remain calm, assume a nonthreatening stance, and never run.
- Do not pat the dog.
- Keep your eye on the dog, but do not stare at it.
- Avoid smiling at the dog.
- To reprimand the dog, say "no" in a harsh voice; do not attempt to hit the dog.
- Do not make any threatening or provocative movement.
- If the dog starts biting you, defend yourself by hitting the dog in the throat, nose, or back of head to stun the animal and create an opportunity to escape.
- Do not let the dog get behind you; keep turning to face it.
- If you are knocked down, feign death, and curl up into a ball until the dog loses interest.
- If the dog punches you with its nose, ignore it.
- If a dog puts one of your legs in its mouth without tearing the flesh, waiting for a reaction, you should remain motionless, if you can.
- If you are attacked by more than one dog, try and stand with your back to a wall or automobile.
- Back away slowly and leave the area when the dog loses interest in you.
- After an attack, contact the dog's owner and appropriate authorities, and attend to any wounds.
- If the interaction occurs when you are cycling, dismount, and keep the bike between you and the dog.

Modified from Wilson S: *Bite busters: How to deal with dog attacks*, New York, 1997, Simon & Schuster; and wikiHow: *How to handle a dog attack*. http://www.wikihow.com/Handle-a-Dog-Attack.

During mating season and when protecting their young, this drive may stimulate even small animals to threaten or attack humans.

A major principle of animal behavior is that physical attack is often the animal's last resort. Animals generally give ample warning regarding their intentions. Elaborate rituals and rules govern spectacular contests between animals that occur in the wild. These displays encourage a nonviolent solution so that the victor may successfully defend itself and its territory with little or no injury. Humans can often avoid attack and injury by successfully interpreting visual, auditory, and olfactory warning signs. If a human slowly and carefully backs away from certain species without making sudden or threatening gestures, usually no harm will be done. However, the ideal reaction depends on the species. For example, mountain lions have been turned from a full charge by a human who acted aggressively or fought back.[40] Given a choice of victims, such a predator prefers the fleeing and panicked victim who demonstrates expected behavior patterns consistent with prey.

If capture of an animal is essential, detailed preparation should be undertaken. For small animals, using nets or heavy cloth and wearing extremely heavy gloves and other protective clothing are advisable. Desperate animals can bite with tremendous force; large carnivores can easily amputate a gloved digit. A wolf can tear apart a stainless steel bowl with its teeth, and a hyena can bite through a 2-inch–thick wooden plank.[105] Four men are needed to subdue an adult chimpanzee; an orangutan can maintain a one-fingered grip that an adult human cannot break. Larger animals generally require a team approach by animal control specialists with equipment such as nets, barriers, cages, and immobilizing drugs. Ideal immobilization techniques for various species are detailed in veterinary and wildlife management publications[159,164] (Box 30-4).

BOX 30-4 Animal Capture and Immobilization Considerations

Equipment*	Considerations	Successful Captures	Capture Methods
Nets	Type of animal	Planned	Immobilizing drugs¶
Vehicles	Number, gender, and age	No unnecessary personnel‡	Tranquilizing drugs¶
Helicopters	Animal health	Are not performed during late winter	Cage traps with or without bait
Drugs	Time of year	Animals are not chased§	Darting from a vehicle or helicopter
Feed	Area of capture		
Bomas (holding pens)	Postcapture transport†		

Modified from Wildlife Campus: *Game capture: Part A.* http://www.docstoc.com/docs/19872015/Game-Capture-Part-A.
*The welfare of the animal is always paramount.
†Large carnivores should remain tranquilized for transport for ease of handling and animal safety.
‡Bystanders increase the potential for injury to both humans and animals. Observers are usually inexperienced and may hinder operations.
§Chasing animals for long distances or long periods is not advised. Animals do not act this way in natural settings, and such stress could prove fatal.
¶In South Africa, the most common drugs used are a compound called M-99 and fentanyl.

BOX 30-5 Summary of Mandatory Animal Bite Wound Treatment for All Wounds

1. Evaluate for potential blunt trauma and injury to deeper and vital structures caused by penetrating teeth, claws, or horns.
2. Ensure appropriate tetanus immunization.
3. Irrigate the wound with a copious volume (minimum, 100 to 300 mL) of normal saline (NS) or 1% to 5% povidone-iodine in saline solution, the latter followed by a NS or disinfected-water rinse.
4. Debride crushed and devitalized tissue.
5. If the animal is suspected to be rabid (e.g., atypical behavior, high-risk species), do the following:
   a. Infiltrate wound edges with 1% procaine hydrochloride.
   b. Swab the wound surface vigorously with cotton swabs and 1% benzalkonium chloride (Zephiran) solution or other soap.
   c. Rinse the wound with NS.
   d. Assess the need for rabies immune globulin and vaccine.
6. Assess risk factors to make decisions about further (selective) treatment (see Box 30-6).
7. Do not culture fresh wounds.
8. Do not give prophylactic antibiotics for routine low-risk bite wounds.

Selective Treatment (Wounds Selected By Risk Factors)

1. Suture, staple, or use adhesive strips to close skin wounds in the usual fashion, unless wounds are high risk (e.g., hand wounds, high-risk species, immunosuppressed patient).
2. Culture infected wounds only if they show signs of established infection or if there is evidence of systemic sepsis.
3. Consider surgical consultation and delayed primary closure for high-risk wounds. Strongly consider administration of prophylactic antibiotics to victims with high-risk wounds.

EVALUATION AND TREATMENT OF INJURIES

OUT-OF-HOSPITAL CARE

Unlike many attacks in the wilderness, attacks by domestic and farm animals are fairly predictable and preventable. In Africa and Southeast Asia, life-threatening attacks by large animals such as water buffalo, lions, tigers, and elephants are common. Attacks by larger animals can result in major blunt or penetrating trauma, with possible major arterial blood loss, airway damage, spinal cord injury, and thoracic and intraabdominal trauma. The victim's condition and availability of rapid evacuation determine the extent of treatment in the field. In cases where medical personnel or supplies are not readily available, the victim must be moved to a hospital or clinic as soon as possible.

Many of the complications and serious infections resulting from animal bites are caused by inadequate first aid and delays in medical care. Local wound treatment should be initiated at the scene of the bite (Box 30-5); more than any other therapy, this can determine the course of healing. Simple first-aid measures must be initiated immediately unless definitive or better treatment is available within a short time. Pressure on the wound or pressure points controls most bleeding. In cases of severe hemorrhage and shock, application of tourniquets can be lifesaving.[239]

Whenever possible, even in out-of-hospital settings, wounds should be cleansed and irrigated thoroughly at the scene as soon as resuscitation efforts are complete. Early cleansing reduces the chance of bacterial infection and is effective at decreasing risk of infection from rabies and other viruses. Effective irrigation, debridement, and decontamination measures are thought to be so likely to be beneficial that a randomized controlled trial (RCT) would be unethical.[261] Irrigation should be delivered with pressure equal to about 8 to 12 psi and wounds debrided as effectively as possible. For some wounds that are not at high risk, attempting field closure is reasonable, and a loose closure with a dressing may help to decrease bleeding, prevent infection, and make self-evacuation possible. However, in general, field closure of contaminated bite and claw wounds is not recommended. Further discussion of bandaging and wound-repair techniques may be found in Chapters 18, 21, and 24.

Potable water, preferably boiled or treated with germicidal agents, is adequate for wound irrigation. Ordinary hand soap may add some bactericidal, virucidal, and cleansing properties. If 1% to 5% povidone-iodine in normal saline solution is available, it may be used as an irrigant for contaminated wounds. Alternatively, thoroughly irrigate the wound with at least a pint of dilute soapy water, followed by rinsing with nonsoapy water, and then gently but carefully debride it of dirt and foreign objects

TABLE 30-3 Recommended Empirical Oral Antibiotics for Bite Wound Prophylaxis and Treatment

Antibiotic	Recommended Adult Dose	Recommended Child Dose*
Agent of Choice		
A) Amoxicillin-clavulanate	875/125 mg twice daily	45 mg/kg per dose (amoxicillin component) twice daily
Alternate Combination Therapy: B or C (with Anaerobic Activity) Plus E, F, G, H, or I		
B) Metronidazole	500 mg three times daily	10 mg/kg per dose three times daily
Or:		
C) Clindamycin	450 mg three times daily	10 mg/kg per dose three times daily
Plus One of the Following:		
D) Doxycycline	100 mg twice daily	Not for use in children <8 yr old
E) Trimethoprim-sulfamethoxazole	160/800 mg (1 DS tab) twice daily	4 to 5 mg/kg (trimethoprim component) per dose* twice daily
F) Penicillin V potassium	500 mg four times daily	12.5 mg/kg per dose four times daily
G) Cefuroxime	500 mg twice daily	10 mg/kg per dose twice daily
H) Moxifloxacin	400 mg once daily	Use with caution in children

Modified from Endom EE: Initial management of animal and human bites. In Danzi DS, editor: *UpToDate,* Waltham, Mass, 2011, UpToDate.
*Child dose should not exceed recommended adult dose.

by swabbing with a soft, clean cloth or sterile gauze. Irrigation with a syringe is preferable (see Chapter 21).

After cleansing, cover the wound with sterile dressings or a clean, dry cloth. Wounds of the hands or feet may require immobilization. If the wounds are at high risk for infection, treatment is hours away, and an appropriate antibiotic is available,[2,119,382] it is reasonable to start immediate treatment with an oral dose (Table 30-3). To prevent subsequent wound infection most effectively, antibiotics should be started within 1 hour of wounding. In wounds at high risk of infection, it is worthwhile to provide the antibiotic, even if delivered substantially later. If the wound is at high risk of infection, medical care will be delayed, and antibiotics are not available, a simple remedy such as filling the wound with honey may be employed as an antibacterial strategy.[326] Because of its high osmolarity and weak hydrogen peroxide concentration when diluted, honey can be effective as an antibacterial when used in adequate quantities.[224,285,348]

In addition to treating the bite victim, some thought should be given to capturing the offending animal for examination, if this can be done without risk of human injury in the process. Unusual behavior, such as unprovoked attack by a wild animal in broad daylight or a complete absence of fear of humans, should raise the suspicion for rabies (see Chapter 31). Live animal capture is optimal, but freshly killed animals are usually satisfactory for examination for fluorescent rabies antibody. Avoid damaging the animal's head and brain (e.g., by gunshot or bludgeoning), because brain tissue is needed for analysis. Availability of the animal can eliminate the need for costly and uncomfortable rabies PEP. If more than 1 hour will elapse before the animal can be transported to a hospital or public health department prepared to process the body for determination of rabies, then refrigerate the body. For shipping, wrap the animal's head and transport it in an insulated container with ice or ice packs. Do not use preservatives. Be sure to include the type of animal, details of the exposure, date of the animal's death, victim information, and a description of the animal's behavior in the report accompanying the specimen.[377] Examination of the animal is not useful for most other diseases and will not help predict local wound infections. Therefore, use good judgment when deciding how much time and energy to expend on capture.

HOSPITAL CARE

Resuscitation with blood products and intravenous (IV) volume expanders may be needed if there is extensive blood loss. When considering diagnostic imaging, the type of animal and its particular attack characteristics should be considered. Blunt trauma often accompanies penetrating injuries such as goring and trampling. Animal attack wounds classified as "high risk for infection" (Box 30-6) include deep puncture wounds, moderate or severe wounds with associated crush injury, wounds with areas of

BOX 30-6 Risk Factors for Infection from Animal Bites

High Risk

Location

Hand, wrist, or foot
Scalp or face in patients with high risk of cranial perforation; computed tomography or skull radiograph examination is mandatory
Over a joint (possibility of perforation)
Through-and-through bite of cheek

Type of Wound

Punctures that are difficult or impossible to irrigate adequately
Tissue crushing that cannot be debrided (typical of herbivores)
Carnivore bite over vital structure (e.g., artery, nerve, joint)

Patient

Age >50 years
Asplenia
Chronic alcoholism
Altered immune status (e.g., chemotherapy, acquired immunodeficiency syndrome, congenital immune deficiency)
Diabetes
Peripheral vascular insufficiency
Chronic corticosteroid therapy
Prosthetic or diseased cardiac valve (consider systemic prophylaxis)
Prosthetic or seriously diseased joint (consider systemic prophylaxis)

Species

Large cat (canine teeth produce deep punctures that can penetrate joints and the cranium)
Primates
Pigs (anecdotal evidence only)
Alligators and crocodiles

Low Risk

Location

Face, scalp, ears, and mouth (all facial wounds should be sutured)
Self-bite of buccal mucosa that does not penetrate full thickness to external skin

Type of Wound

Large, clean lacerations that can be thoroughly cleansed (the larger the laceration, the lower the infection rate)
Partial-thickness lacerations and abrasions

Species

Rodents
Quokkas
Bats (although there is a high risk for rabies)

underlying venous or lymphatic compromise, wounds on the hands or close to a bone or joint, and bite wounds in compromised hosts (e.g., immunocompromised, absent spleen or splenic dysfunction, diabetes mellitus). Surgical consultation and hospital admission should be considered early in such patients.

Wound Management

Animal bites are not clean lacerations and may be crush injuries with devitalized tissue. All bites should be treated as contaminated wounds. Evaluate all victims of animal bites for blunt trauma and internal injuries, which may be less obvious than the bite wound (see Box 30-5). Internal organ, deep artery, and nerve damage and penetration of joints are possible. Particularly in children, animal bites can penetrate vital structures, such as joints or the cranium.[59,79] Radiographs and scans may be employed whenever these injuries are suspected. A complete head-to-toe evaluation for trauma is advised in all but the most trivial and isolated bite injuries. Laboratory tests are of little use when evaluating animal bite injuries. Unless hematocrit is being assessed for evidence of blood loss, the complete blood cell count is not useful, because it is a nonspecific and unreliable gauge of infection. Definitive trauma evaluation and treatment are discussed in detail in Chapter 18.

Routine wound cultures obtained at the time of initial wounding do not reliably predict whether infection will develop or, if it does develop, the causative pathogens.[157] Therefore, culturing an uninfected bite wound does not yield any useful data.[53,69,157] If a bite wound appears infected, cultures and Gram stain of infected tissue or secretions should be obtained before antibiotics are administered. It is useful to alert the laboratory technician that the culture is from a bite wound, because organisms such as *Pasteurella multocida* are often misidentified.

Many bite injuries are simple contusions that do not break skin. The infection potential of these injuries is low; superficial wound cleansing and symptomatic treatment of pain and swelling suffice. Treatment should include prompt and liberal application of ice or other cold packs during the first 24 hours. However, this is not beneficial for snakebite (see Chapters 35 and 36) and is obviously impractical in many locations.

When skin is broken, the risks of local wound infection or transmission of systemic disease are incurred. Infection can be caused by organisms carried in the animal's saliva or nasal secretions, by human skin microbes carried into the wound, or by environmental organisms that enter the wound during or after the attack.[278]

Debridement removes bacteria, clots, and soil much more effectively than does irrigation.[157] In addition, debridement is intended to create cleaner surgical wound edges that are easier to repair, heal faster, and produce a smaller scar. Topical antiseptic ointments are highly effective for promoting healing of minor skin wounds.[168,256] Although appropriate for abrasions produced by animal bites, topical ointments may be less effective for punctures and sutured wounds.

A sutured wound should be covered by a simple, sterile, and dry dressing to protect it from rubbing against clothing or repetitive minor trauma. Delayed primary closure requires that the wound be kept moist; this is usually done with a moist saline dressing twice daily until closure, which is generally planned for 72 hours after wounding.[157]

Wound Closure and Infection Risk Factors

Three major considerations govern the decision of whether to suture a wound: cosmetics, function, and risk factors. Cosmetic appearance virtually mandates suturing all facial wounds, which are usually low risk. Similar reasons may dictate closure of wounds on other visible portions of the body. Function is of critical importance for wounds of the hand, a high-risk area in which infection can have disastrous consequences. Thus, in general, all but the least complex hand wounds should initially be left open. Risk factors are many and complex and provide a useful logical framework for making the decision of whether to suture, administer antibiotics, or undertake other treatments. For more information about surgical procedures, see Chapters 21 and 22.

The amount of time elapsed after wounding is a critical risk factor; for some mammal bites, the longer the interval, the more likely the chance for infection. After the first few hours, adequate wound cleansing is unlikely to be carried out. In developed countries, many victims are seen within hours of wounding, and the results are usually very good. In remote and undeveloped areas and countries, wounds usually do not receive medical attention for half a day or more, thereby putting them into a high-risk category that may eliminate the possibility of primary repair. Certain species, including primates, wild cats, pigs, and large wild carnivores, seem to inflict infection-prone wounds. In contrast, dog bites may not be as high risk. One study showed that delayed surgical debridement and washout of dog bites in pediatric patients did not increase the infection rate.[10] Wounds that involve crush injuries, puncture wounds, hands, or feet, or that affect a compromised host are at high risk for infection, and primary closure should be attempted only after careful consideration and with surgical consultation and concurrence. If primary closure is not chosen or deemed too risky, surgical consultation for a discussion of other options, including delayed primary closure or vacuum-assisted closure, is prudent.[61,157]

Many minimally contaminated bites can be safely sutured after proper wound preparation. Data suggest that carefully selected mammalian bite wounds can be sutured with an approximately 6% rate of infection.[97] Two studies examining the risk of infection after primary closure reported rates of 7.6% (7 of 92 cases)[266] and 5.5% (8 of 145 cases),[97] respectively. The authors of the latter study concluded that the rate of infection after primary closure was acceptable, particularly if a good cosmetic outcome was needed.[97] These studies focused on dog, cat, and human bites.

Optimal conditions for primary repair include prompt medical treatment, which is seldom available in remote and undeveloped areas. In these circumstances, leaving bite wounds open (or closed with an incorporated drain, although this is also controversial) is the more prudent course.

Bites of the Hand

Because hand bites are common and infection can be disastrous,[411] the hand is considered at high risk for complications (see Box 30-6). The hand contains many poorly vascularized structures and tendon sheaths that poorly resist infection. The fascial spaces and tendon sheaths communicate with each other, and movement seals off the wound from external drainage and spreads bacteria and soil internally. Because of the unique anatomy of the hand, thorough irrigation of wounds is often impossible.

Data regarding hand wound infection have been collected mostly from experience with domestic dog and cat bites. From a retrospective study in Oslo, Norway, it was determined that almost all hand bite wounds healed uneventfully when the wounds were left open, either without antibiotics or with penicillin after wound treatment.[122] In another European center, the total infection rate was 18.8% in hand bite wounds; this increased to 25% when the hand wound was closed primarily. The average time from injury to first medical treatment was 11 hours in infected and 2 hours in noninfected wounds.[8] The infection rates for primary closure and no closure in a study of dog bites were 56% and 44%, respectively.[266]

Because of the high morbidity and permanent residual impairment that occurs with hand infections, treating them aggressively is best (see Box 30-5). Hand bite wounds should be irrigated, debrided if possible, and in higher-risk wounds, initially left open.[157,411] Small, uncomplicated lacerations can be repaired primarily if accomplished within 12 to 24 hours. The hand should be immobilized with a bulky mitten dressing in an elevated or neutral position, and the victim started promptly on antibiotics. Specialty consultation and follow-up are mandatory for patients with established infection, and hospitalization should be considered. Persons who are not hospitalized should be rechecked daily until signs of infection clear. In the patient without initial evidence of infection, 5 days of splinting and oral antibiotics should suffice if no complications develop.[71] Radiographic examination to search for fractures and foreign bodies should be considered for all significantly injured extremities.

Puncture Wounds

Punctures may occur as a result of biting, clawing, or goring. The infection rate is related to difficulty irrigating properly and degree of contamination, which is highest in bites. Puncture wounds can be contaminated with pieces of the victim's clothing. Usually, attempts to irrigate narrow punctures simply result in rapid development of tissue edema from infused irrigant solution, which does not cleanse the wound. However, if the wound is large or can be held open wide enough to permit fluid readily to escape, irrigation is worth the effort. Large, goring-type puncture wounds up to 20 to 25 cm (8 to 10 inches) deep from bison have a low incidence of infection when closed primarily after irrigation and debridement.[110] For most smaller puncture wounds, irrigate or debride them as well as possible, suture only if cosmetic or functional considerations require it, and treat as having a high risk of infection.[157] Use delayed primary closure liberally.

Facial and Scalp Wounds

Facial and scalp wounds tend to heal rapidly, with minimal risk of infection. In general, these wounds may be sutured primarily and do not require prophylactic antibiotics. Typical dog bites of the face and neck (including punctures) have an infection rate of only 3%, even when sutured.[8,122,127,419] Generally, primary cosmetic closure of facial wounds is acceptable because of the lower incidence of infection. Standard of care in most cases is primary closure of an animal bite wound of the face.[419]

A major risk associated with facial and scalp wound victims of large carnivores is that teeth can easily perforate the cranium, producing depressed skull fracture, brain laceration, intracranial abscess, or meningitis.[90,322] In young children with such wounds, or in adult victims of large-carnivore bites, computed tomography (or in the absence of CT, skull radiography) should be routinely employed to look for evidence of perforation that would mandate immediate neurosurgical consultation and admission to the hospital.

Follow-Up Care

Assuming that the possibility of major or occult trauma has been ruled out, follow-up care for animal bites depends on the risk factors present (see Box 30-6) and the patient's response to treatment. With only a superficial abrasion, infection is unlikely, and no return visit is needed. With an ordinary, low-risk bite wound, one follow-up visit in 2 days to assess for infection will suffice. If the patient is reliable and no sutures have been placed, a return visit may not be necessary. Infected wounds dictate much closer follow-up, with the frequency depending on the wound's response to treatment and the patient's risk factors. In a high-risk wound or compromised patient, the initial follow-up visit should be made within 24 hours if the patient is not hospitalized.

Infection: Zoonoses and Rabies

Immense numbers of bacteria inhabit animals' mouths and can be inoculated into a bite wound. Claw and scratch wounds may be contaminated with soil, urine, and feces. Pathogens depend on the biting species (Box 30-7). If inoculated in sufficiently large numbers, these microorganisms can cause localized cellulitis and abscess formation, the most common forms of infection. Wild animals also act as vectors for diseases, such as rabies, cat-scratch fever, monkeypox virus, simian herpesvirus, tularemia, hantavirus, tetanus, Q fever, Ebola virus disease, and toxoplasmosis (see Chapters 31 and 34).

Rabies

Rabies is discussed in detail in Chapter 31, so comments here are limited to brief remarks about epidemiology, assessment of risk in the bite victim, and local wound treatment.

Rabies is a rhabdovirus that occurs in wild and domestic animals and is transmitted through the saliva of an infected animal. It is generally believed that no true reservoir host exists for rabies (i.e., no species harbors a latent and nonfatal infection).

The epidemiology of rabies varies widely in different parts of the world. In the United States, Western Europe, and Canada, wild animals are by far the main vectors of rabies, accounting for more than 88% of all reported cases from the past two decades.[241] In India, 95% of rabies PEP treatment follows bites from stray dogs.[99] Currently, the United States spends $300 million annually for PEP.[77] With these interventions, rabies prophylaxis has been successful. Over the last century in the United States, human deaths have declined from over 100 per year to 2 to 3 per year.[340] Before 1960, the majority of rabid animal bites were domestic; currently, 90% occur from wildlife, primarily wild carnivores and bats.[77] Raccoons continue to be the most frequently rabid wildlife species (36.5% of all animal cases in 2010), followed by skunks (23.5%), bats (23.2%), foxes (7.0%), and other wild animals, including rodents and lagomorphs (1.8%).[340] Hawaii is the only state without reported rabies.[144] Because of local variations in animal vectors and endemics, consultation with the state or local health department is prudent before a decision is made to initiate rabies PEP.[241] Although the number of human cases has declined, as many as 40,000 people per year in the United States receive rabies PEP.[214]

Outside the United States, virtually all rabies occurs in dogs. Worldwide, dogs account for 91% of all human rabies cases; cats 2%, other domestic animals 3%, bats 2%, foxes 1%, and all other wild animals 1%.[102,423] About 75% of animal injuries to travelers occurred in rabies-endemic countries, including Thailand, India, Indonesia, China, Nepal, and Vietnam.[166] Each year in India, 25,000 humans die from rabies, and 500,000 receive rabies vaccine.[386] In Thailand, 50% of human rabies cases occur in children who are less than 15 years old.[392] In Africa, Latin America, and most of Asia, dogs are the principal vector, and some jackals carry the virus. In South America and Mexico, rabid vampire bats cause occasional human infection. During recent years, disruption of the natural ecology of vampire bats as a result of introducing humans and domestic animals to the rain forest has produced epidemics of rabies. In Israel, wolves and jackals are the chief vectors. The mongoose prevails in Puerto Rico. In Eastern and Central Europe, the raccoon dog (*Nyctereutes procyonoides*) is an increasingly common vector, although foxes are

BOX 30-7 Common Bacteria in Animal Bites

Dog Bites
- *Staphylococcus* spp.
- *Streptococcus* spp.
- *Eikenella* spp.
- *Pasteurella* spp.
- *Proteus* spp.
- *Klebsiella* spp.
- *Haemophilus* spp.
- *Enterobacter* spp. DF2 or *Capnocytophaga canimorsus*
- *Bacteroides* spp.
- *Moraxella* spp.
- *Corynebacterium* spp.
- *Neisseria* spp.
- *Fusobacterium* spp.

Cat Bites
- *Pasteurella* spp.
- *Actinomyces* spp.
- *Propionibacterium* spp.
- *Bacteroides* spp.
- *Fusobacterium* spp.
- *Clostridium* spp.
- *Wolinella* spp.
- *Peptostreptococcus* spp.
- *Staphylococcus* spp.
- *Streptococcus* spp.

Large Reptiles (e.g., crocodiles, alligators)
- *Aeromonas hydrophila*
- *Pseudomonas pseudomallei*
- *Pseudomonas aeruginosa*
- *Proteus* spp.
- *Enterococcus* spp.
- *Clostridium* spp.

Herbivore Bites
- *Actinobacillus lignieresii*
- *Actinobacillus suis*
- *Pasteurella multocida*
- *Pasteurella caballi*
- *Staphylococcus hyicus* subspp. *hyicus*

Swine Bites
- *Pasteurella aerogenes*
- *Pasteurella multocida*
- *Bacteroides* spp.
- *Proteus* spp.
- *Actinobacillus suis*
- *Streptococcus* spp.
- *Flavobacterium* spp.
- *Mycoplasma* spp.

Rodent Bites (i.e., rat-bite fever)
- *Streptobacillus moniliformis*
- *Spirillum minus*

Data from Garth AP: *Animal bites in emergency medicine.* http://emedicine.medscape.com/article/768875-overview.

the primary offenders in Europe.[102] Some countries, such as Germany, have eliminated rabies in wild populations by using innovative vaccination programs.[102,294]

Risk of rabies exposure depends on several factors, including the type of animal, its behavior, and whether rabies is known to be endemic to that region. The incidence of rabies in local species is important. In the United States, urban dogs and cats, domestic ferrets, rodents, and lagomorphs (e.g., rabbits, hares) are at low risk. Description of the animal's behavior is sometimes helpful and is easily evaluated in wild animals because most tend to shun humans. The appearance of a skunk, fox, or bat in an urban setting that has no fear of humans during broad daylight, or other atypical behaviors, should raise suspicion for rabies. The incidence of rabies is so high for dogs in some developing countries that rabies PEP should always be given serious consideration.

In addition to situations involving animal bites, contact of mucous membranes with rabies virus–containing saliva or an animal scratch should prompt consideration for rabies PEP. In the United States and other areas where bat rabies is endemic, if a person is found in a room with a bat and is unable reliably to report the absence of contact that could have resulted in exposure (e.g., unattended child, sleeping or mentally incompetent adult), rabies PEP should be administered.

Thorough and rapid early treatment of wounds from suspected rabid animals may decrease viral load. Immediately cleanse all bite wounds and scratches with soap and water and a virucidal agent (e.g., 1:10 mixture of povidone-iodine solution and isotonic saline).[240] Other irrigation solutions, such as chlorhexidine, may be associated with tissue toxicity.[182] Evaluate all persons exposed to a possibly rabid animal for rabies PEP. The 2011 CDC guidelines recommend that, for previously unvaccinated persons, the entire dose of rabies immune globulin (20 IU/kg body weight) should be infiltrated at the wound site, if possible. In the United States, two types of rabies vaccine are currently available: human diploid cell vaccine and purified chick embryo cell vaccine. Either vaccine is given in 1-mL doses on days 0, 3, 7, and 14 after exposure. Rabies immune globulin should not be administered to previously vaccinated persons, who should instead receive two 1-mL doses of vaccine on days 0 and 3[84] (see Chapter 31).

Other Neurotropic Infections

Although Creutzfeldt-Jakob disease (CJD) is not caused by bites or wounds, oral transmission of this spongiform encephalitis has been reported to result from the practice of eating the brains of wild goats, pigs, or squirrels (even when cooked). CJD is characterized by progressive dementia, ataxia, and myoclonus and is untreatable. It is caused by a virus also identified in the brains of domestic sheep and mule deer.[226] The annual death rate from CJD in the United States has steadily increased from 175 per 1 million persons in 1979 to almost 400 per million in 2010.[88]

Chronic wasting disease (CWD) is another transmissible spongiform encephalitis, found in elk and deer in the Four Corners area of the United States, where Colorado, New Mexico, Arizona, and Utah meet. Food-borne transmission of CJD has raised concerns that the species barrier (i.e., the difficulty an infectious disease encounters during transmission from one species to another as a result of structural protein differences between the agent and host) may not protect against CWD. In vitro conversion of CWD to a human infective form has been demonstrated, but further studies are needed. Between 2001 and 2003, six people—all of whom died—were identified as having a CJD variant. All were known to have consumed venison from CWD-endemic areas, although strong data linking CJD with exposure to CWD were lacking. The risk of transmission to humans, even in CWD endemic areas, remains extremely low.[41]

Variant Creutzfeldt-Jakob disease (vCJD), including bovine spongiform encephalopathy (BSE, "mad cow disease") is discussed in Chapter 34.

Indications for Wound Culture

Culture of fresh animal bite wound surfaces, whether judged quantitatively or qualitatively, is useless as a predictor of infection. Some of the pathogens of greatest concern (e.g., genus *Eikenella*) can take 10 days to multiply in culture to the point of identification, by which time most therapeutic decisions have been made. Other organisms (e.g., *Pasteurella*) are fastidious, challenging to identify, and frequently missed by laboratory technicians, who rarely encounter them.[174]

If a wound is infected or bite wound sepsis suspected, obtain wound cultures to guide subsequent antibiotic therapy. In certain cases, cultures should be sent to reference laboratories, such as those in state health departments or at the CDC in Atlanta, Georgia, because reference laboratories have successfully isolated more pathogens on identical samples sent simultaneously to both reference and local laboratories.[390]

Prophylactic Antibiotics

Currently, the weight of evidence does not support use of prophylactic antibiotics for wounds that are not high risk. Human-to-human bites have similar risks for infection as other animal bites. A double-blind study of 125 people with superficial low-risk human bites showed no statistically significant difference in infection rates between antibiotic and placebo groups.[58] Several controlled studies of dog bite wounds found no significant benefit for using prophylactic antibiotics to treat low-risk facial and scalp wounds.[132,256] Other studies recommend the use of prophylactic antibiotics only for high-risk wounds or patients.[122,127,179,411,419] A Cochrane Database Systems review of eight RCTs found no evidence that the use of prophylactic antibiotics is effective for cat or dog bites, except in bites to the hand.[278] Using prophylactic antibiotics is advisable for hand wounds; the speed of development, frequency, severity, and complications of hand wound infections can be impressive.[157,411]

Persons with other risk factors may benefit from prophylactic antibiotics (see Table 30-3). These factors include prolonged time from injury to treatment; complex wounds with massive crushing; heavily contaminated wounds; wounds communicating with tendons; fractured bones or joint spaces; or medical conditions such as asplenia, diabetes mellitus, vascular insufficiency, and immune deficiency.

To be most effective, prophylactic antibiotics must be administered early. The offending bacteria are already present in the wound immediately following the incident. Therefore, bite victims who require early antibiotic treatment should be identified promptly, preferably during triage on entry to the treatment facility. The victim should promptly receive antibiotics by protocol. Oral antibiotics with high bioavailability are acceptable in the treatment of limited infections. The current recommendation for duration of antibiotic prophylaxis is 3 to 5 days (see Table 30-3). IV administration is preferred for severe infections.

Therapy should be tailored to the largest variety of most likely pathogens for a particular type of bite. For most terrestrial mammals, the choice of antibiotic is based on experience with human, dog, and cat bites. However, with an alligator or crocodile bite, or other wounds incurred in freshwater, antibiotic choice should be directed against *Aeromonas hydrophila*[204,279] (see Chapter 33). Wounding that occurs in the ocean raises concern for infection from *Vibrio* species, among others.

Tetanus Prophylaxis

In the United States, cases of human tetanus from animal bites exceed cases of rabies infection by a ratio of 2:1 each year.[34] Spores of *Clostridium tetani* are ubiquitous in soil, on teeth, and in the saliva of animals; therefore, the risk of tetanus may be present from any animal injury that penetrates the skin. Rates of tetanus vaccination are highest in the developed world and fall dramatically in the developing world. WHO data from 2013 reveal that 94% of people in the United States completed their tetanus series, whereas residents of equatorial Guinea have the lowest rate, at 24%.[311] Even with high compliance with initial tetanus vaccination series, U.S. adults may not be as conscientious about booster immunizations. The CDC reported that, of a sample of 3525 U.S. residents, 2.1% had received a tetanus booster (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis [Tdap]) in the past 2 years, and the vaccination rate for tetanus during the prior 10 years was 57% ($n = 1727$).[30,87] Because

TABLE 30-4 Wound Management and Tetanus Prophylaxis

History of Doses of Adsorbed Tetanus Toxoid	Clean and Minor Wound		All Other Wounds*	
	DTaP,† Tdap,‡ or Td	TIG	DTaP,† Tdap,‡ or Td	TIG
<3 or unknown	Yes	No	Yes	Yes
≥3	Only if last dose given ≥10 years prior	No	Only if last dose given ≥5 years prior	No

Modified from American Academy of Pediatrics. Tetanus: Guide to tetanus prophylaxis in routine wound management. In Kimberlin DW, Brady MT, Jackson MA, Long SS, editors: *Red Book: 2015 Report of the Committee on Infectious Diseases,* 30th ed, Elk Grove Village, Ill, 2015, American Academy of Pediatrics.

DTaP, Diphtheria and tetanus toxoids and acellular pertussis vaccine; *Tdap,* booster tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine; *Td,* adult-type diphtheria and tetanus toxoids vaccine; *TIG,* tetanus immune globulin (human).

*Includes wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns and frostbite.

†DTaP is used for children younger than 7 years.

‡Tdap is preferred over Td for underimmunized children 7 years and older who have not received Tdap previously.

tetanus is preventable and many persons still do not receive tetanus immunoprophylaxis in accordance with guidelines, proper emergency prophylaxis against tetanus remains the critical but often underaccomplished intervention (Table 30-4).

For a clean wound that contains little devitalized tissue and that can be easily irrigated and debrided, a previous full course of tetanus immunization plus a booster within the last 10 years is sufficient. For a deep puncture or wound with much devitalized tissue that is difficult to irrigate and debride, and that is thus predisposed to anaerobic growth, a full series of previous immunizations plus a booster within the last 5 years is sufficient. If there is any uncertainty regarding the status of a victim's immunizations, 0.5 mL of diphtheria-tetanus or Tdap booster vaccine should be administered. A high-risk wound should prompt consideration of administration of intramuscular injection of 250 to 500 units of tetanus human immune globulin.

General Complications

Wound infection is generally diagnosed on the basis of erythema, swelling, and tenderness of the wound margins that eventually progresses to production of pus, cellulitis, lymphangitis, and local lymphadenopathy. Lymphadenitis and lymphangitis, which are much less common, occur when local defenses are overwhelmed. Signs and symptoms of systemic infection are rare and suggest bacteremia or sepsis.

Wound infection from animal bites should be treated like any other trauma-related infection. Elevate the wound, immobilize the affected part, remove sutures or staples if present, and provide antibiotic therapy (see Table 30-3). Empiric treatment includes a combined β-lactam/β-lactamase inhibitor antibiotic, a second-generation cephalosporin with anaerobic coverage, or combination therapy with either penicillin and a first-generation cephalosporin, or clindamycin and a fluoroquinolone.[157,281,390] Additional studies recommend azithromycin, trovafloxacin, or telithromycin, which demonstrate good in vitro activity against unusual aerobic and anaerobic animal pathogens.[174-176,390] Garenoxacin, a des-fluoro(6) quinolone, was very active against 240 aerobic and 180 anaerobic isolates from animal bite victims. It inhibited 403 of 420 (96%) isolates, including those of *Moraxella* spp., CDC group EF-4, *Eikenella corrodens*, all *Pasteurella* spp., and *Bergeyella zoohelcum*. *Fusobacterium russii* and 6 of 11 *Fusobacterium nucleatum* isolates of animal bite origin were resistant.[177]

Extremely rare pathogens can cause infection (see Box 30-7). Culture of debrided tissue is the only reliable identification technique, and sensitivity testing may take weeks. In 2002, a 7-year-old girl developed a wound infection as a result of a tiger bite; DNA sequence analysis revealed that one of the causative organisms was a previously undescribed subspecies of *Pasteurella multocida,* which the authors designated "*Pasteurella multocida* subspecies *tigris*."[72] This organism is usually sensitive to ciprofloxacin, cefoxitin, and perhaps rifampin.[329] A diabetic patient developed tenosynovitis caused by *Mycobacterium kansasii* after an accidental bite by his pet dog.[378] *B. zoohelcum* has been reported as a fastidious species that is difficult to culture from patients with infected cat bites.[364]

Septic Complications

Bacteremia and sepsis, although theoretical risks with any animal bite pathogen, have so far been reported with only a limited number of species.[12,156,242,322] Clinical manifestations include cellulitis, endocarditis, meningitis, pneumonitis, Waterhouse-Friderichsen syndrome, renal failure, shock, and death. Purpuric lesions are seen in one-third of cases and may progress to symmetric peripheral gangrene and amputation. Domestic cats are an increasing source of human plague in the southwestern United States. Since the onset of the human immunodeficiency virus (HIV) epidemic, *Rochalimaea* infection (bacillary angiomatosis and aseptic meningitis with bacteremia) has become more prominent and is closely associated with exposure to cats. Although sepsis after an animal bite incident is reported more often among immunosuppressed patients (e.g., fatal *Pasteurella dagmatis* peritonitis and septicemia in patient with cirrhosis[227]), there are reports of fatal cases of purpura fulminans with gangrene, sepsis, and meningitis caused by *Capnocytophaga canimorsus* among previously healthy patients after dog bites.[130,252]

Allergic Reactions

Up to 11% of laboratory workers have allergic reactions to laboratory animal dander, hair, or urine.[421] There have been multiple cases of rodent bite–caused anaphylaxis.[64,253,391,395] One case of hypersensitivity to rat saliva after a bite has been reported.[421] The patient subsequently proved to be allergic to the saliva (presumably to saliva proteins) and not to other portions of the rat. The bite produced lymphangitic swelling and itching that subsided within 24 hours. Two cases of anaphylaxis after dwarf hamster bites have been reported.[302]

Psychiatric Consequences of Animal Attacks

Victims of traumatic or life-threatening events may develop post-traumatic stress disorder (PTSD). We have recognized this syndrome as a result of wild animal attack, and it is rarely reported in the scientific literature.[128] PTSD has been described among children who are victims of dog bites.[324] In one study, 12 of 27 pediatric patients developed either complete or partial PTSD as a result of dog bites.[324] A study in China found 19 of 358 of children developed PTSD after dog bites.[220] After physical recovery from an attack, the victim may be plagued by recurrent nightmares and flashbacks of the event and may develop an aversion to outdoor travel. Violent and multiple attacks or those associated with deep bites have a higher probability of causing PTSD symptoms.[324] Critical incident stress debriefing and post-trauma intervention counseling may be important aspects of care for victims of animal attack.[128]

WILD ANIMAL ATTACKS

Neither the annual number of wild animal bites nor the base human population at risk can be reliably estimated, especially when the human population to be considered is only that exposed to a wild animal or in a wilderness setting. The world supports approximately 5500 species of mammals, 10,000 species of birds, and 9000 species of reptiles. The population of wild animals worldwide is estimated to be in the billions. Many people who have relatively minor injuries caused by wild animals do not seek medical attention unless infection or another complication occurs or they fear exposure to rabies. If the injury is minor, patients are generally treated and released without creation of a record. The following sections consider published data and

species-specific information to discuss prevention of attacks and care for human victims.

CANINES

There are approximately 35 species of wild canines; they are present on every continent except Antarctica. Dingoes, found in Australia, are technically not wild canids, but are descended from dogs.

Coyotes

Coyotes (*Canis latrans*) have not only survived the onslaught of development in the United States, but also have thrived and multiplied. Perhaps as a result, more and more coyote attacks on people have been reported, even in urban areas such as Los Angeles.[20,73,207] Most of these incidents occurred in Southern California near a suburban-wildland interface. One study in 1982 was intended to show the coyote density at such a location. Traps were set for the animals within a half-mile radius of a particular residence, and 55 coyotes were trapped during an 80-day period.[205] Between 2004 and 2007, 541 coyotes on average were removed from Illinois; 312 were from the Chicago area. It is estimated that there are 1250 coyotes in the suburban area surrounding Washington, DC.[387]

Between 1998 and 2003, there were 41 coyote attacks on humans in California, and most were unprovoked; it appears that nonrabid coyotes are becoming more aggressive with humans.[91] Rabies is less prevalent among coyotes and foxes with the advent of an oral rabies vaccine for these species.[365] From 2008 through 2014, at least 42 coyote attacks were reported combined in Arizona, Texas, Minnesota, Oregon, Georgia, Utah, Ohio, Kanas, Pennsylvania, New York, New Hampshire, Massachusetts, and Colorado.[118]

Attack incidents are typically preceded by a sequence of increasingly bold coyote behaviors. These may include nighttime coyote attacks on pets; sightings of coyotes in neighborhoods at night; sightings of coyotes during morning and evening hours; attacks on pets during daylight; attacks on pets on leashes; coyotes chasing joggers and bicyclists; and midday sightings in the vicinities of children's playgrounds[396] (Figure 30-2).

Since the 1970s, more than 100 coyote attacks on humans have been recorded in southern California, with one-half involving children age 10 years or younger.[91] There is a well-documented fatality of a child in 1981 in Glendale, California, who, despite being rescued by her father, died of blood loss and a broken neck.[91] The second confirmed fatality occurred in a 19-year-old woman who was killed by two coyotes (likely coyote-wolf hybrids) in Nova Scotia, Canada, while hiking on a trail in October 2009; the woman died of blood loss from multiple bites, and although one of the animals was wounded, neither was captured.[181]

The safe environment provided by a wildlife-loving public, which rarely displays aggression toward coyotes, is considered a major contributing factor to the increasing numbers of attacks.[91] There has been an increase in reports of coyote attacks in national parks by animals that are subsequently captured and found to be disease free.[73]

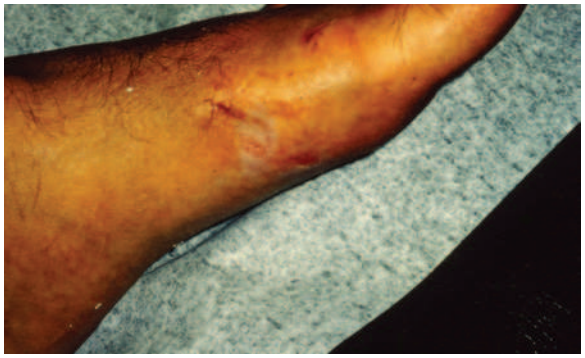

FIGURE 30-2 Hiker at a trailhead bitten on the foot by a coyote while napping. *(Courtesy Luanne Freer, MD.)*

FIGURE 30-3 Yellowstone National Park wolves. *(Courtesy Rick McIntyre.)*

A coyote bite should be treated as a dog bite with respect to antibiotic choice and closure issues; if the animal cannot be captured and examined, rabies prophylaxis should be undertaken. Coyotes have been identified as the reservoir for the human pathogen *Bartonella vinsonii* subsp. *berkhoffii*.[92]

Wolves

The gray wolf (*Canis lupus*), also known as the timber wolf, is the largest wild member of the *Canidae* family (Figure 30-3). There are an estimated 7700 to 11,200 gray wolves in Alaska and more than 5600 in the lower 48 states.[183] Worldwide, the wolf population is estimated at 200,000 in 57 countries.[126]

Wildlife experts suggest that attacking wolves are habituated to humans and human food sources. However, most unhabituated wolves are traditionally timid. Historically, the majority of predatory attacks occurred during summer months, and victims were predominantly women and children. Predatory attacks by wolves against humans tend to occur in clusters, indicating that human killing is not normal wolf behavior, but rather specialized behavior that single wolves or packs develop and maintain until they are killed.[412]

Throughout Europe and Asia, wolves have well-documented histories of cunning behavior, pack attacks, and human killing.[260] In one Indian state, 100 children were injured and 122 killed between 1980 and 1986.[341] Between 1840 and 1861, Russia reported 273 wolf attacks, resulting in the deaths of 169 children and seven adults.[237] North America has fewer verified cases, although recent research indicates 80 events in Alaska and Canada, during which wolves closely approached or attacked people (there were 39 cases of aggression by apparently healthy wolves and 29 cases of fearless behavior by nonaggressive wolves).[258,276] Five wolf attacks on humans occurred within a 12-year period in Algonquin Provincial Park in Ontario, Canada, and a kayaker was pulled from his sleeping bag by wolves in British Columbia, Canada.[258] In 2005, a hiker in Northern Canada was eaten by wolves, although he likely died first of other causes.[142,167] In March 2010, a woman was killed by wolves while jogging in Alaska in what is thought to be the first documented fatal attack by wolves in the United States in modern times.[295] Villagers in the area had noted increasing aggression from local wolves preceding the attack; wolves are the only large predator in the region and had been frequenting the edges of settlements and entering villages at night.

A substantial number of attacks by rabid wolves in Iran over a 10-year period provided the clinical population on whom the human diploid cell vaccine for rabies was tested.[28] The reintroduction of wolves to wild habitat in the Yellowstone ecosystem and Idaho in 1995 has resulted in successful proliferation of many new wolves. However, there has not yet been a negative human interaction.[184]

Comparison of victims of fatal attacks by domestic dogs and wild wolf packs reveals distinct differences in bite-mark patterns. The necks and faces of domestic dog attack victims were the primary sites of injury, whereas a wolf pack victim was spared damage to the neck but had destroyed facial tissue.[420] Most punctures are found on the ventral aspect of the body of victims of domestic canine attacks, as opposed to dorsal punctures in victims of wild or feral canines. Differences in bite-mark patterns between wolves and dogs may be attributed to differences in genetics, training, breeding, socialization, and impetus of attack.[420] Wild canine bites involve characteristic crushed and macerated tissue and should be debrided carefully. Other treatment should follow the same guidelines as for victims of domestic canine attacks. It is speculated that most wounds are attributable to the dominant animals of a pack.

Foxes

Most attacks on humans by foxes are inflicted by rabid animals. Fox bites have caused eyelid lacerations in children sleeping in tents and toe and leg punctures in adults.[238,282,389,405] Foxes typically cause more puncture wounds than do other canines, making their bites more prone to infection. One child died of rabies from fox bites despite appropriate PEP.[389] A rabid gray fox bit several people during a single afternoon in Arizona.[18] A suspected rabid fox attacked three people and several animals in a 12-hour period in Framingham, Massachusetts.[280] Oral vaccination of fox populations has led to decline in the number of rabid animals in some areas, whereas changes in weather and animal migration have increased the burden of endemic rabies in others.[365] Providers should be vigilant to changes in the patterns of rabies endemic to their local area.

Hyenas

Hyenas have tremendously strong jaws, with a bite force of 1000 psi, and can leave teeth marks in forged steel (Figure 30-4). They can amputate limbs and behead small children.[262] Hyenas frequently attack humans in Africa, and in certain areas where locals leave dead or dying people in the bush for predators to eat, hyenas become accustomed to human flesh. Hyenas forage around campsites and villages and are wary of awake people. During the summer months, when Africans sleep outside their huts, many are assaulted with one massive bite that removes the face or entire head. Young children have been dragged from their huts while sleeping when a family member leaves briefly without latching the door. It is common for the hyena to injure or amputate the thumb of a sleeping victim as it drags the victim (by the thumb) to a more convenient place for consumption.[3] Campers are frequently bitten on the face or limbs while they sleep at night, particularly if they have left food nearby. Victims usually survive but are massively disfigured. In some parts of Africa, hyenas are more consistent man-eaters than are leopards and lions.

FIGURE 30-4 African hyena. *(Courtesy Kappa Meadows, MD.)*

Other Canines

In Australia during a 5-year period, dingoes that had been habituated to humans were responsible for 224 attacks, several of them fatal, that required medical treatment.[338] However, dingoes are disappearing from Australia quickly[221] and in general pose little threat to humans.

Jackals are found in Africa, southeast Europe, and Asia. Jackal attacks are typically only from rabid animals. From 1998 to 2005, there were 220 cases of jackal attacks on humans in central India.[9] In 2008, a jackal attacked within five Indian villages, injuring 36 people, four of whom are suspected to have died of rabies.[147] An attack in another Indian town injured 11 people.[201] In many areas of the developing world, the main concern with jackals is transmission of rabies to domestic dogs.

Other canines that traditionally hunt in packs include the cape hunting dog of Africa. Although these pack-hunting animals are feared by indigenous human populations, they typically do not deliberately attack humans.

FELINES

Adult cats have 30 permanent teeth, arranged in rows of 16 upper and 14 lower. The upper teeth overlap the lower, resulting in an overbite; this helps the animal lock its teeth into prey and exert twisting and tearing forces. Compared to canines, feline bites are much shorter and more rounded, and the incisors are narrower and sharper.

If a big cat is encountered in the wild, humans should not run but instead stand their ground; running provokes an instinctive response from the cat to chase. Humans should make themselves look as large as possible, such as by raising arms and jackets over the head. Shouting and acting aggressively may deter an attack. Humans should not turn their backs or crouch when confronted by a big cat. As with other large animals, fighting back once an attack has begun may cause a cat to abandon the attack.[98]

Big cats typically attack from behind and bite the neck and occiput of their prey in an attempt to maneuver their canine teeth between the victim's cervical vertebrae and into the spinal cord.[108,349,410] The goal of rapidly paralyzing the prey is also accomplished by a violent shake of the cat's head, which fractures the cervical spine. In a study of fatalities from jaguar attack, 77% of victims were bitten on the nape of the neck, and one-half of bites were made to the base of the skull.[108] In 20% of cases, the killing bite was to the head, with at least one canine tooth piercing the skull or ear canal. Cheetahs prefer to attack the throats of their prey, crushing the larynx and strangling victims; this method is also used by lions and leopards.[260] In addition, big cats claw prey and produce deep and parallel incised wounds. Several victims have died of exsanguination without evidence of strangulation or cervical spine injury.[108,349] Because of the growing propensity for people in developed countries to keep exotic animals as pets or raise them for profit for hunting purposes, injuries by big cats can occur anywhere. If a victim is encountered in the wilderness after an attack, cervical spine precautions should be taken.

Wound care is the same as for other species, with special attention paid to evaluation for major internal injuries. In particular, observe for penetration of deep structures of the cranium and neck, and rule out injuries of the cervical spine and deep cervical vessels (see Box 30-5).[108] One victim with an apparently trivial puncture wound after a bite to the neck from a pet cougar was discharged from the ED.[232] Within hours, her voice was hoarse; on return, she recalled that the cougar had shaken her in its jaws when it bit her, and air was found in the prevertebral and retropharyngeal spaces on radiographic examination.

As with domestic cats, big cats usually carry *Pasteurella* as normal flora. Because of the deep penetration of the large teeth, *Pasteurella* septic arthritis, meningitis, and other serious deep infections may occur.[165] A patient who was bitten by a lion developed pyogenic arthritis of the shoulder, and an 11-year old child developed purulent meningitis within hours of being bitten on the back of the occiput and neck by a Bengal tiger.[65] Cat-scratch disease caused by *Bartonella henselae,* usually from domestic cats, may also be transmitted by wild cats; the organism has been isolated in puma and bobcat populations in the Americas.[103]

Tigers

Tigers (*Panthera tigris*) are members of the Felidae family and the largest of the four big cats in the genus *Panthera*. They are territorial and solitary animals that need large areas of habitat to support prey demands. Because they are endemic to some of Earth's most populated areas, opportunities are plentiful for major conflict with humans. About 100 years ago, the tiger population in India was as high as 40,000. A 2008 Indian government census report through the Tiger Conservation Authority estimated the tiger population at 1411, largely the result of diminishing habitat and poaching. This trend may slowly be reversing.[121]

Tigers are a major threat to human life in the cats' native regions.[274] Although the number of tigers in the world has dramatically declined, historically they have been the number-one animal killer of humans. Although it is rare for tigers to prey exclusively on humans, man-killing behavior almost invariably results from stress (e.g., illness, injury, advanced age) or loss of habitat and natural prey.[273,361] A tiger subsisting solely on human meat would have to kill approximately 60 adults per year; documented cases in selected regions have approached this rate over periods of up to 8 years.

Unlike leopards, tigers rarely enter human settlements, preferring to remain on the outskirts. Man-eating tigers in India between 1906 and 1941 ate an estimated 125 persons each, and one had killed 436 persons. However, compared with lions, tigers are not thought to become exclusive man-eaters; rather, they are opportunistic man-eaters, in the place of plentiful natural prey, and tiger biologists hypothesize that these animals have become unafraid of humans.[274]

Over the last five centuries, an estimated 1 million people have been eaten by tigers. During the 19th century, the tigers' toll in India averaged 2000 victims per year. From 1930 to 1940, the annual number never dropped below 1300. During the late 1940s, the rate decreased to 800 per year, where it remains. In other regions, such as the Sundarban Islands of northern India, rapid habitat loss as a result of climate change has caused an increase in tiger attacks. In this region, seven fishermen were reported to have been killed by tigers during the first half of 2008.[146] Conservation efforts responsible for the growth in tiger population may lead to more attacks. Within the first 2 months of 2014, 10 people were killed by a prowling tiger who strayed from a national park to villages in the northern Indian states.[301]

Adult tigers are so powerful that their human victims are often killed instantly. It is not unusual for a limb to be severed with a single bite,[138,254] and a tiger's swiping blow to the human head can cause skull fracture.[333] As with many big cats, tigers typically strike without warning from behind, biting the head and neck and often shaking the head violently to sever the victim's spinal cord.[236]

Lions

The lion (*Panthera leo*) is grouped with the four big cats of the genus *Panthera* (Figure 30-5). Despite their appearance and reputation, lions are not as feared or respected by experienced hunters as are tigers (Figure 30-6). Lions are primarily scavengers, making fewer original kills than hyenas.

Conversion of wild lions to eating humans has been blamed on drought, famine, and human epidemics in which large numbers of corpses are abandoned in the bush. Consideration has been given to the theory that infirm lions are more prone to man-eating behavior. Although tooth decay may explain some incidents, prey depletion in human-dominated areas is a likelier cause of lion predation on humans.[318] There is an historical predator-prey relationship between *Panthera* and primate genus members, which suggests that man-eating behavior is neither unusual nor aberrant.[323] Lion attacks tend to cluster during harvest times and during periods when prey is scarce.[315] Wounded or provoked animals, usually in dense brush, pose the greatest risk to hunters (Figure 30-7).

American and Tanzanian scientists report that predation of humans in rural areas of Tanzania increased from 1990 to 2005. At least 563 villagers were attacked and many eaten over this period.[315] Lions are estimated to eat 300 to 500 Africans per year,

FIGURE 30-5 African lion. *(Courtesy Cary Breidenthal, RN.)*

FIGURE 30-6 Lion. *(Courtesy Kappa Meadows, MD.)*

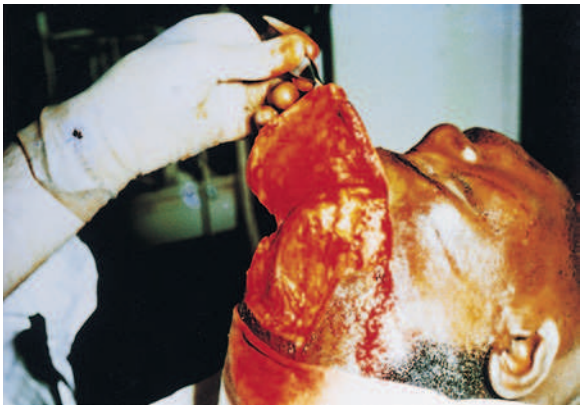

FIGURE 30-7 Lion attack victim. This African victim was rescued by bystanders while his head was in the lion's mouth. His only injury was a degloving scalp laceration. *(Courtesy Harold P. Adolph, MD.)*

and rank second to tigers as successful predators on humans. During the late 1930s and early 1940s, three generations of a single pride in Tanzania were credited with between 1500 and 2000 human kills. A protected population of 250 Asiatic lions in India attacked 193 humans, killing 28 between 1977 and 1991; biologists credit drought and lion baiting within tourist shows for this carnage.[350] Lack of habitat also plays a role. The International Union for the Conservation of Nature (IUCN) demonstrated the need to reduce the increasing human-lion interface as the geographic ranges in Africa and Asia decrease.[35]

Lions that subsist exclusively on human flesh require approximately 40 victims per year to stay alive. They usually kill instantly with one bite to the head or neck or with a swipe of the paw, which can break an ox's neck. Lions have tremendous strength and can easily carry a human victim for a mile without rest.

A threatening gesture or shout may repel a lion, although a lioness guarding her cubs is more likely to attack. Experienced hunters find when a charging lion is faced head-on and confronted, it will often turn tail and run. Many wildlife organizations advise standing one's ground defensively because an intended human victim who flees is more likely to be attacked.[54,114] However, this may not be as effective for pumas, where immobility may be a sign of vulnerability.[384] Historically, many victims who survived the initial mauling later died of infection. Although most lions in captivity become passive and dull, circus and zoo lions periodically kill attendants; many such deaths have occurred when keepers accidentally have backed into or trod on an animal.

Leopards

Leopards are the smallest of the four big cats in the genus *Panthera* (Figure 30-8). As with the other big cats, leopards experience loss of habitat and hunting pressure that have reduced their range. Originally inhabiting wild lands from Korea through Africa, leopards now exist primarily in sub-Saharan Africa, with isolated pockets across the Asian subcontinent.[198] However, leopard population numbers still exceed all others in the genus *Panthera*.

Most attacking leopards have been previously wounded or attacked by a dog; when wounded, trapped, or cornered, a leopard is unpredictable, sometimes attacking the first person within striking distance. Unmolested and in normal health, the leopard is a shy and nervous animal with a marked fear of humans. Unlike a lion or tiger, the leopard relies on fast claw work and biting. Like the jaguar, the leopard may go for the neck (in an effort to sever the spinal cord) or attempt disemboweling by raking at the victim's abdomen with its claws. The leopard seems inclined to retreat when much resistance is offered; the chance of surviving a leopard attack is higher than the chance of surviving a lion or tiger attack. There is a documented report of a man armed only with a screwdriver who fought and killed an attacking leopard.[243,244] Before the era of antibiotics, three-fourths of people mauled by leopards died from wound infection; however, modern morbidity from these attacks is estimated to be less than 10%.[29,105]

FIGURE 30-8 Leopard. *(Courtesy Kappa Meadows, MD.)*

Mauling by leopards is much more common than killing; estimated casualties are 400 per year, mostly in Africa. The leopard does not often turn into a man-eater; when it does, it attacks mainly children or sick adults. In the state of Bihar in India, leopards ate 300 people between 1959 and 1960.[105] The leopard of Rudraprayag in India killed 150 people between 1918 and 1926. Becoming increasingly bold, it eventually took its prey by smashing down doors, leaping through windows, or clawing its way through the walls of mud huts. The Panar leopard killed more than 400 people after injury by a poacher made it unable to hunt normal prey.[195] As with lions that hunt humans, leopards completely change their normal hunting patterns when the prey becomes exclusively human.

Jaguars

The jaguar is the final of the four big cats in the genus *Panthera* and the only one native to the Americas. It is not known to prey on humans, although attacks do occur. Jaguars typically stalk and ambush rather than chase.[361] In February 2007, a U.S. zookeeper was mauled to death by a jaguar.[283] In January 2009 in Maryland, a worker at a private zoo was severely mauled.[161] There have also been reports of jaguar attacks in the jungles of South and Central America.

The jaguar is the largest feline in the western hemisphere. It has an exceptionally powerful bite, one of the strongest for large felid carnivores.[427] It employs a variation of the deep throat bite and suffocation technique used by other *Panthera*. Using its canine teeth, the jaguar pierces directly through the temporal bones of the skull between the ears of its prey, piercing the brain.[145]

Cougars

The North American cougar (*Puma concolor*), also called *mountain lion, catamount,* and *puma,* is a clever and shy cat. It is the most widely distributed large animal on the American continent, and the second largest cat in the western hemisphere, although it is more closely related to smaller cats. The traditional range of cougars has been greatly constricted because of government-sanctioned hunting bounties. In the last 50 years, as cougar populations have rebounded from historic lows, they have begun to reoccupy traditional territories in the western United States that are now settled or frequented by humans. This has led to increased probability of human-cougar interactions.[234] The current cougar population in Oregon is estimated to be more than 5700,[310] and the U.S. cougar population is estimated at 16,000.[399] Humans live, exercise, or picnic in cougar country with increasing frequency.[383] Thus, modern suburban dwellers (who are typically ignorant of wild animal behavior) are now, often unwittingly, in regular close contact with cougars near their homes and in parks.

In North America between 1890 and 2004, there were 88 confirmed cougar attacks on humans, resulting in 48 nonfatal injuries and 20 human deaths.[17] More people have been attacked since 1975 than during the entire previous century,[6,25,153] and most attacks occurred in the western United States and Canada. Throughout the United States, cougars ranked 16th in recent years as an animal-related cause of deaths, just behind jellyfish and goats.[342] The first cougar attack in New Mexico in 34 years occurred in 2008.[299] In California, no attacks occurred from 1925 until 1986, when two children were attacked in a regional park in southern California.[232] Between 1986 and 2013, 14 confirmed attacks on humans occurred, three of which were fatal.[259]

Victims jogging and biking may evoke a predatory response. Young animals that are newly independent and establishing their

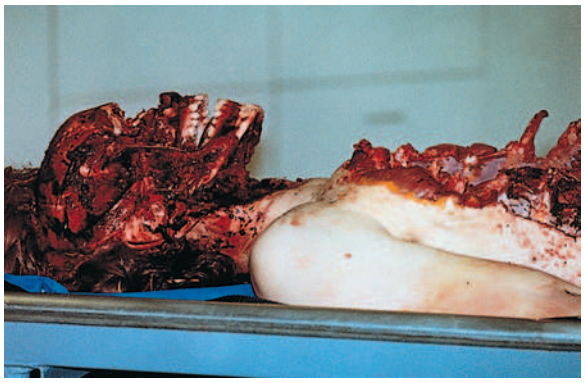

FIGURE 30-9 Victim of cougar predation and fatal mauling. *(Courtesy Ben Galloway, MD.)*

territory are the most likely to attack humans.[234] Children tend to be preferred victims; 64% of attacks and 86% of fatalities involve children.[40,218,225] There has been only one alleged report of a cougar preying exclusively on humans, but cougars usually consume victims of their attacks[37,349] (Figure 30-9).

The cougar hunts like a domestic cat: crouching, slinking, sprinting, pouncing, and breaking the neck of its prey. Neck, head, and spinal injuries are common and sometimes fatal. As with many potentially dangerous wild animals, the cougar can often be frightened off by the victim's aggressive behavior, even after the attack has begun.[196] In 2002, a man fought off and killed an attacking cougar with a 7.5-cm (3-inch) pocketknife.[406] In fact, individuals who remain stationary are more likely to sustain severe injuries than individuals who run when attacked.[116] This is thought to result from the cougar assessing immobility as a sign of inattention or disablement.

Bobcats

The North American bobcat (*Lynx rufus*), found throughout the United States, is probably named for its short tail, which is 15.3 or 17.8 cm (6 or 7 inches) long. Its natural range extends from Canada to northern Mexico and expands in the more northern latitudes. The bobcat has long legs and large paws, can weigh up to 13.6 kg (30 lb), and is capable of killing animals as large as deer.

Although unusual, bobcats occasionally attack humans. In most of these cases, the bobcat is rabid and unusually aggressive. In 2000, a Minnesota woman reported puncture wounds to her hand and arm that were consistent with the bites of a bobcat. Another woman was the victim of a witnessed bobcat attack in Big Bend National Park, Texas.[49] In this case, although experts believed that the animal was behaving normally, the victim was empirically treated for rabies exposure. A hunter sustained injury to the eye and ocular adnexa requiring surgical repair after a bobcat attack.[202] This patient was given rabies prophylaxis.[203] Two people were attacked by a rabid bobcat in 2008 in Arizona while hiking in the mountains, with puncture wounds and scratches; the bobcat was described as unusually aggressive and pursued the couple up a hill.[155] A man in Florida reported being attacked by a rabid bobcat on his front porch, where he was clawed and bitten until he managed to strangle the animal.[267]

PRIMATES

The Primates order is divided into two main groups: the *prosimians,* which have characteristics most like those of the earliest primates, and the *simians,* comprising monkeys and apes. Simians are further divided into New World monkeys of South and Central America and Old World monkeys of Africa and Southeast Asia (Figures 30-10 and 30-11).

Monkeys and other primates inflict vicious bites that have a high infection rate despite use of prophylactic antibiotics.[178] In developed countries, human-primate conflict is an uncommon problem limited to laboratory and zoo workers. In tropical developing countries, large apes (e.g., baboons) are large and frequently aggressive. Weighing up to 40.8 kg (90 lb), a large baboon can be dangerous, if not lethal, particularly when the animal has frequent contact with humans and loses fear of them. There are multiple reports of baboon attacks in South Africa against visitors, typically when the baboon is foraging for food.[70] There have been numerous reports of packs of wild monkeys driven out of the jungle by hunger, attacking humans who block their access to food sources.[345,352,380] Feral macaque populations exist in regions of Texas and Florida.[313]

Monkeys often bite hands and have been known to amputate parts of fingers. A literature review revealed 132 cases of simian bites in which *Bacteroides, Fusobacterium* spp., and *Eikenella corrodens* were isolated from some of the wounds.[178] Three victims of simian bites with infected wounds grew diverse bacteria, including β-hemolytic streptococci, enterococci, *Staphylococcus epidermidis,* and Enterobacteriaceae.[178] Simian bites should be considered high risk and treated in the same manner as human bites.

Old World macaque monkeys (i.e., rhesus macaque, cynomolgus, and other Asiatic macaque monkeys) are often infected with simian herpesvirus B. Transmission to humans is rare, but the risk is real, especially for animal control and laboratory workers.[135,300] As with rabies, local wound treatment may be important; of 61 persons bitten by likely infectious monkeys who received wound cleansing with cetrimide and iodine solution, none became infected.[398] The mortality rate for persons infected with simian herpesvirus is 80% without treatment. Since identification of the virus in 1932, there have been 31 documented cases of human infection, 21 of which were fatal.[335] The most recently

FIGURE 30-10 Monkeys groom each other at Swayambhunath, a holy temple complex in Kathmandu, Nepal. Every year, tourists are bitten by monkeys who mingle in crowds begging for food. *(Courtesy Luanne Freer, MD.)*

FIGURE 30-11 Baboons in Africa. *(Courtesy Kappa Meadows, MD.)*

documented case occurred in 2008 and involved a woman who was bitten by a vervet monkey in the Democratic Republic of the Congo[305,409] (see Chapter 34).

The wild gorilla, despite its reputation and appearance, is shy and avoids humans. Although it may charge in defense, it seldom attacks and can be easily confronted and forced to retreat. When a gorilla attacks, it typically takes one bite and runs. In Africa, gorillas are responsible for two or three attacks per year; none is fatal, and few are severe. Chimpanzees occasionally attack humans, but usually only if provoked or cornered.[19] Rare cases of chimpanzees eating children and women have been reported. The baboon is responsible for one to two attacks per year, almost all in South Africa, usually by pets. Human predation has been reported.[109,197,430] The incidence of hunting and meat eating by these animals has increased over the last century, perhaps paralleling the evolution of humans into hunters and meat eaters.[105]

People who own monkeys as pets may not appreciate the danger such a pet can pose. Even the most docile pet monkey has wild animal tendencies and instincts and can attack without warning. According to People for the Ethical Treatment of Animals (PETA), between 1990 and 2014, several incidents involved captive primates, resulting in the deaths of 35 primates and one human, as well as injuries to 230 humans.[124]

HERBIVORES AND UNGULATES

Herbivores are animals that adapted to consuming only autotrophs, such as plants, algae, and bacteria. They are a diverse group of mammals that includes horses, pigs, cattle, camels, deer, rhinoceri, zebras, and hippopotami. The term *ungulate* refers to "hoofed animal." Most ungulates are herbivores, although some, such as pigs, are omnivores and opportunistic feeders that consume a wide variety of plants and animals.

Wild Swine

Wild pigs are more likely than their domestic counterparts to inflict injury. With a population of over one-half million roaming the French countryside, wild pigs cause crop loss and occasionally gore and bite humans.[265] A typical wild boar attack can result in multiple penetrating injuries to the lower part of the body caused by the boar's tusks (Figure 30-12). Injuries occur primarily in the lower extremities due to the height of the animal.[188] In an unusual incident, an Indian laborer was gored from behind by a boar, which then returned and attacked his head while he was on the ground; the man died of severe craniofacial injuries.[268,362]

Domestic pigs can easily become feral, and such populations often revert to the behavior and appearance of a wild boar. In the United States, feral pigs, some weighing up to 181 kg (400 lb) with 10-cm (4-inch) tusks and prolific breeding qualities (litters of up to 19 have been reported), are experiencing explosive population growth. More than 1.5 million wild swine roam the state of Texas, and motor vehicle collisions as well as attacks on humans have increased.[60] In 2008, it was estimated that the population of 4 million feral hogs cause approximately $800 million worth of property damage per year in the United States.[57] Swine wounds should be treated as high risk for infection, warranting broad-spectrum prophylactic antibiotics and close follow-up if the victim is not admitted to a hospital.

FIGURE 30-12 Wild boar. *(Copyright iStockphoto.com/Neil_Burton.)*

FIGURE 30-13 African water buffalo with calf. *(Courtesy Cary Breidenthal, RN.)*

African Buffalo

Known as one of the "big five" (i.e., the five most difficult African animals to hunt on foot: buffalo, lion, elephant, black rhinoceros, and leopard), African buffalo (*Syncerus caffer*) gore and kill more than 200 people each year. The unprovoked African buffalo usually does not attack. However, when provoked (e.g., shot or cornered), it charges, is difficult to avoid or stop, and can "hook" the victim 3 m (10 feet) into the air with its horns (Figure 30-13). Buffalo that charge humans are usually elderly solitary bulls that have left the safety of the large herds, most often because of wounds from poachers' snares or spears or from lion attacks. The buffalo is wily and intelligent; wounded buffalo may lie in wait for trackers or may double around and come up behind hunters on the trail, often with fatal consequences for the humans.

When the victim is prostrate, the buffalo gores him into the ground with its horns and the heavy horny boss across its forehead, and then whips its head from side to side, disemboweling the victim with the sharp horn tips. The horns are often covered with mud, so goring wounds may be heavily contaminated.[360]

Once a common wild animal on the Indian subcontinent and in Southeast Asia, water buffalo currently are primarily domesticated work animals in these regions. Domesticated animals pose little threat to humans but are still capable of attack if provoked. A water buffalo attacked and gored a man to death in Australia in 2005, the first recorded death there from a water buffalo in 12 years.[394] The buffalo had been acting strangely for several weeks, charging people and entering towns, and was thought to be stressed because of drought in the region.

American Bison

Brought back from the brink of extinction, a free-ranging herd of North American bison (*Bison bison*) with a fluctuating population of 2300 to 5000 now lives on land in and around Yellowstone National Park.[297] Fifty-six injuries and three deaths were documented from 1975 to 1993 in the park as a result of bison-human interactions.[111] Despite warnings to avoid approaching these animals any closer than 7.6 m (25 feet), most attacks involve close human approaches to obtain photographs. One man in 2012 was seriously gored by a bison after failing to retreat as it approached him.[337] Two more people were injured in 2015, both within less than 1.8 m (6 feet) of the animal.[293] The mechanism of injury in bison attack is usually penetrating injury, with punctures from goring by horns and blunt injury caused by being tossed in the air and falling or being butted by the animal's massive head (Figure 30-14). Goring injuries most frequently involve the buttocks or posterior thighs as the victim turns away from the bison to flee (Figure 30-15).[111] Gored abdomens and

FIGURE 30-14 American bison. *(Courtesy Luanne Freer, MD.)*

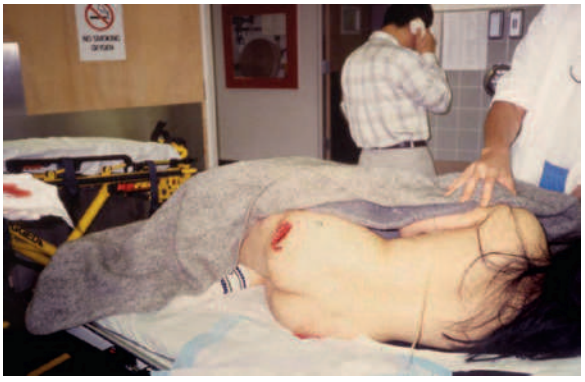

FIGURE 30-15 Wound from bison goring. *(Courtesy Karen Hansen.)*

eviscerations have been reported. Despite the inevitable contamination of these deep punctures, wound infection is rare if careful operative irrigation and debridement with closure are combined with broad-spectrum prophylactic antibiotics. In one series of reported injuries, cephalosporins were used in most cases.[111]

Elephant

The elephant (*Proboscidea elephantidae*) can be one of the most dangerous wild animals and was, until recently, probably the greatest killer of hunters. It is the largest land animal (Figure 30-16). There are three species: African forest (*Loxodonta cyclotis*), African bush (*L. africana*), and Asian (*Elephas maximus*). The annual human death toll related to these animals in central Africa is probably between 200 and 500.[105] Most injuries

FIGURE 30-16 African elephant. *(Courtesy Kappa Meadows, MD.)*

FIGURE 30-17 African elephant bluff-charges the photographer. *(Courtesy Cary Breidenthal, RN.)*

occur when humans accidentally approach elephants too closely, which the animals interpret as a threat. However, elephants turn rogue occasionally and deliberately attack and kill humans (Figure 30-17). As humans and elephants compete for the same space and humans devastate forests, conflicts will likely increase (Figure 30-18).

Elephants that are captive in zoos and circuses cause deaths. Since 1990, captive elephants have killed 39 humans and injured more than 100 worldwide.[321] In 2007, a domesticated elephant in Vietnam gored his two handlers to death after they forced him to work without eating.[199] A few rare stories suggest that elephants may actually eat human flesh, as in 1944 at the Zurich Zoo. In 2011, an elephant in India was found with human remains in her stomach after killing 17 people in India.[432]

Some experts theorize that elephants are capable of vindictive motivation for attack.[209,368] In Africa, groups of young elephants have attacked villages in what is thought to be revenge for the destruction of their society by massive hunting done during the 1970s and 1980s.[200] It has also been theorized that the same elephant responsible for 17 human deaths in India in 2011 was driven by rage after the elephant's calf was killed.[432]

India is home to most of the world's 40,000 Indian elephants (subsp. *Elephas maximus indicus*) that reside throughout the subcontinent. Elephant attacks have become so common that a new statistical category known as *human-elephant conflict* has been created by elephant researchers.[366] An estimated 100 to 300 humans are killed each year during crop raiding in India.[216] Elephants kill about 50 people each year in Sri Lanka. Such encounters force some families to sleep in trees. Elephants in one area with a human population of only 25,000 kill at least

FIGURE 30-18 Tourists swim with Asian elephants. *(Courtesy Luanne Freer, MD.)*

FIGURE 30-19 Asian elephant. *(Courtesy Luanne Freer, MD.)*

four people a year.[22] In 2004, 22 people were killed in Assam by rogue elephants that repeatedly trampled homes and ate local crops. Reportedly, the elephants were also seeking rice beer, for which they had developed a taste[21] (Figure 30-19).

Elephants kill by trampling, goring with the tusks, or striking and throwing with the trunk. After the victim has been run over or skewered with the tusks, the elephant may then crush the victim by kneeling. Elephants have been known to use weapons during their attacks; a villager who retreated safely up a baobab tree was hit by a tree branch that a bull elephant had picked up in its trunk and used as a club. Elephants frequently rip the victim's body apart and scatter the pieces, later covering them with grass and branches. Another elephant tactic is to toss a victim into the trees or straight over the back; a number of victims have survived this experience. Some hunters pursued by elephants have diverted them by throwing off items of clothing.

Hippopotamus

The hippopotamus (*Hippopotamus amphibius*) is a frequent killer in Africa (Figure 30-20). Its placid appearance in zoos belies its activity and personality in the wild; they are ill-tempered at best and have been known to attack crocodiles. A hippopotamus can run at speeds up to 72.4 km/hr (45 miles/hr) on land. It will attack boats and people in the water if it feels trapped (e.g., between a boat and deep water) (https://www.youtube.com/watch?v=TEXYw91lQuY0), or if its calf is threatened. Hippopotami graze on land and habitually run along established narrow tracks back to the river, mostly at night but also in the day. They are not known to change course when challenged, and humans who make the mistake of staying in their tracks may be trampled. With its large canine teeth, a hippopotamus can chop canoes (and the people in them) in half, as occurs several times a year on the Zambezi River in Zimbabwe. Surviving a hippopotamus attack is uncommon. Injuries are typically very extensive and can include significant crush injuries to internal organs and other tissues, as well as long-bone fractures.[141,257,327]

FIGURE 30-20 Hippopotami. *(Courtesy Leda Phillips, BSN.)*

Rhinoceros

The black rhinoceros has been represented as one of the most aggressive animals in Africa because it charges any moving object, including trains. A click of a camera, gentle movement, or scent is enough to induce a charge. Because the rhinoceros has poor eyesight but excellent hearing, it may well be running toward sounds to investigate them. Contrary to the popular belief that because of its nearsightedness it can be easily sidestepped, the rhinoceros is quite agile.[104] At the end of its charge, it usually hooks right and left with its horns, and may toss the victim high (3.7 m [12 feet]) in the air. However, as with so many large wild animals, it probably does not desire confrontation. Rhinoceri often flee after they have identified a sound as originating from something dangerous (e.g., a human), and persons who have fallen while running from a charge have been investigated with a few typical snorts and then ignored. However, severe injuries can result if the person fails to get out of the way of a rhinoceros. Black rhinoceri in Africa kill a handful of people each year.[141] As from the hippopotamus, injuries and death may have more to do with being in the path of a very large and fast-moving object than with the animal's malicious intent. The white rhinoceros is typically docile; attacks on humans are extremely rare.

Tapir

The tapir (*Tapirus terrestris*) lives in the rain forests of South America, Central America, and Mexico. The female reaches a length of up to 2 m (6.6 feet) and height of up to 1 m (3.3 feet), and weighs up to 200 kg (441 lb). Tapirs are herbivorous and generally docile. They seek refuge in brush when threatened or submerge themselves in water until the threat is gone; however, they may defend themselves by biting with powerful jaws and teeth. A tapir bit off the arm of a zookeeper who came between the usually docile animal and its calf,[135,210] and a man died of exsanguination from arm and neck lacerations after a tapir attack in Brazil.[189,415] The Environmental Minister of Costa Rica sustained a tapir bite in Corcovado National Park in 2006; this attack also involved a female defending its calf.[343]

Moose and Elk

Moose (*Alces alces*) are large animals. Although typically docile, they can become aggressive, especially during fall rutting and spring calving seasons. When fed by humans, moose may become more aggressive when food is no longer available.[11] Engrained through the forces of evolution, moose still respond to dogs as predators and will attack and kill them without provocation. Moose may express impending aggression (e.g., charging) by raising their rump hairs, laying back their ears, or licking their lips. The object of the attack should quickly move behind a large, solid object for protection. If knocked to the ground by a moose, the person should roll into a ball, protecting the head with the hands and arms and remaining still until the moose leaves.[11] Deaths by moose attacks are exceptionally rare and almost inevitably involve poor human judgment. In 1995, a man was killed by a moose in urban Alaska when he approached a cow with a calf that had been harassed by students throwing snowballs.[298]

Most human injuries caused by moose result from moose-related motor vehicle collisions, which are notably hazards in New England and Sweden.[51,151] Because of their large body mass and high center of gravity, moose pose a unique danger to unwary motorists. In moose-related auto collisions, the bumpers often only contact the moose's long legs, so the body continues to travel unimpeded through the windshield with significant blunt trauma to front-seat occupants. A New England report states that an average of two persons per year are seriously injured when their vehicle strikes a moose, usually after dark; 70% of persons injured have head and facial injuries, and 26% have cervical spine injuries.[151] The mortality rate in this series was 9%, and morbidity declined with the use of seat belts and

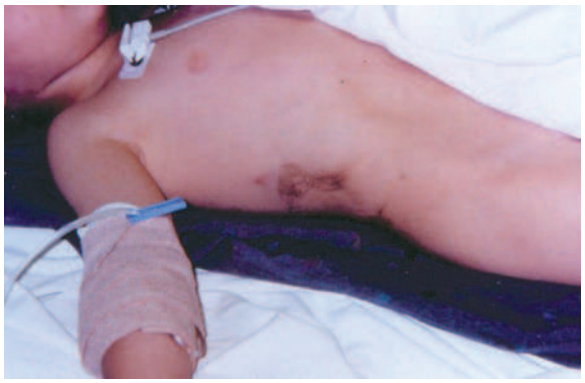

FIGURE 30-21 Toddler victim of a moose attack. *(Courtesy Luanne Freer, MD.)*

rear-seat location. A more recent study reported by the Maine Department of Transportation showed that the yearly collision rate with moose was 53 per 100,000 population. Again, the majority of collisions occurred after dark.[215] Each year in British Columbia, it is estimated that three people are killed and an additional 368 injured in wildlife collisions (deer, moose, and elk); 17,200 animals are killed by these collisions as well[388] (Figure 30-21). Similar to moose, bull elk may attack people during rutting season, and cows may attack by butting and stomping when protecting their young.[319]

Deer

The deer population continues to grow in parts of the United States. As a disease reservoir host to vector ticks, deer contribute to the increasing incidence of human Lyme disease.[290] One study examined deer density, tick abundance, and human cases of Lyme disease in a Connecticut community from 1995 to 2008. Cases of Lyme disease were strongly correlated to deer density. Reducing deer density to 5.1 deer per square kilometer resulted in 80% reduction in resident-reported cases of Lyme disease.[231]

Deer rarely attack humans, but deer–motor vehicle collisions are quite common in densely populated areas. About 1.5 million deer-vehicle collisions occur each year in the United States,[106] causing about 150 deaths and $1.1 billion in property damage. More than 21,000 collisions occurred in Finland in 1 year, most during the first hour after sunset.[190]

Deer attacks on humans are very rare. One deer jumped through a window of a law office and injured an attorney.[24] A buck in rut carried a man in its antlers for 45 minutes, then pinned the man on the ground until he was rescued.[44] A startled buck gored a child when the boy was feeding the animal; the antler penetrated the child's axilla, lacerated his pulmonary artery, and caused death by exsanguination.[150]

Deer may bite and, like other ungulates, may carry *Pasteurella* as oral flora. Female deer bite other deer when fighting. Males bite when testosterone levels are low; at these times, antlers are soft and pain sensitive and cannot be used as weapons.[235] Foreleg kicks are more common, because the deer stands on its back legs. Because deer have a dental pad rather than upper incisors, bites are rarely serious and usually directed at the arms or back, which are normally well covered by clothing. These bites are usually single nips.

Yak and Dzo

Yaks (*Bos grunniens* and *Bos mutus*) and dzo are typically found throughout the Himalaya region of southern Central Asia. They are one of the largest bovids and can weigh up to 1000 kg (2200 lb). Dzo (male) and dzom (female) are crossbreeds of yak and cattle. Some Westerners have difficulty telling these species apart and often use the more colloquial term "yak." In general, most yaks are domesticated and have been for thousands of years, whereas wild yaks tend to avoid humans. Aggression is not usually encountered unless the animals are defending their young or during mating season.[255] When encountered on mountain trails, they should be given reasonable berth, preferably by positioning oneself safely on the uphill side of the trail.

Guanaco and Llama

The guanaco (*Lama guanicoe*) is a camelid native to South America. It shares the same genus as the domesticated llama. Adult llamas grow "fighting teeth," consisting of modified canine and incisors.[129] Attacks on humans are rare. However, a condition known as *aberrant behavior syndrome,* or berserk male syndrome, has been described in some llamas exhibiting aggressive behaviors toward people because of oversocialization with humans.[1]

Other Wild Herbivores

Other wild species, such as the giraffe, may turn rogue, but this is exceedingly rare. The black wildebeest has killed one or two zookeepers, as have the spiral-horned kudo and bushbuck. Other antelopes have killed or wounded hunters or zookeepers with their sharp horns. Zebras are known to bite tourists who approach too closely.[397]

BEARS

See Chapter 32.

KANGAROOS

Kangaroos (family Macropodidae) are the largest living marsupials, weighing up to 79.4 kg (175 lb). They use their tails for balance when they jump and can leap almost 9.1 m (30 feet) forward and 2.4 m (8 feet) high. They are active in the evening and at night, when groups of kangaroos, called *mobs,* forage on grasses and other plants. A study from New South Wales reported that kangaroos account for 60% of all animal-related automobile crashes in Australia resulting in fatalities, and for 40% of automobile-animal crashes resulting in injuries.[276] From 1996 to 2006, there were 2100 kangaroo-vehicle collisions and 13 human deaths from kangaroo-vehicle incidents. In remote areas of Australia, the possibility of hitting a kangaroo is so high that residents fit their vehicles with "roo bars" to deflect kangaroos off the front of the vehicle.[5]

In 2004, several unprovoked kangaroo attacks in Australia led to speculation about a rabies-like disease affecting marsupials; however, there is no published evidence to support this theory. The only well-documented kangaroo attack resulting in a fatality was in 1936, when a hunter was killed trying to separate his dogs from a fight with a kangaroo. Erratic kangaroo behavior may also result from extreme thirst and hunger.[413] Kangaroos attack using a combination of kicking and trampling with their powerful hind legs. They are capable of delivering slashing wounds with their feet. In 2013, a 13-year-old Australian female jogger received several deep scratches to her legs after encountering two kangaroos.[217]

LARGE BIRDS

Ostriches (*Struthio camelus*) are responsible for one to two deaths per year, mostly in Africa, where they are raised commercially[23] (Figure 30-22). Most of the fatal attacks involve kicks to the head and abdomen. Disembowelment and eye injuries have been reported.[96,228] The ostrich can kick only forward, but when it does, a sharp toenail flicks out like a switchblade and can penetrate the abdomen. Because the ostrich can easily outrun a person, the only protection is to lie prone to protect against disembowelment and to cover the neck to protect against pecks. Eventually, the ostrich loses interest and allows the person to escape.

The cassowary, which is common in New Guinea, can easily disembowel a hunter with a single kick from its long, sharp toe claws. Birds of paradise have been found to secrete venom on their feathers, although no cases of human toxicity have been reported, and the phenomenon is little studied. The emu is a flightless bird native to Australia that may weigh 45.4 to 68 kg

FIGURE 30-22 African ostriches. *(Courtesy Cary Breidenthal, RN.)*

(100 to 150 lb). It is usually docile, but when cornered or frightened, may lacerate a handler by kicking.[222]

RACCOONS

Raccoons (*Procyon lotor*) are medium-sized animals native to North America that adapt well to a wide range of changing habitats. The raccoon is at home as much in urban settings as in deciduous forest ranges and can be found across the United States. A population was established as a game animal in Germany during the mid-20th century and is now well established in several northern European countries.[414] As raccoons expand their range to include urban settings, conflicts with humans will increase. Raccoons are occasionally kept as pets. Raccoons tend to be opportunistic foragers; keeping food and garbage cleaned up and stored properly can eliminate potential encounters.

Of the 6153 documented animal rabies cases reported in the United States in 2010, 2246 (36.5%) were in raccoons, which represents the highest carrier rate for rabies.[336] In the United States, large raccoon rabies epizootics in New England and the mid-Atlantic states are spreading, and most rabies-positive animals are captured near private homes.[368,416] In 2003, raccoon variant rabies caused a human death in the United States, although the route of transmission was unclear because there was no bite.[81] Because rabies is so common in raccoons, rabies PEP should be strongly considered for victims of attack or unusual close contact. Some other important diseases associated with raccoons are leptospirosis, listeriosis, tetanus, and tularemia.[264] Raccoons are the definitive host of *Baylisascaris procyonis,* a zoonotic nematode parasite that may cause larva migrans syndromes in humans.[431]

PORCUPINES

Porcupines are a member of the order *Rodentia,* further divided into New World species (12 identified) and Old World species (11 identified). They are rarely reported to bite, but their quills may become embedded in the skin of humans. Quills are released on contact or can be shed when the porcupine shakes its body, but cannot be launched at attackers. Because of the structure of quills, they not only embed themselves and are extremely difficult to extract, but also can migrate as much as 25 cm (10 inches) under the skin. The average porcupine has 30,000 quills, which range from less than 2.5 cm (1 inch) to 10 cm (4 inches) in length. The quills are barbed, and their cores are spongy; if they are not removed from a "quilled" victim immediately, they absorb body fluid and expand, causing them to flare farther outward. Thus, each movement of the victim's muscles or body helps a quill embed deeper. Anecdotally, such migration has led to internal organ damage and death in humans. Quilled dogs have developed a variety of illnesses, including brain penetration as a result of migration[125] (Figure 30-23). Infection seldom results, because quills have mild antiseptic properties, presumably to protect the porcupines, which sometimes impale themselves.

No medical reports of appropriate human treatment or complications of porcupine quill injuries exist, although anecdotal reports of human tetanus from porcupine quill puncture have come from Africa.[3] Most veterinarians remove quills from animals by simple extraction; the same technique is probably sufficient in humans after local anesthesia and disinfection of the skin.

COATIS

The ring-tailed coati (*Nasua nasua*) is widely distributed in the Americas. It is a social animal whose omnivorous diet includes insects, fruits, and small vertebrates. There is only one published report in the medical literature describing a coati attack; two children in their home were injured by a startled coati, causing skin lesions from deep scratches and bites[50] (Figures 30-24 and 30-25).

QUOKKAS

The quokka (*Setonix brachyurus*) is one of the smallest members of the wallaby family, which resides in western Australia. The quokka typically only bites humans who attempt to feed or pet it. Bites usually occur on the finger or hand. On Rottnest Island, Australia, quokkas have been known to steal food after breaking into homes. The island's infirmary reported 60 quokka bites in 2006.[140] Despite the presence of mixed coliform bacteria in quokka mouth cultures, the incidence of bite wound infection in this series was zero.[272]

OPOSSUMS

The American opossum (*Didelphis virginiana*) is a native species adapted to urban living and presents difficulties for animal control agencies. Opossums typically bite when accidentally provoked while being hunted in the wild or handled in captivity. They comprise a major reservoir of endemic typhus in Los Angeles County in California.[117]

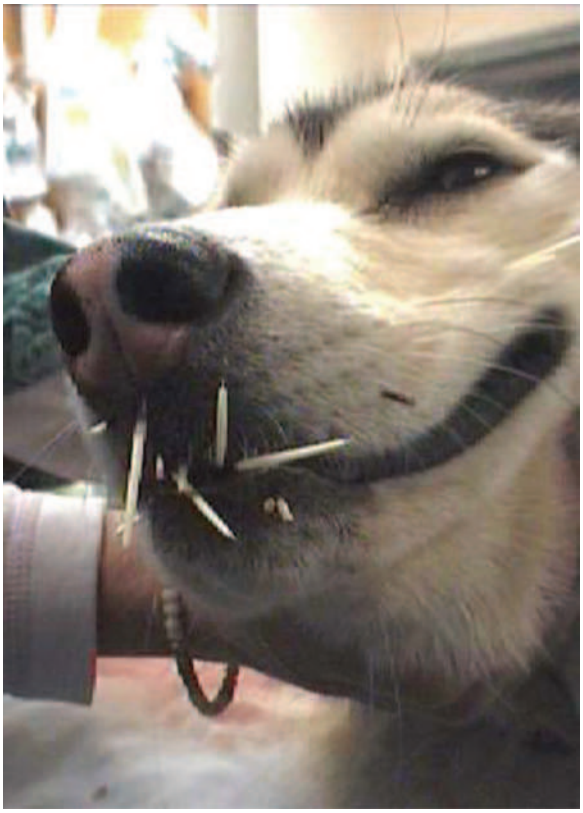

FIGURE 30-23 Domestic dog impaled with porcupine quills. *(Courtesy Luanne Freer, MD.)*

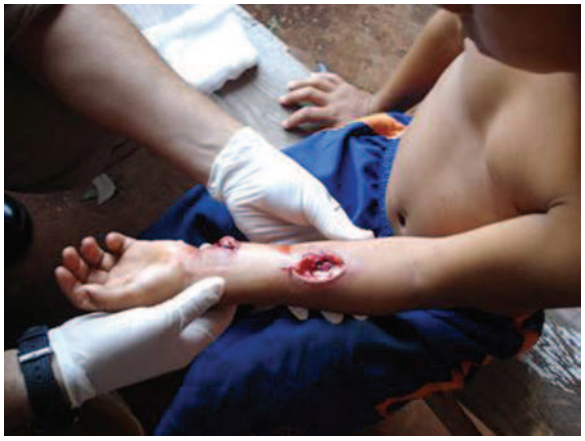

FIGURE 30-24 Coati bite. *(Courtesy Luanne Freer, MD.)*

Aerobically cultured organisms from the mouths of seven wild opossums included streptococci, coagulase-positive and coagulase-negative staphylococci, *Aeromonas* spp., *Citrobacter freundii, Eikenella corrodens,* and *Escherichia coli*.[206]

SKUNKS

Skunks are small mammals belonging to the family Mephitidae, order Carnivora. They are capable of secreting a strong, foul-smelling odor. A skunk's most frequent means of defense is spraying the secretions of its anal sac. A skunk that is ready to spray directs its hindquarters toward the enemy, with its feet firmly planted and tail straight in the air, often stamping the front feet in warning. The spray is accurate to 4 m (13 feet), and, contrary to popular belief, can be discharged when the animal is lifted by its tail.[134,417]

Skunk musk causes skin irritation, keratoconjunctivitis, temporary blindness, nausea, and occasionally convulsions and loss of consciousness.[159] The chief component of the musk is butyl mercaptan; this can be neutralized by strong oxidizing agents, such as sodium hypochlorite in a 5.25% solution (household bleach) further diluted 1:5 or 1:10 in water. The chlorine forms odorless sulfate or sulfone compounds by oxidizing mercaptan and breaking the sulfur free from the carbon chain. This solution can be cleansed with tincture of green soap and followed by a dilute bleach rinse. Other effective means of eliminating skunk odor include a mixture of 1 quart of 3% hydrogen peroxide, 0.25 cup of baking soda, and 1 teaspoon of liquid soap. Using a commercial vaginal douche product may be effective. Tomato juice is not an effective means of removing skunk odor.

FIGURE 30-25 Coati. *(Courtesy Luanne Freer, MD.)*

The CDC recorded 1446 cases of rabies in skunks in the United States in 2010; this was 23.5% of reported cases in all species.[336,340] Skunks bite readily when captured, but in one series, only 21 bites were reported for the entire United States for a 10-year period.[131]

BATS

Bats are mammals in the order *Chiroptera*. There are about 1100 species worldwide, which represents 20% of all classified mammal species.[422] Bats carry a large number of zoonotic pathogens, including rabies virus, coronaviruses, hantaviruses, and possibly Ebola viruses.[95,170] Less than 1% of all bats carry rabies. However, the few cases of rabies reported in the United States each year not caused by dogs are usually caused by bats.[271] Bats infected with rabies are clumsy and have difficulty flying, making it more likely they will come into contact with humans.

Vampire bats are a vector of rabies in Central and South America; 177 cases were reported from 1980 to 1990, with 27 of these in Brazil.[34] Approximately 81% (113 of 139) of the human rabies cases reported in Peru from 1996 to 2010 were associated with vampire bats.[354,407] Sometimes small "epidemics" of bites occur in isolated villages in the jungle, as in one outbreak of 26 bat bites in Honoropois, Brazil; all victims were treated with rabies prophylaxis, and no clinical human rabies was reported.[34] In 2004, a rabies outbreak from vampire bats occurred in Columbia, resulting in 14 human deaths.[402] Such clusters of attacks may be triggered by human destruction of wild or domestic hosts of the bats (e.g., pigs).[270] One study surveyed two communities in Peru that were at risk of vampire bat depredation and tested otherwise healthy adults who were at risk of rabies exposure. Of the 63 individuals tested, seven (11%) were found to have rabies-neutralizing antibodies in their serum. Only one of the seven individuals had reported prior vaccination. The authors suggested that the nonfatal exposure of rabies was associated with vampire bat depredation and that rabies exposure is not invariably fatal.[171]

Vampire bats feed at night on animal blood, including that of humans, by making an incision in the skin to lap up the blood from the victims' earlobes, forehead, fingers, or toes. One bat can eat a maximum of 1 oz of blood per night. A cave of 1000 bats needs 15 gallons of blood each night, which amounts to more than 5750 gallons per year.[104] Protection against vampire bats is effectively achieved by using mosquito nets.

Insectivorous bats (e.g., free-tailed bats) are noteworthy for the nearly undetectable bite wounds they leave on their victims.[169] All bats should be considered high risk for rabies, and contact, even with captive "pet" bats, should be avoided. The known pathogenesis of rabies and available data suggest that almost all cases of human rabies attributable to bats were transmitted by bat bites that were minimized or unrecognized by the victims. Nonbite transmission of rabies is very rare, and aerosol transmission has never been well documented in the natural environment.[169] Some situations mandating rabies prophylaxis are bizarre and reveal more about human nature than about rabies or bats. For example, rabies prophylaxis was initiated after a patient dunked a dead bat in his beer, chewed on the bat's ear, and then drank the beer.[136] In a similar case, prophylaxis was needed when a miner swallowed a live bat on a bet.[47] Most bats have small teeth that cannot penetrate human skin, so the risk of bacterial wound infection is low.

VENOMOUS MAMMALS

Only two types of venomous mammals are known. The short-tailed shrew (*Blarina brevicauda*) of the northeastern United States secretes a protein venom from its maxillary venom glands and injects it with the lower incisors. The venom may cause edema, a few days of burning sensation, and pain that lasts up to 2 weeks.[90] No specific antivenin is available, and treatment is symptomatic. No bites from this species have been reported since the 1930s. A similar venom is possessed by the European water shrew (*Neomys fidiens*) and the primitive Cuban insectivore

(*Solenodon paradoxus*).[62] Documented bites from these animals are exceedingly rare, but have been caught on video with social media.[286]

A second type of venomous mammal is the male platypus (*Ornithorhynchus anatinus*), which injects venom from a hollow spur in its hind leg. This venom resembles snake venom and causes local pain, edema, and lymphangitis.[62] The pain can be excruciating and unresponsive to IV narcotics. Regional nerve block has been reported to be effective in combination with limb immobilization.[153] Localized edema also occurs; however, no specific treatment is available, and the exact pathophysiology is unknown. Functional recovery may be delayed for up to 3 months. The echidna, or spiny anteater, possesses a similar spur and venom, but envenomation has not been reported.[159]

LARGE REPTILES (See Chapters 35 and 36)

Historically, the Nile crocodile (*Crocodylus niloticus*) has accounted for 1000 human deaths per year in Africa[104] (Figure 30-26). Most attacks take place in the water, where crocodiles are accustomed to scavenging for dead, sick, and deformed human infants tossed into the water to be disposed of by these reptiles. The crocodile has tremendous grip strength and locks its grip by slotting two lower teeth into holes in the upper jaw. When a crocodile is unable to drag the victim completely underwater, it may grasp a limb and then repeatedly spin over until the limb is detached.

During a 10-year period in Australia, there were 16 attacks and four fatalities caused by crocodiles; most victims were swimming or wading at night, and alcohol ingestion was present in half of them. Wound infections with *Aeromonas hydrophila, Pseudomonas pseudomallei,* and *Proteus, Enterococcus,* and *Clostridium* spp. were reported in 6 of 11 survivors in this series.[279] In Malawi, over 4 years, 60 victims were admitted to hospitals after injury by crocodiles; 40% had serious injuries resulting in permanent deformity, and one person died from sepsis.[404]

The American alligator (*Alligator mississippiensis*) is thriving in the southern United States, and its habitat is so greatly threatened by human expansion that incidents of alligators appearing in suburban backyards and swimming pools are now common (Figure 30-27). Between 1928 and 2009, there have been 567 reports of adverse encounters with alligators, with 24 deaths reported in the United States, the majority in Florida.[249] The average age of the alligator bite victims was 35.1 years, and 62 (13.1%) were children. The most common activity at the time of the attack was handling the alligator. The alligator causes crushing injuries to the torso and open extremity fractures, and it may roll underwater with the victim, resulting in drowning. Blunt trauma may result from a strike by the animal's massive tail. Prevention of alligator attacks includes avoiding touching or feeding the animal and not swimming at feeding time (dusk) with a dog or in waters with heavy vegetation.[111]

FIGURE 30-26 Crocodile. *(Courtesy Kappa Meadows, MD.)*

FIGURE 30-27 Alligator. *(Courtesy Stuart Coleman.)*

Komodo dragons (*Varanus komodoensis*), native to Indonesia, have also experienced habitat and prey depletion. Members of the monitor lizard family, Komodo dragons have sharp teeth built for tearing and a venomous bite containing several different toxic proteins. Their bite is not designed for crushing; in fact, its force is similar to that of a house cat, but given their size, they may have significantly more success using pull forces to tear at prey.[33,123] The venom causes inhibition of blood clotting, paralysis, and hypotension, leading to shock and loss of consciousness in bitten prey.[7,163] With the discovery of venom action, the previous assumption that bacteria found in the dragon's saliva and teeth cause death has been disproved. However, saliva of the dragon, given its primary food source of carrion, predisposes its bite to contain diverse bacteria, including *E. coli, Staphylococcus* and *Providencia* spp., *Proteus morgani,* and *P. mirabilis*. Up to 57 different strains of bacteria have been identified in a Komodo dragon's saliva, including resistant strains of four usually susceptible pathogens.[287] Captive animals have cleaner mouths, possibly because they are fed a cleaner diet. Komodo dragons are apex predators that hunt game using stealth, ambush, and a keen sense of smell.

Komodo dragon attacks on humans are rare but have increased over the past decade. Reports of dragon-related injuries and deaths date back to the 1940s, and five people have been reported as killed by dragons since 1974. The animals are considered especially dangerous to children. In 2007, a Komodo dragon attacked an 8-year-old boy on Komodo Island; the boy died of massive bleeding.[26] Locals blamed the attack on the suspension of goat sacrifices, claiming that the hungry dragons wandered into settlements in search of food. In 2009, two Komodo dragons killed a fisherman after he fell out of a tree and was then left bleeding profusely from bites to his hands, body, legs, and neck.[6] A well-publicized incident involving a publisher occurred in 2001 at the Los Angeles Zoo in California, when the man was invited into a Komodo dragon exhibit and was bitten on the foot.[36]

MARINE MAMMALS

Marine mammals account for about 120 different species of animals and include cetaceans (whales, dolphins), sirenians (manatees), pinnipeds (true seals and walruses), and mustelidaens (otters). Polar bears (see Chapter 32) are sometimes considered marine mammals as well, because they spend most of their lives on pack ice; however, this section only considers seals, walruses, and otters.

One survey revealed that 54% of workers in contact with marine mammals reported experiencing at least one injury or illness (mostly cuts, scrapes, bites, and rashes).[401] Eleven percent reported developing "seal finger," discussed later. Injury occurred in 52% of these individuals while they were handling the animals or animal tissue. Of these injuries, 36% were severe and included deep wounds and fractures. In another survey of 483 marine mammal workers, 50% had an injury caused by a marine mammal, and 23% developed a skin rash.[212] Marine mammal work–related illnesses reported by survey participants most often included seal finger, conjunctivitis, viral dermatitis, bacterial dermatitis, and nonspecific contact dermatitis. Severe illness was less frequently reported and included tuberculosis, leptospirosis, and brucellosis. Traumatic injury included deep wounds (77), bites (38), wounds requiring sutures (26), and fractures (Figure 30-28).

Marine mammals carry many of the pathogens associated with food-borne gastroenteritis, such as *E. coli, Salmonella,* and *Listeria,* although there are no documented cases of transmission to humans. As with other wildlife, seals and sea lions can shed the protozoan *Giardia lamblia* in their feces. In rare cases, marine mammals have been infected with rabies virus or *Mycobacterium tuberculosis*. From 1972 to 1977, five researchers were diagnosed with leptospirosis after working with California sea lions.[374]

Seal finger is a condition that has been frequently reported by seal researchers and handlers (see Chapter 76). The organism most likely responsible for seal finger is *Mycoplasma phocacerebrale*. Although seal finger is usually treated effectively with tetracycline, serious sequelae, including septicemia, have been reported.[212,400] In 1998, a calicivirus (San Miguel sea lion virus) was isolated from blisters on the hands and feet of a laboratory worker.[403] Sealpox is a cutaneous condition caused by parapoxvirus that usually affects seal handlers who have been bitten by infected harbor or grey seals.[403] In 1987, two researchers developed cutaneous lesions consistent with sealpox after working with grey harbor seals.[401]

Seals

Pinnipeds are comprised of true seals, earless seals, and walruses. Attacks on humans are rare. Grey harbor seals (*Halichoerus grypus*) have pointed sharp teeth for tearing and grasping and often use their back teeth for crushing shells. On average, 10 seal bites per year are reported in the United States[344] (Figure 30-29). In 2005, a woman was trying to help a seal back into the water when it bit off her nose.[356] In San Francisco, California, in 2006, the Aquatic Park reported 14 separate biting incidents, all attributed to the same baby harbor seal.

The much larger leopard seals of the Antarctic are apex predators, weighing up to 500 kg (1102 lb) with canine teeth that are 2.5 cm (1 inch) long. Attacks on humans are rare. In 1985, an explorer reported having been bitten twice by a leopard seal as it tried to drag him into the sea. In 2003, a leopard seal killed a researcher when she was pulled underwater and drowned.[74,314]

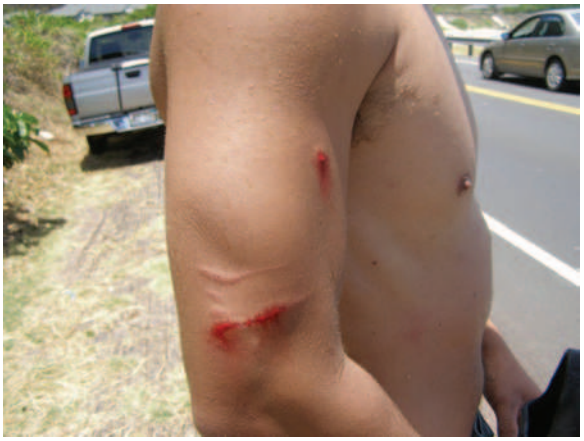

FIGURE 30-28 Monk seal bite. *(Courtesy D.B. Dunlap.)*

FIGURE 30-29 Monk seal. *(Courtesy National Oceanic and Atmospheric Administration Fisheries, Pacific Islands Fisheries Science Center, taken under Marine Mammal Protection Act/Endangered Species Act Permit #848-1365.)*

Ernest Shackleton described a leopard seal attack that occurred during his ill-fated Antarctic expedition.[314]

Walruses

Walruses (*Odobenus rosmarus*) are large marine mammals with a discontinuous circumpolar distribution in the Arctic Ocean. The most prominent physical features of the walrus are long tusks (actually, elongated canines) that are present in both genders and can reach a length of 1 m (3.3 ft). They have few other teeth and use the tusks to rake the ocean bottom for food.[46] A full-grown bull can weigh 1814 kg (4000 lb) and challenge a polar bear. Few human attacks by walruses have been documented because of their geographic isolation and their generally shy nature. The rare human conflict usually involves an injured or provoked animal.

Sea Lions

Sea lions (family Otariidae) have four large canine teeth with smaller incisors and cone-shaped teeth. A sea lion's teeth are designed for grasping and tearing rather than chewing. Sea lions tend to flee, if possible, but are capable of delivering powerful bites when threatened. In 2004, a sea lion pulled a fisherman from his boat, but he was able to escape unharmed.[418] Although sea lions are not typically aggressive, a series of attacks was reported in San Francisco Bay in 2006, when 14 people were bitten. The sea lion population continues to grow along the California coast, contributing to more aggressive territorial interactions with humans.[123]

Elephant Seals

Elephant seals (genus *Mirounga*) are very large mammals that can move surprisingly fast on land. Attacks on humans are rare and in most cases provoked (e.g., when the seal is surprised or approached too closely). Northern (*Mirounga angustirostris)* and southern (*M. leonina)* species are found in the Pacific region. Elephant seals have large incisors and are capable of breaking bones with even a small bite.[275] In 2007, a series of attacks was attributed to one bull elephant seal in the San Francisco Bay Area; the animal bit a surfer, a kayaker, and a pit bull dog.[275] As with other marine mammals, seal finger is a potential complication of elephant seal bite.[39]

River Otters

The first recorded biting of a human by a river otter was in 1998 in Minnesota. In 2004, a family of three was attacked while swimming in calm river water near Belden, California.[192] A 12-year-old boy was suddenly attacked both above and below the water by a river otter, sustaining multiple bites and scratches. The otter then attacked the child's mother and father when they arrived to help. The attack was described as "vicious and unrelenting" despite many attempts by the three to strike and repel the animal. State game officials were unable to locate or capture the animal. The victims' sutured lacerations healed without incident after

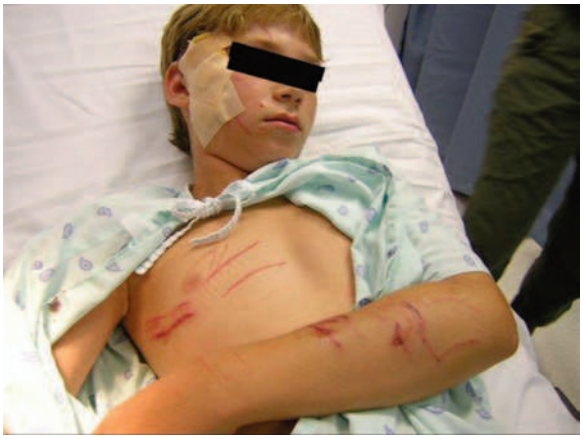

FIGURE 30-30 Victim of a river otter attack. *(Courtesy Jill Hanna, MD.)*

prophylactic treatment with amoxicillin-clavulanate, and the bitten patients received rabies PEP (Figure 30-30).

The CDC has recorded 24 rabies cases in river otters, and wildlife experts suppose that, as a result of low population densities and a semiaquatic existence, otters probably have limited opportunities to contract diseases from other species. Otters travel along rivers while denning, allowing contact with raccoons, which carry a rabies strain that is enzootic in raccoon populations.[358]

DOMESTIC ANIMAL ATTACKS

Most animal bites are from domestic dogs and cats. The great majority of bites (80% to 90%) are inflicted by dogs.[186] Dog bites continue to be a public health problem, affecting 1.5% of the U.S. population annually; 1 of every 322 persons receives medical care after a dog bite.[172] Domestic cats account for about 5% to 15% of treated bites, although some studies report a figure as high as 25%.[186,269,426] The bite location and affected populations vary by animal. Most dog bites occur on the extremities. Facial bites are more common among children, and up to two-thirds of cat bites are on the upper extremities, especially the hand.[173,372]

A comprehensive study that evaluated 50 patients with dog bites and 57 patients with cat bites identified a median of five bacterial isolates per culture (see Box 30-7).[390] *Pasteurella* spp. were the most common pathogens found in bites of both dogs (50%) and cats (75%). The association of *Pasteurella* with infections of rapid onset was confirmed. *Streptococcus, Staphylococcus, Moraxella, Corynebacterium,* and *Neisseria* were the next most frequent aerobic isolates. *Eikenella corrodens,* usually associated with human bite infections, was found in only one cat and one dog bite wound. *Capnocytophaga* spp. and *Weeksella zoohelcum,* both of which can cause invasive sepsis, were uncommon in this study and may be opportunistic pathogens. *Fusobacterium, Bacteroides, Porphyromonas,* and *Prevotella* were common anaerobic isolates.[32]

DOGS

Dogs are the only species whose bites have been well studied in large numbers. Although they have been domesticated for at least 12,000 years, dogs retain many of their wild instincts (e.g., territoriality in a guard dog).

Dogs less than 1 year old are responsible for the highest incidence of bites.[85] Incidence of biting increases substantially during the summer months. Increased susceptibility of children results from their smaller size, relative inability to defend themselves, interest in animals, and unintentional abuse of animals.

Wounds from dog attacks may be a mixture of biting, clawing, and crushing forces. The jaws of an adult dog can exert 200 to 300 psi of pressure.[15] As a result, deeper tissues may also be injured. Treatment may naturally focus on the crush component of the wound, but the penetrating component may cause the most morbidity. The dog may move and shake its head during the attack, further tearing tissue. Snorting, grunting, or wound manipulation by the biting animal may force air into the tissues. In addition to infectious organisms, foreign debris and teeth may be deposited. During a severe attack, the dog may eat tissue and blood or scavenge on an unconscious or intoxicated victim.[185,331] Dog bites to the genitalia have been reported, rarely resulting in orchiectomy.[139,179]

Dog attacks kill an average of 19 people in the United States annually. The majority of persons killed are children. Forty-nine states have reported dog-related fatalities, with Alaska reporting the highest death rate from dog attacks. The number of dog-related deaths appears to be increasing.[248]

Worldwide, dogs are responsible for about 50% of animal-related injuries to travelers.[166] A study done in Thailand of adult travelers at the international airport reported that 1.3% had been bitten by a dog.[325]

In Africa, the ratio of people to dogs is higher in cities than in villages. In Asia, the inverse is true.[233] This would suggest that a person is more likely to be bitten by a dog while traveling in rural Africa or urban Asia.

One study examined law enforcement reports, animal control reports, and investigator statements to identify factors contributing to fatal dog attacks. Co-concurrent factors included absence of an able-bodied person to intervene, incidental or no familiar relationship of victims with dogs, owner failure to neuter dogs, compromised ability of victims to interact appropriately with dogs, dogs kept isolated from regular positive human interactions, and owners' history of abuse or neglect of dogs.[317] Many dogs that seriously wound or kill humans have long histories of aggressive behavior. Strategies that reduce biting risk include education of owners and the public, selection of dogs, and training, care, and socialization (see Box 30-2).

CATS

Domestic cats that become feral are an increasing problem in the United States, as the population of stray animals grows and opportunities increase for exposure to wild vectors of rabies. Cats now account for 50% of animal control calls, which has led to proposals for leash and licensing laws for cats.

Cats have a weaker biting force than dogs but possess sharp, slender teeth, often producing deep puncture wounds. Their bites are associated with a 15% to 80% infection rate,[390] and a higher incidence of osteomyelitis and septic arthritis compared with dog bites. Cat bites frequently introduce two risk factors for infection: hand location and increased depth of puncture. Other risk factors in cat bites associated with wound infections include older victims, longer delay to ED treatment, wound inflicted by a pet rather than a stray, wound care at home, and more severe wounds.[132]

Cat-scratch disease (or cat-scratch fever) is an uncommon condition. About 90% of cases are caused by scratches from domestic cats, although it has also been reported in one big-cat attack victim.[115,232] The average incubation period is 3 to 10 days. The characteristic feature is regional lymphadenitis, which usually involves lymph nodes of the arm or leg. In most cases, clinical diagnosis is based on finding three of the following four criteria[115]:

1. Single or regional lymphadenopathy without obvious signs of cutaneous or throat infection
2. Contact with a cat (usually an immature one)
3. Detection of an inoculation site
4. A positive skin test for cat-scratch disease

Detailed information about the diagnosis and treatment of cat-scratch disease is found in Chapter 34.

Because the hands and lower extremities are common sites of injury and wounds may be deep and penetrating, most cat bites are considered to be high risk for infection. Such wounds should prompt administration of prophylactic antibiotics (see Table 30-3). Superficial cat bites and scratches elsewhere on the body are not high risk and should receive standard wound care without antibiotic coverage.

RODENTS

Rodents do not tend to bite unless severely provoked; their bites are usually small and do not cause much disability. The exact number of rodents in the world is unknown but probably numbers in the hundreds of millions. A 2012 U.S. pet ownership survey showed the following population per 1000 households: 748 ferrets, 1146 hamsters, 1362 guinea pigs, 468 gerbils, and 868 other rodents.[376] Despite these numbers, rodent bites account for only 1.7% to 10% of animal bites brought to medical attention.[309]

Rodent bites are infrequent, seldom cause any problems for the victim, and often occur among lower socioeconomic groups without good access to medical attention. Other populations at risk include laboratory workers who handle rodents used in research. Insufficient data exist to determine any differences in outcomes between wild and domestic rodent bites.

Rats, Mice, and Other Small Rodents

Rat bites have an infection rate of 2% to 10%, even without treatment, and the rate is usually on the low end of this spectrum.[309] Other than bites inflicted by laboratory animals, the vast majority occur in poor communities while the victim is sleeping and involve the face and neck, usually of infants or physically or mentally disabled adults.[308,309] There were 415 reported rat bites in New York City between 1986 and 1994.[100] Sometimes these can be severe; a week-old infant was bitten around the eyes by a rat, resulting in perforations of the globe, an estimated vascular loss of 55% of red blood cell mass (initial hematocrit value of 20%), and eventual blindness.[296] Despite the rat's reputation for spreading disease, however, infection did not occur. Similar bites in infants have resulted in loss of more than three-fourths of the eyelids.[429]

The bacteriology of a rat bite is similar to other animal species; the various systemic diseases transmitted by rats are discussed in Chapters 31 and 34. Sporotrichosis has been reported; this widely distributed saprophyte is found on various plants, in the soil, and on many animals.[162]

Although rodents occasionally become infected with rabies, they seldom secrete this virus in saliva. Therefore, they inflict extremely low-risk bites with regard to transmission of the disease. However, local epidemics can occur, as documented in the 1980s among rodents and lagomorphs on the U.S. East Coast.[291] During that epidemic, woodchucks constituted 80% of all rabid animals; the remainder were squirrels, beavers, rabbits (*lagomorphs,* not rodents), and one rat. Some of these rabid animals were very aggressive; a woodchuck attacked and knocked down an elderly woman in her garden, biting her repeatedly. Rabies was isolated from the buccal cavity of the woodchuck in question. A reasonable current recommendation is that a biting wild rat in the United States should be caught and examined for rabies, and rabies PEP should be initiated only if the rabies test is positive. Rabies PEP is probably appropriate for bites from uncaptured rodents inflicted outside the United States and Canada.[309] A case has been reported of a cowpox virus–like infection transmitted by a probable rat bite.[419] Rodents are believed to be the natural reservoir of the cowpox virus.

Rat-bite fever (or rat-bite disease) is an acute illness caused by *Streptobacillus moniliformis* or *Spirillum minus,* which are part of the normal oral flora of rodents, including squirrels. It may also result from bites of wild and domestic carnivores, such as weasels, dogs, cats, and pigs, which may have become infected when hunting rats and mice.[359] Carrier rates among wild rats vary from 50% to 100%.[408] Fewer than 100 cases have been reported in the North American literature, and rat-bite fever is not a reportable disease in the United States.[408] Although relatively rare, cases can occur in any setting and can easily be fatal, particularly when the proper diagnosis is not suspected[115,355,408] (see Chapter 34).

Plague is caused by the bacterium *Yersinia pestis*. Wild plague is endemic in many parts of the world, chiefly among rats, mice, moles, marmots, squirrels, hares, cats, and mongooses. One of the larger areas of endemic plague is the western United States, where voles, field mice, ground squirrels, prairie dogs, and pack rats carry the infection. Between 1971 and 1999, there was an average of 13 cases of plague per year in that area of the country. Worldwide, there were 2861 cases reported by 10 countries.[120] In 2006, there were two fatalities from plague in New Mexico, the first reported deaths in the states in 12 years.[328] The infection is usually transmitted to humans by the bites of arthropods that infest infected animals. Handling infected animals allows *Y. pestis* to enter cuts and abrasions, as seen among veterinarians and hunters who skin and clean infected rabbits.[83] Transmission by bite or scratch has never been reported. The disease is mentioned here because of its historical significance and the frequency of occurrence among wild animals (see Chapter 34).

Tularemia represents various syndromes caused by *Francisella tularensis*. This bacterium normally parasitizes about 100 different mammals and arthropods, most frequently cottontail rabbits, rodents, hares, moles, beavers, muskrats, squirrels, rats, and mice. The primary mode of transmission to humans is by a bloodsucking arthropod (e.g., a tick) or by skin or eye inoculation resulting from skinning, dressing, or handling diseased animals. Other routes of infection include ingestion of water contaminated by urine or feces and dust inhalation. Infections after bites or scratches from dogs, cats, skunks, coyotes, foxes, and hogs have been reported, although these are rare.[339] Tularemia is an occupational hazard of hunters, butchers, cooks, campers, and laboratory technicians. Humans are quite susceptible, and, although tularemia was removed from the national reportable disease list in 1995, 105 cases were reported in 1997 in the United States[86] (see Chapter 34).

Rabbits

Rabbits are common household pets. They are not true rodents but rather part of the Lagomorpha order and more closely related to horses. Rabbits cannot see in front of their noses, so they may bite a hand that is placed there. They also nip as a means of communication, although such behavior on the part of the rabbit can be interpreted as aggression. Biting is uncommon, but rabbits can inflict painful scratches with their rear limbs when restrained.[194]

Pasteurella multocida from scratches may cause cutaneous infection in humans.[193] Other diseases to which rabbits are susceptible, such as salmonellosis, yersiniosis, and tularemia, are rare. Direct zoonotic transmission of *Yersinia pseudotuberculosis* from domestic rabbits has been documented.[160] More often, some external parasites of the rabbit, including fur mite acariasis (*Cheyletiella*) and dermatophytosis (*Trichophyton*), may be transmitted to humans.[193]

Ferrets

The two species of ferret in the United States are the common ferret *Mustela putorius furo,* which is sold as a domestic pet, and the wild black-footed ferret *Mustela nigripes,* which is an endangered species. The pet ferret was domesticated from the wild European polecat and was first introduced into the United States during the late 19th century. Ferrets are kept in increasing numbers as domestic pets, especially by urban apartment dwellers (Figure 30-31).

Ferrets were bred to hunt and kill small game and rodents in their burrows and are particularly attracted to suckling animals, possibly because of the scent of milk. The animals have 34 teeth and sharp claws on all four feet. Severe injuries caused by ferrets are not common.

In a comprehensive review of 452 ferret attacks over 10 years, virtually all unprovoked attacks were on the faces of unattended infants, typically sleeping or in a crib.[112] Several injuries were severe, and one child died. Bites were usually multiple, and sometimes the ferret's jaws had to be pried open or the ferret had to be killed to secure release.[316] In these attacks, the face, ears, and nose may be mutilated.[16] Scratches, lacerations, and puncture wounds are seen, and the ferret may chew on a victim (e.g., a baby's ear). The fingers and neck are also common targets. The areas of injury are generally round, crateriform, and with chewed irregular edges and often substance loss.[154] Almost all provoked incidents involve neglect, abuse, or roughhousing

FIGURE 30-31 Pet ferret. *(Courtesy Luanne Freer, MD.)*

with the ferret that is likely perceived as an attack. Some of the animals involved in these incidents were ferret–polecat hybrids.[42]

Ferrets are unusually adept at escaping from cages and enclosures, guaranteeing that they will occasionally be loose unsupervised in the house and also that they can escape to the wild, where they may be exposed to endemic rabies. In one study, 4% of biting ferrets tested positive for rabies virus.[112] Ferrets are now classified in the same category as cats and dogs (rather than as wild terrestrial carnivores) with regard to rabies pathogenesis and viral shedding patterns. They may be confined and observed for 10 days rather than being routinely euthanized after biting. An effective rabies vaccine for ferrets, IMRAB-3, has been available since 1990; it requires annual vaccination.

Little is known about infection rates or bacteriology in ferret-inflicted wounds, although unusual species, such as *Mycobacterium bovis,* have been observed.[223] Initial treatment should be the same as for dog bites.

DOMESTIC HERBIVORES AND UNGULATES

In 2013, there were 22 occupational fatalities in the United States related to animals.[67] Many of these incidents involved domestic farm animals.[94,284] Between 1990 and 1993, horses were the second leading cause of farm-related injuries.[347] Farm animals cause a disproportionate number of injuries relative to other animals, especially among youth; 6438 on-farm injuries occurred among young victims in 1998. Approximately 41% of persons injured were under 10 years old; 37% of incidents involved horses and 31% involved cattle. Most cattle-related injuries were work related, whereas horse-related injuries were mainly nonoccupational. One of every five youth injuries that occurs on U.S. farms is animal-related.[373] A Wisconsin study showed that for farm-related injuries requiring hospital admission, domestic animals were the cause of 40% of the injuries. The types of injuries caused by farm animals include those to the head, upper extremities, maxilla, legs, and thoracoabdominal region.[107] A study of youth on farms in Australia indicated that 86% reported working with farm animals; 44% of their injuries were caused by a farm animal.[94] In addition, 72% of youths in this survey perceived working with animals as the most dangerous activity on the farm. In a 2014 study of human-animal interactions on Minnesota dairy farms, most injuries were from working with cattle and thought to be caused by poor cattle-handling skills. Surveys from these individuals revealed that proper cattle-handling techniques were more likely to be learned from a family member than from formal stockmanship training.[375]

Little is known about incidence of wound infection after herbivore bites, but the infection rate after camel bites may be as high as 86%.[251] Species of *Actinobacillus lignieresii, A. suis,* and *Pasteurella multocida* have been isolated from infected horse and sheep bites.[43,320] Most domestic herbivores carry *Pasteurella,* and most are given frequent and regular doses of different antibiotics, especially in their feed, leading to antibiotic resistance of bite wound organisms.[332] *Pasteurella caballi* has been isolated from a horse bite wound.[149] *Staphylococcus hyicus* subsp. *hyicus,* a well-known cause of disease in many animals, has been reported as a human wound pathogen after a donkey bite.[312] Bites from horses, donkeys, cattle, sheep, camels, deer, and most other herbivores are treated with the same antibiotics as are bites from dogs, cats, and other humans (see Table 30-3).

Horses and Donkeys

The horse is inclined to both bite and kick, but most horse-related injuries follow a fall during riding activities (Figure 30-32). More accidents occur per hour riding horses than during motorcycling.[101] Young females are most often injured by falls,[63] and head injuries cause the majority of deaths.[191] Appropriate helmets and footwear help to reduce the severity of injuries. A report of a series of horse- and cow-related injuries found a high correlation of occult craniofacial and torso injuries when field assessment documents the presence of upper-extremity injury.[304] Falls from horses typically result in head and upper-extremity injuries; the most common injuries are fractures, lacerations, and contusions.[78] From 1992 to 1994, 109 traumatic brain injuries (TBIs) caused by falls from horses were reported in Oklahoma, with three deaths.[82] Twenty-three other TBIs resulted from horse-caused injuries but were not associated with riding; 21 resulted from a direct kick to the head.[82] Although head injuries in children are more likely to result in hospitalization or death, severe injury can occur from hoof kicks to an unmounted child, representing about 30% of horse-related injuries.[219] Horse kicks from the rear legs can be extremely powerful and cause severe blunt trauma, including cardiac rupture[55] and massive pulmonary embolism.[330]

Horse bites are common but usually do not cause severe injuries. The occlusal surfaces of both the horse's lower and upper incisors are flattened. However, most male horses possess canines that may be used to grab onto a mare's neck during mounting. The soft tissue contusions inflicted by a horse can be substantial, but, in a series of 24 horse bites, 21 healed uneventfully.[143] Bites can still produce significant injury, including muscle rupture and fat necrosis, with no external wound. Horses also have a propensity for biting human nipples, which are at the same height as a horse's mouth. Donkeys also bite, and death has been reported from fat embolism caused by fractures after a donkey bite.[52]

Cattle

Cattle are usually docile but can inflict a variety of injuries. Serious bites are infrequent, because these animals possess neither upper incisors nor canines. A cow typically weighs 635 kg (1400 lb), and bulls can exceed 1360 kg (3000 lb). Accidental treading on human victims or butting can cause major crush injuries and fractures. Farm animals in Wisconsin kill about

FIGURE 30-32 Domestic horses disagreeing about something. *(Courtesy Gary Matthews.)*

FIGURE 30-33 Domestic cattle. *(Courtesy Gary Matthews.)*

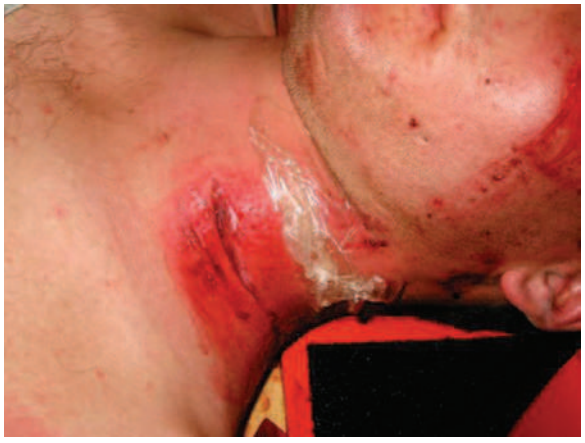

FIGURE 30-34 Domestic bull goring victim. *(Courtesy Luanne Freer, MD.)*

six people each year.[68] One hospital in rural Wisconsin treated an average of 22 persons per year for horse and cattle injuries, most of which were inflicted by a kick or other assault. In addition, domestic cattle can become infected with rabies (Figure 30-33).

Cattle horn injuries or gorings present typical and unique damage patterns (Figure 30-34). The horns are used in an inward hooking motion to butt and fling the victim, or the horn tip can be used for goring. Goring injuries seen in bullfighting typically involve the perineum and thigh; they tend to be deep and sometimes fatal. By contrast, bull horn injuries from domestic cattle involve a sweeping arc at the level of the bull's head, which is at the level of the human abdomen. The semicircular motion of the horn often produces a relatively superficial laceration that leaves deeper structures of the abdomen intact. In one series of 29 cases in which the peritoneum was breached, which usually produced prolapse of bowel or omentum, 27 laparotomies demonstrated no additional injuries; in only a few cases was the bowel itself damaged.[363] The wound infection rate in this series was high (54%), probably as a result of delayed treatment. Initial presentation of occult small-bowel injury after attacks can be falsely reassuring, leading to a delay in diagnosis.[428]

There were 108 cattle-related deaths in the United States between 2003 and 2007. Twenty-one deaths from working with domestic cattle were reported between 2003 and 2008 in the four U.S. states that accounted for 16% of all cattle operations. Ten of these fatalities involved attacks by bulls, six were attacks by individual cows, and five involved multiple cattle. In seven attacks, the bull or cow was known to have exhibited past aggressive behavior, and one-third of the deaths occurred in March and April. The victims' most common activities at the time of death were working with and treating cattle in enclosed spaces (e.g., pens, chutes) and moving or sorting cattle in pens, barns, or pastures. In 16 of the cases, the animal was deemed to have purposefully struck the victim; five other deaths were caused by being crushed against a stationary object or struck by a gate. All but one death resulted from blunt force trauma to the chest, head, or both.[80]

Bulls should be approached only with a protective device (e.g., heavy stick) and a planned exit strategy. A ring in the bull's nose gives a victim something to hang onto beside the horns and a way to yank the bull's nose up, which may stop the attack. Dehorning the bull does not eliminate the potential for crushing. If struck by a bull or cow, the victim should not attempt to stand, because this will provoke being thrown to the ground again, but should try to crawl to safety. Children must be educated about the risks of large animals and kept away from them whenever possible.

Camels

In regions in which camels are used for domestic or agricultural purposes, bite injuries are quite common.[251] Although herbivores and usually docile, camels are much more likely to bite in the winter rutting season, and bite fatalities have been reported. Camels have 34 teeth, including large backward-inclined upper canines, or tushes (Figure 30-35). The lower tushes are placed relatively forward, and the resultant mouth grip is very effective. Jerking movements of the animal's head during biting result in severe tissue damage and limb avulsion and rarely can break the human victim's neck. The forearm is often injured, and bites to the face are well documented.[76,230,307,369] Virtually all camel bites are single.[353] Injury or death can also occur if the camel presses the victim to the ground and crushes him or her after gripping the person in its jaws.[251]

Domestic Swine

Bites from domestic swine are rare. When pigs attack, however, they can be aggressive and can inflict deep goring or bite injuries, often on the posterior thigh as the pig approaches from behind.[31,303]

Pigs have a reputation for inflicting bites that are at high risk for infection, and care should include thorough wound exploration and debridement. The usual wide range of bacterial pathogens is reported, including *Pasteurella aerogenes, P. multocida, Bacteroides, Proteus, Actinobacillus suis,*[148,187] and β-hemolytic streptococci, including *Streptococcus milleri.*[31] Unusual gram-negative bacteria, such as *Flavobacterium* group IIb, have been isolated, as has *Mycoplasma.*[47,289] Both these organisms are resistant to amoxicillin-clavulanate, so the addition of ciprofloxacin is recommended as prophylaxis for serious pig bite wounds.[289] Of note, more recent studies have shown high prevalence of nasal methicillin-resistant *Staphylococcus aureus* (MRSA) colonization in people frequently in contact with live pigs.[229,371,211]

FIGURE 30-35 Camel and its owner/trainer in Marrakech, Morocco. *(Courtesy Luanne Freer, MD.)*

BIRDS

Birds may be kept as domestic pets or on farms and can cause serious injuries. On farms, rooster attacks, often by male fowl defending their territory, are well documented. Children, especially infants, are particularly vulnerable to attack. Rooster injuries have included serious clawing of the face and a fractured skull.[334] In one report, a rooster spur was retained in a wound, resulting in chronic infection.[113] Septic arthritis was reported in a child after a bite from a domestic fowl.[208]

MEDICOLEGAL CONSIDERATIONS

In some cities and regions, animal bites must be reported to public health authorities. Reporting suspected exposure to rabies is mandatory in most regions, and failure to report could become the basis for legal action. Reporting often leads to examination of the offending animal by public health authorities and sometimes to quarantine or euthanization of the animal. Reporting animal bites also improves data collection and statistical evidence regarding the problem.

Although most wild animals by definition do not have an owner, some exotic species are kept as "pets." An owner's failure to meet local regulations regarding licensure and vaccination can lead to legal action. In addition, the victim may seek compensation from the owner of the animal, with the result being that the health care provided and the victim's medical record will be reviewed in court. The injury may be related to the victim's employment, generating workers' compensation or other insurance claims. Therefore, injuries and their circumstances should be documented as fully as possible, with line drawings or photographs added to the medical record whenever possible. In an example in Connecticut, a woman was attacked by a friend's pet chimpanzee. Her injuries required extensive surgery and a face transplant.[19] In 2012, she received $4 million from the estate of the chimp's owner.[75]

Certain types of animal bites, particularly those of the hand, are prone to infection and can lead to litigation-prone permanent complications. A complete medical record is essential in these circumstances.

DOCUMENTATION OF THE INJURY

Accurate documentation of the bite injury in the field is important. There is often confusion and sometimes chaos around a serious injury in the wild, so eliciting eyewitness observations can be helpful. The size and type of animal are important to note. Accurate documentation of time and date of the injury are essential for ongoing treatment, establishing antibiotic recommendations, and dressing changes. Photographs of the initial wound and of the animal can be helpful.

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Complete references used in this text are available online at expertconsult.inkling.com.

CHAPTER 31
Rabies

CHARLOTTE A. LANTERI, KEN NGUYEN, AND ROBERT V. GIBBONS

Rabies, one of the oldest known infectious diseases, is nearly 100% fatal and continues to cause tens of thousands of human deaths globally. The word is derived from the Latin *rabies,* meaning "madness," which in turn may be related to the Sanskrit *rabhas,* "to do violence." Rabies has been recognized since 2000 BC. The first written record of rabies was in the Mesopotamian Codex of Eshnunna (Babylon). Animal rabies was described by Democritus around 500 BC. Wound cauterization subsequently became standard treatment and was used for management of suspected rabid bites until the mid-20th century. This treatment remained the mainstay of therapy until Pasteur introduced a vaccine based on an attenuated rabies virus in 1885.[15] Despite its ancient origin and lethality, however, rabies is a largely preventable disease.

In industrialized nations where human rabies is rare, animal rabies abounds, and humans are protected from infection only by vigorous animal vaccination programs, elimination of stray animals, and postexposure immunization. In developing countries, tens of thousands of people die each year, and more than 10 million endure agonizing anxiety following exposure to a possibly rabid animal.[258] In the United States, approximately 23,000 persons receive postexposure prophylaxis (PEP) each year.[85,212] An encounter with this uniformly fatal infection, globally the most common form of viral encephalitis, leaves "a more indelible stamp of horror" than does any other disease.[166]

CURRENT STATUS

Globally, rabies is the tenth most frequent cause of death from infectious disease.[130] The actual number of deaths is unknown because reporting in developing countries, where this infection is common, is unreliable. In Tanzania, the estimated annual incidence of human rabies mortality was 1499 (95% confidence interval, 891 to 2238), but the average number of deaths officially recorded was 10.8.[89] Most of these countries do not have laboratory facilities capable of establishing a dependable diagnosis.[83] The World Health Organization (WHO) currently estimates the number of annual rabies deaths globally at 40,000 to 70,000, although the median number of 55,000 deaths is widely accepted. That is an average of approximately one death every 10 minutes.[276]

Some, perhaps many, human rabies infections are not diagnosed, even in nations with sophisticated medical systems. This problem was vividly dramatized in 2004 by the rabies deaths of four U.S. organ transplant recipients from a donor whose rabies infection had not been recognized.[67,69] Only a few months later, three organ transplant recipients in Germany died of rabies, and three others with liver and corneal transplants required PEP.[144] A review has suggested that rabies may be underdiagnosed in the United States because physicians see it so infrequently that they do not include it in their differential diagnoses.[258]

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In addition to being undiagnosed, rabies is probably incorrectly diagnosed with considerable frequency. Of 33,000 human rabies deaths reported worldwide in 1997, laboratory confirmation was available for less than 0.5%.[83]

THE RABIES VIRUS

Rabies viruses belong to a family of nonsegmented, negative single-stranded RNA viruses called Rhabdoviridae, genus *Lyssavirus.* Lyssaviruses are bullet shaped, with an average size of 180 nm in length and 75 nm in width.[280] The virion is composed of a helical nucleocapsid with 30 to 35 coils of between 4.2 and 4.6 nm in length.[230] These structures are enclosed in a lipoprotein envelope with a thickness of 7.5 to 10 nm. Glycoprotein spikes of 10 nm cover the entire viral surface except at the blunt end.[97]

The *Lyssavirus* genome is approximately 12 kilobases (kb), which encodes five genes: *N, P (NS), M, G,* and *L.* The *N* (nucleoprotein) gene product is responsible for efficient replication of viral RNA.[35,279,281] The nucleoprotein is potentially immunogenic, and routine antigenic typing of virus variants is directed toward this structure.[123] More recently, molecular sequence analysis of G (glycoprotein), P (nonstructural), and L (large polymerase) has been used to identify virus lineages among virus variants. The P protein may control the L protein, an RNA-dependent RNA polymerase.[158,239] The M (matrix) protein is located between the nucleocapsid and lipoprotein envelope and, in conjunction with G protein, is responsible for assembly and budding of bullet-shaped virions.[167] The N and M proteins determine a balance between transcription and replication.[111,112] The G protein plays a role in cellular reception and induces virus-neutralizing antibodies. The variability of this protein is used for serotyping among lyssaviruses.[215]

OTHER LYSSAVIRUSES

There are four major genera of the Rhabdoviridae family that infect animals: *Lyssavirus, Vesiculovirus, Ephemerovirus,* and *Novirhabdovirus.* The *Lyssavirus* genus comprises 12 major species (Table 31-1). The seven major species include rabies virus, Lagos bat virus, Mokola virus, Duvenhage virus, European bat lyssavirus types 1 and 2, and Australian bat lyssavirus.[11] More recently, five species were discovered and added to the *Lyssavirus* genus: Irkut virus, Aravan virus, Khujand virus, West Caucasian bat virus, and Shimoni bat virus.[138,154] Based on their biologic properties, these viruses are further subdivided into two phylogroups consisting of 12 genotypes: genotypes 1 and 4 through 10 belong to phylogroup 1; genotypes 2, 3, and 12 belong to phylogroup 2; and genotype 11 belongs to phylogroup 3.[138] The nucleocapsid region of lyssavirus is highly conserved from genotype to genotype across both phylogroups; however, experimental data show that the lyssavirus strains used in vaccinations are only from the classic rabies virus.[11]

RABIES BURDEN OF DISEASE

Given lack of accurate reporting, the real burden of rabies is not known. Lyssaviruses are zoonotic and found throughout the world; however, rabies virus is the only one prevalent in humans. It is found on all continents except Australia and Antarctica; many smaller island nations are also free of rabies. The number of annual human deaths caused by rabies is estimated at 60,000 to 69,000,[221,272] much greater than the number officially reported.[149] More than one-third of cases occur in Asia, approximately one-third in Africa, and the remainder in Latin America, the Caribbean, and Eastern Europe. Two factors contribute significantly to the disease burden: (1) the disease is invariably fatal, and (2) most victims of rabies are young, with 40% to 50% less than 15 years of age.[149,233] Globally, rabies is responsible for 2 million disability-adjusted life-years annually.

Poor reporting is a consequence of weak rabies surveillance. This is caused by poverty (lack of sufficient public health resources to support robust diagnostics and data collection), cultural limitations, and more than 80% of cases occurring in remote rural areas.[274] For each fatal case of human rabies, access to PEP varies widely by region; in Latin America, more than 41,000 PEP courses are administered, whereas much less PEP is applied in Asia (200) and Africa (8).[221]

Importantly, dogs are the principal vector worldwide, accounting for 99% of human rabies transmission.[271] Locations without the funds or political will to control canine rabies invariably have a higher incidence of human rabies; 99% of human rabies cases occur in Asia and Africa.[118,272]

The greatest burden of rabies is in Asia.[222] India has the highest incidence (1.1 deaths per 100,000 population) of rabies in the world.[233] Moreover, despite administration of more than 9 million PEP courses, an estimated 38,000 deaths occur annually in Asia from rabies.[222,272]

Although data are sparse,[178] rabies is responsible for an estimated 25,000 to 31,000 deaths annually in Africa,[100,222,272] where approximately 260,000 PEP courses are administered each year.[222] Various factors, such as enzootic canine rabies, ignorance of disease risk, and lack of available treatments, contribute to this high mortality burden. In addition, the lesser (or even lack of) attention rabies receives compared with other infectious diseases makes it difficult to obtain funding and international coordination toward virus eradication. The Africa Rabies Expert Bureau (AfroREB) was established in 2008 to improve coordination. AfroREB, a network of rabies experts from 14 French-speaking countries on the African continent, has set two goals: increasing public officials' and health institutions' awareness of rabies, and

TABLE 31-1 Members of the *Lyssavirus* Genus

Virus	Genotypes	Phylogroup	Reservoirs
Rabies	1	I	Bats and carnivores, found worldwide except for Antarctica, New Zealand, Sweden, Norway, Spain, Taiwan, Japan, and some islands
Lagos bat	2	II	Probably enzootic in fruit bats; no reported human cases
Mokola	3	II	Probably an insectivore or rodent species limited to parts of Africa; a few domestic animals and two human cases reported
Duvenhage	4	I	Insectivorous bats; cases identified in South Africa, Zimbabwe, and Senegal
European bat lyssavirus 1 (EBLV1)	5	I	European insectivorous bats (*Eptesicus serotinus*)
European bat lyssavirus 2 (EBLV2)	6	I	European insectivorous bats (*Myotis dasycneme, Myotis daubentonii*)
Australian bat lyssavirus	7	I	Flying foxes and insectivorous bats; three human deaths reported
Irkut	8	I	Siberian insectivorous bats (*Murina leurogaster*)
Aravan	9	I	Central Asian insectivorous bats (*Myotis blaythi*)
Khujand	10	I	Central Asian insectivorous bats (*Myotis mystacinus*)
West Caucasian bat	11	III	Insectivorous bats (*Miniopterus schreibersi*), Caucasian region
Shimoni	12	II	Bats (*Hipposideros commersoni*), Kenya

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enhancing health professionals' and patients' knowledge to ensure better access to proper care following rabies exposure.[100]

Since 1990, reported human rabies in Latin America has declined by more than 90%, although underreporting of the true disease burden is likely throughout this period.[272] This marked reduction in rabies was largely a result of controlling the incidence of canine rabies.[178] From 2010 through 2012, only 111 cases were reported, with the majority (56.8%) resulting from exposure to infected bats and the remaining cases from exposure to infected dogs (36%) and other infected animals (7.2%). Approximately 220,000 courses of PEP are given annually in Latin America.[222]

In contrast to Africa and Asia, Europe reported only 210 human rabies deaths from 1990 through 2012, and 31 of those were acquired from other endemic areas.[90] In the United States from 2003 through 2013, a total of 34 cases were reported; 10 were acquired outside the country. An estimated 40,000 U.S. residents are administered PEP annually.[77]

In 2005, the annual global economic cost of rabies was estimated to be more than $4 billion U.S.[149] Excluding human deaths, the economic toll in Asia, Africa, and Latin America is estimated to be $530 million. As of 2011, annual cost attributed to rabies, including animal vaccinations, control programs, and health care, was more than $300 million in the United States alone.[77]

RABIES IN THE UNITED STATES

INCIDENCE IN HUMANS

The epidemiology of human rabies reflects that of local animal rabies reservoirs. In areas with significant numbers of human cases, canine rabies remains common; the intimate human-dog relationship has led to the vast majority of human cases resulting from dog bites. In regions where dogs are free of rabies, usually through aggressive immunization programs or areas free of terrestrial rabies, most human cases follow exposure to rabid wildlife. There are much lower rates of human rabies in such places.

In the United States, rabies viruses in dogs and from wildlife spillover are rare. Rabies surveillance data have identified the four major animal reservoirs to be bats, raccoons, skunks, and foxes (Figure 31-1). Bat exposures may go unrecognized, because of the minimal injury or pain from a bite, and are the most common cause of human rabies. Small rodents, such as chipmunks, squirrels, gerbils, rabbits, rats, and mice, are not a risk for viral transmission to humans. Imported cases of canine rabies continue to be reported in the United States. In 2011, a fatal case of human rabies occurred in an Army soldier 7 months after canine exposure in Afghanistan, which was confirmed as a canine rabies virus variant.[81]

TABLE 31-2 Human Rabies Infections in the United States, 1946–2008

Time Period	U.S. Infections*	Cases/Year	Non-U.S. Infections†
1946-1949	94	23.5	0
1950-1959	136	13.6	0
1960-1969	38	3.8	3
1970-1979	17	1.7	6
1980-1989	3	0.3	7
1990-1999	22	2.2	5
2000-2008	20	2.5	6

*Rabies infections acquired within the United States.
†Rabies infections acquired outside the United States.

The incidence of human rabies in the United States fell dramatically from 23.5 infections per year in the late 1940s to 1.0 infection per year during the 1980s (Table 31-2). However, 27 infections were reported from 1990 through 1999, and 26 were reported from 2000 to 2002. From 1980 to 1989, seven infections were acquired outside the United States; from 1990 to 1999, five infections were acquired outside the United States; and from 2000 to 2008, six infections were acquired in other countries.[58,64-69,264] Of the human rabies infections acquired in the United States, one originated from a skunk (1981) and two originated from dogs (1991 and 1994). The two dog infections were associated with the epizootic in coyotes that developed when rabies spread across the Rio Grande River from unvaccinated dogs in Mexico. The remaining 42 infections originated from bats. Of the 18 human rabies infections acquired outside the United States during these 28 years, 17 originated from dogs. An infection in 2008 in California was determined to have originated from a Mexican free-tailed bat[34] (Table 31-3). Recent data collected by the Centers for Disease Control and Prevention (CDC) indicate 34 total cases of human rabies have been diagnosed in the United States from

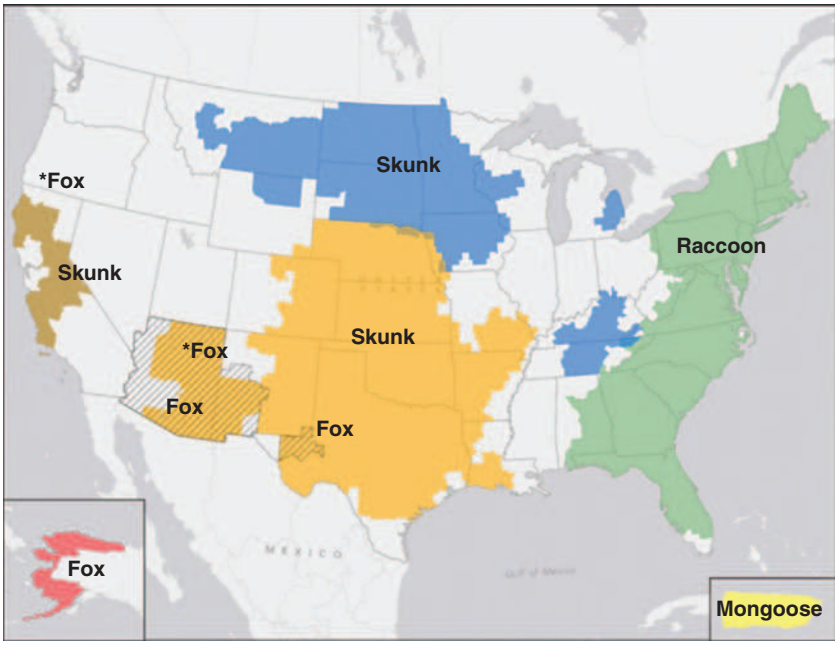

FIGURE 31-1 Wild animals capable of transmitting rabies in the United States. *(From* http://www.cdc.gov/rabies/resources/publications/2012-surveillance/reservoirs.html.*)*

TABLE 31-3 Rabies Deaths in the United States Since 1980 from Infections Contracted Outside the Country

Patient	Age	Gender	Onset of Rabies	Location	Exposure Location	Attacking Animal
1	40	M	8/81	AR	Mexico	Dog
2	30	M	1/83	MA	Nigeria	Dog
3	12	F	7/84	TX	Laos	Dog*
4	72	F	9/84	CA	Guatemala	Dog
5	19	M	5/85	TX	Mexico?	Unknown
6	13	M	11/87	CA	Philippines	Dog*
7	18	M	1/89	OR	Mexico	Dog*
8	11	M	4/92	CA	India	Dog
9	69	M	11/93	CA	Mexico	Dog
10	40	M	6/94	FL	Haiti	Dog*
11	26	M	2/96	FL	Mexico	Dog
12	32	F	8/96	NH	Nepal	Dog
13	54	M	9/00	NY	Ghana	Dog
14	72	M	2/01	CA	Philippines	Dog
15	41	M	2/04	FL	Haiti	Dog*
16	22	M	10/04	CA	El Salvador	Dog*
17	11	M	11/06	CA	Philippines	Dog*
18	16	M	3/08	CA	Mexico	Bat, Tb*

Tb, Tadarida brasiliensis.
*No documented exposure; source of infection identified by nucleotide analysis.

2003 through 2014 (Table 31-4), with three patients (8.8% of total cases) surviving infection. The majority (76%) of cases were infections acquired in the United States or Puerto Rico. Five of the 24 (20.8%) domestic rabies cases occurred from organ or tissue donors who died of rabies but in whom the disease was not diagnosed until rabies developed in transplant recipients (Table 31-4).

Although reliable rabies vaccines and antisera first became available during this 62-year period, extensive vaccination of domestic animals, particularly household pets, and elimination of unrestrained and stray animals are considered primarily responsible for the decline in the human infection rate.[59,60,185] Such programs reduced the incidence of laboratory-confirmed rabies in dogs from 6949 in 1947 to 75 in 2008.[34] The annual cost for these programs is more than $300 million, most of which is borne by pet owners.[229]

RABIES IN WILD TERRESTRIAL ANIMALS

In the United States and Canada, a vast reservoir of rabies persists in wild animals.[229] During 2008, 49 states and Puerto Rico reported 6841 rabies infections in animals, approximately 93% in wild animals and 7% in domestic animals. However, some states accept only animals responsible for a human or domestic animal incident for rabies testing; others test all submitted specimens. Furthermore, the number of rabid wild animals that die without being detected is estimated to be more than 90% of the total, so the identified infections represent only a small fraction of wild animal rabies.[152]

Several major rabies epizootics are currently recognized. An epizootic of rabies started in Arctic foxes in northern Canada in the late 1940s and early 1950s and swept southward in the middle and late 1950s to involve red foxes in Alberta, Saskatchewan, Manitoba, Ontario, and Quebec. The epizootic crossed the St Lawrence River in 1961, where it involved red foxes in upper New York State, although currently it appears to be limited to the adjacent Canadian provinces, which are experiencing a lower incidence of fox rabies.[13,32,153] The epizootic, which moved westward to involve arctic foxes in Alaska and the Northwest Territories,[226] surrounds the North Pole and may cover the largest land area of any observed outbreak[32] (Figure 31-2).

An outbreak of raccoon rabies started in central Florida in the 1940s and spread at the rate of about 40 km (25 miles) per year, reaching Georgia in the early 1960s and Alabama and South Carolina in the 1970s. In the late 1970s, a second outbreak appeared on the Virginia–West Virginia border. That epizootic has now spread north to all of New England; in 1999, it crossed into Canada. It has also spread south to join with the epizootic coming north from Florida in North Carolina.[61,83,84] The second outbreak developed when raccoons were translocated from Florida for restocking for hunters. Although the animal suppliers held legal permits and health certificates, inclusion of some rabid animals among the more than 3500 transported raccoons has been documented.[143,268]

As of 2002, more than 50,000 rabies infections in raccoons had been reported in the United States since 1975. The land mass affected by this epidemic is approximately 1 million km^2 (383,000 miles^2) and includes the residences of 35% of the U.S. human population (Figure 31-3). The raccoon epizootic is considered particularly threatening because many raccoons live in densely populated urban and suburban areas.[83] However, the only known human rabies infection resulting from this epizootic occurred in 2003.[64] The spread of rabies from raccoons to humans appears to have been limited in part because raccoons are large animals and their bites are obvious. To some extent, well-vaccinated dogs and other pets form a barrier between wild animals and humans. Perhaps of greatest significance is the nonaggressive behavior of rabid raccoons. In 38 rabid raccoon incidents in Florida over a 5-year period, bites were inflicted only when humans or dogs tried to kill or capture raccoons that seemed tame.[265]

Before the raccoon epizootic, most terrestrial rabies in the United States was in skunks. Human rabies resulting from exposure to a spotted skunk in California was reported in 1826.[82] Four epizootics are recognized, one of which is in the province of Quebec, Canada, and New York State and is associated with the fox epizootic in that area. A larger epizootic started in Iowa in 1955. It has spread east to Ohio, west to Montana, north to the Canadian provinces of Manitoba (1959), Saskatchewan (1963), and Alberta (1971), and south to meet with a third epizootic that originated in Texas and has spread to surrounding south-central states, particularly Oklahoma and Arkansas. The fourth epizootic in skunks is located in northern California[82] (Figure 31-4).

An increase in the number of rabid skunks in the East Coast states has recently occurred, but analysis of these infections indicates they result from raccoon rabies spilling over into skunks and are not indicative of a separate skunk epizootic.[127]

Screening of rabies virus isolates from the epizootics has disclosed five distinctive patterns. Red foxes and skunks in New York and adjacent Canada present one pattern; raccoons from the Atlantic states present a second. The skunks in the south-central states present a third, and a fourth is represented by a small outbreak in gray foxes in Arizona. The fifth pattern is found in skunks

TABLE 31-4 Cases of Rabies in Humans in the United States and Puerto Rico, 2003 through July 2014, by Circumstances of Exposure and Rabies Virus Variant

Date of Onset	Date of Death	Reporting State	Age (yr)	Sex	Exposure*	Rabies Virus Variant†
10 Feb 03	10 Mar 03	VA	25	M	Unknown	Raccoon, eastern United States
28 May 03	5 Jun 03	PR	64	M	Bite, Puerto Rico	Dog/mongoose, Puerto Rico
23 Aug 03	14 Sep 03	CA	66	M	Bite	Bat, Ln
9 Feb 04	15 Feb 04	FL	41	M	Bite, Haiti	Dog, Haiti
27 Apr 04	3 May 04	AR	20	M	Bite (organ donor)	Bat, Tb
25 May 04	31 May 04	OK	53	M	Liver transplant	Bat, Tb
27 May 04	21 Jun 04	TX	18	M	Kidney transplant	Bat, Tb
29 May 04	9 Jun 04	TX	50	F	Kidney transplant	Bat, Tb
2 Jun 04	10 Jun 04	TX	55	F	Arterial transplant	Bat, Tb
12 Oct 04	Survived	WI	15	F	Bite	Bat, unknown
19 Oct 04	26 Oct 04	CA	22	M	Unknown, El Salvador	Dog, El Salvador
27 Sep 05	27 Sep 05	MS	10	M	Contact	Bat, unknown
4 May 06	12 May 06	TX	16	M	Contact	Bat, Tb
30 Sep 06	2 Nov 06	IN	10	F	Bite	Bat, Ln
15 Nov 06	14 Dec 06	CA	11	M	Bite, Philippines	Dog, Philippines
19 Sep 07	20 Oct 07	MN	46	M	Bite	Bat, unknown
16 Mar 08	18 Mar 08	CA	16	M	Bite, Mexico	Fox, Tb related
19 Nov 08	30 Nov 08	MO	55	M	Bite	Bat, Ln
25 Feb 09	Survived	TX	17	F	Contact	Bat, unknown
5 Oct 09	20 Oct 09	IN	43	M	Unknown	Bat, Ps
20 Oct 09	11 Nov 09	MI	55	M	Contact	Bat, Ln
23 Oct 09	20 Nov 09	VA	42	M	Contact, India	Dog, India
2 Aug 10	21 Aug 10	LA	19	M	Bite, Mexico	Bat, Dr
24 Dec10	10 Jan 11	WI	70	M	Unknown	Bat, Ps
30 Apr 11	Survived	CA	8	F	Unknown	Unknown
30 Jun 11	20 Jul 11	NJ	73	F	Bite, Haiti	Dog, Haiti
14 Aug 11	21 Aug 11	NY	25	M	Contact, Afghanistan	Dog, Afghanistan
21 Aug 11	1 Sep 11	NC	20	M	Unknown (organ donor)‡	Raccoon, eastern United States
1 Sep 11	14 Oct 11	MA	40	M	Contact, Brazil	Dog, Brazil
3 Dec 11	19 Dec 11	SC	46	F	Unknown	Tb
22 Dec 11	23 Jan 12	MA	63	M	Contact	My sp
6 Jul 12	31 Jul 12	CA	34	M	Bite	Bat, Tb
31 Jan 13	27 Feb 13	MD	49	M	Kidney transplant	Raccoon, eastern United States
16 May 13	11 Jun 13	TX	28	M	Unknown, Guatemala	Dog, Guatemala

From Dyer et al: *J Am Vet Med Assoc* 245(10), 2014.
Dr, *Desmodus rotundus*; Ln, *Lasionycteris noctivagans*; My sp, *Myotis* species; Ps, *Perimyotis subflavus*; Tb, *Tadarida brasiliensis*.
*Data for exposure history are reported when plausible information was reported directly by the patient (if lucid or credible) or when a reliable account of an incident consistent with rabies virus exposure (e.g., dog bite) was reported by an independent witness (usually a family member). Exposure histories are categorized as bite, contact (e.g., waking to find bat on exposed skin) but no known bite was acknowledged, or unknown (i.e., no known contact with an animal was elicited during case investigation).
†Variants of the rabies virus associated with terrestrial animals in the United States and Puerto Rico are identified with the names of the reservoir animal (e.g., dog or raccoon), followed by the name of the most definitive geographic entity (usually the country) from which the variant has been identified. Variants of the rabies virus associated with bats are identified with the names of the species of bats in which they have been found to be circulating. Because information regarding the location of the exposure and the identity of the exposing animal is almost always retrospective and much information is frequently unavailable, the location of the exposure and the identity of the animal responsible for the infection are often limited to deduction.
‡Infection was not identified until 2013, when an organ recipient developed rabies.

from the north-central states and from California, in dogs from the Mexico border states, and in a small rabies outbreak in gray foxes in central Texas[225] (Figure 31-5).

Rabies in rodents is an intriguing problem. Rodents are the animals of choice for rabies virus isolation in the laboratory; yet rabies in small, free-living rodents is rare. One explanation is that rodents may usually be killed rather than simply infected by the bites of rabid animals, although rodents are carrion eaters and can be infected by that source as well. In recent years the largest number of rodent rabies infections has been in large rodents, such as woodchucks that have been infected by rabid raccoons. Rabid beavers have attacked and bitten humans in North Carolina. However, no transmission of rabies to humans by rodents has been documented.[241]

RABIES IN BATS

With the exception of Antarctica, rabies in bats is global. In Canada, the United States, parts of South America, Western Europe, and Australia (where rabies in carnivores, particularly dogs and foxes, has been controlled), bats are the most prominent source of human rabies.[181]

Rabies was diagnosed in insectivorous bats in Brazil in the 1920s and in frugivorous bats in Trinidad during the 1930s, although the principal subject of these studies was rabies in hematophagous ("vampire") bats that was being transmitted to humans. The first definitive diagnosis of rabies in nonhematophagous bats was made in a frugivorous bat that flew into a "chemist's shop" in Port of Spain, Trinidad, on September 10, 1931. However, the incident that drew widespread attention to bat rabies occurred in Tampa, Florida, on June 23, 1953. The 7-year-old son of a ranch hand was looking for a baseball near some shrubbery when a lactating female yellow bat suddenly flew out of the bushes and bit the boy on the chest, remaining firmly attached until knocked off by the boy's mother. The ranch owner had heard of rabies in vampire bats in Mexico and insisted the bat be examined for infection. Negri bodies were found in smears of the brain, and the diagnosis was confirmed by mouse

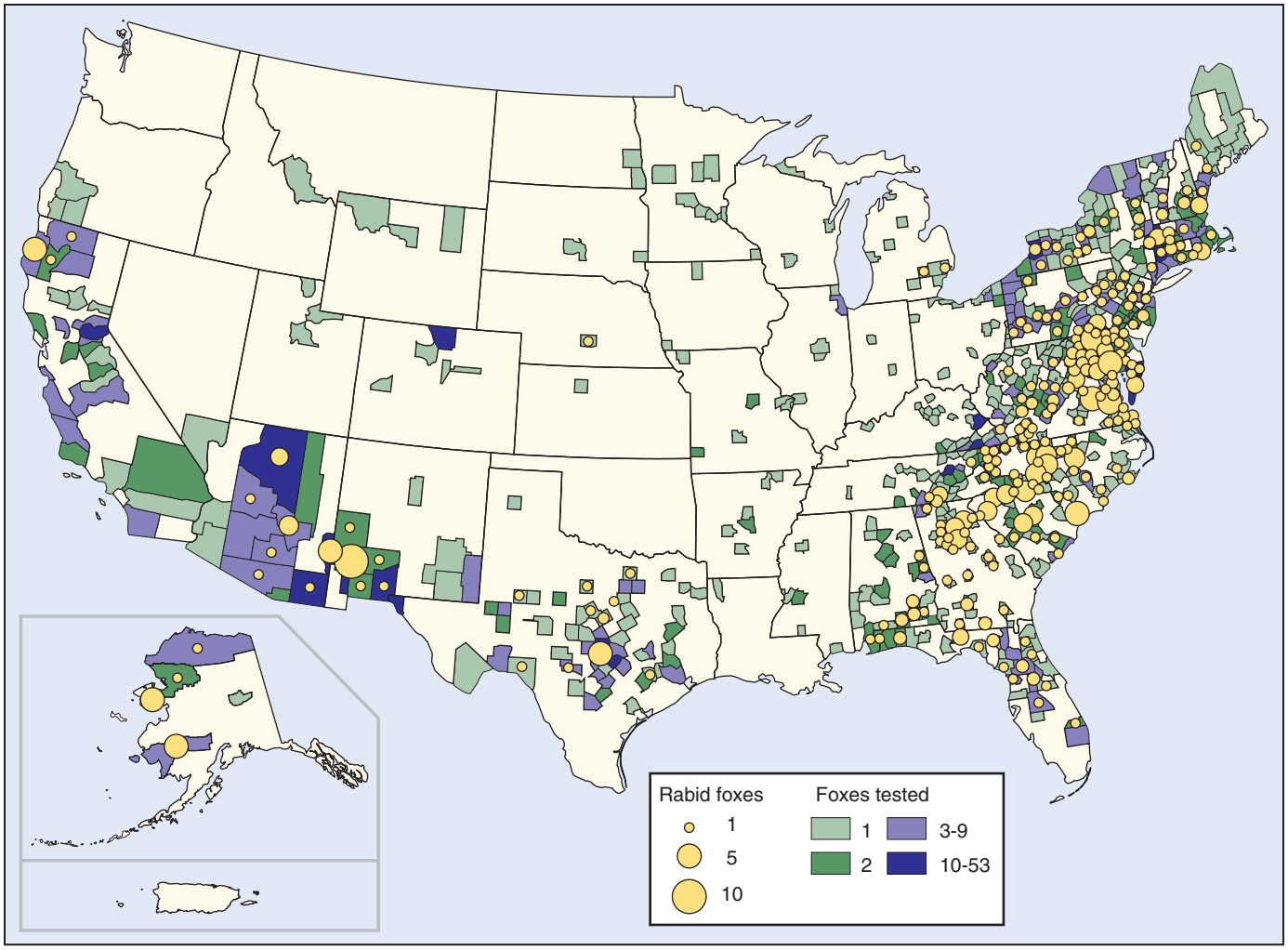

FIGURE 31-2 Rabid foxes reported in the United States in 2008. *(From* http://www.cdc.gov/rabies/resources/publications/2008-surveillance/foxes.html.*)*

inoculation of brain tissue. The boy was given postexposure treatment and did not develop an infection.[20,84,278]

The publicity given this event led to many more bats being submitted for rabies examination. Subsequently, rabies has been found in bats in every state except Hawaii, as well as in eight Canadian provinces.[20,198] In 2008, bat rabies was reported from all 48 of the continental states and the District of Columbia (Figure 31-6). The estimated incidence of rabies in bats in the United States is 0.5% to 1.0%; the incidence in bats that appear ill or injured is much higher, 7% to 50%.[20,242]

Rabies virus variants from bats are species specific rather than geographically specific[225] and are distinctly different from those of terrestrial animals in the same locations, including the major terrestrial epizootics. Clearly, little exchange of infection between bats and terrestrial animals takes place, although occasional animals infected with rabies virus strains typical of bats are found. Many large areas of the United States, particularly the Pacific Northwest and New England (before the raccoon epizootic), report rabies in bats but in no other species. Even though cats and foxes catch and eat bats, only 3 of 136 cat and fox rabies isolates over a 2-year period were antigenically similar to bat rabies strains.[20,96,225]

Approximately 70% of human rabies infections and 75% of cryptic rabies deaths in the United States have been caused by the variant associated with silver-haired and the eastern pipistrelle bats, which are reclusive animals rarely found around human habitation. Infections by variants associated with bats that frequent human dwellings are much less common. Infections in other animals by this variant are also disproportionately very high. These bats are small, and their bites are difficult to detect. However, compared with other rabies virus variants, the variant associated with these two bats replicates better in fibroblasts and epithelial cells and better at the low temperature of 34° C (93.2° F). These features indicate this variant is better able to replicate in the peripheral tissues involved by most bites.[169]

RABIES IN DOMESTIC ANIMALS

Since rabies in dogs has been controlled, rabies infections in cats have outnumbered infections in dogs (295 to 75 in 2008).[34] A major problem in vaccinating cats is establishing ownership. Farmers value cats for rodent control but do not recognize them as property. Cats wander from farm to farm and contact wild animals with rabies. Capturing feral cats so they can be vaccinated is difficult.[47] Rabies is not rare in other domestic animals, including cattle, horses, mules, sheep, and goats (Table 31-5).

SOURCES OF HUMAN INFECTION

In the late 1940s and 1950s, most human rabies in the United States resulted from bites by dogs or cats. Of 146 infections from 1946 to 1961 for which a source of exposure could be identified, dogs were responsible for 120 and cats for 9 (88.4%). Foxes (7), skunks (5), and bats (5) were responsible for the rest.[59] However, after rabies in domestic animals was controlled, human rabies

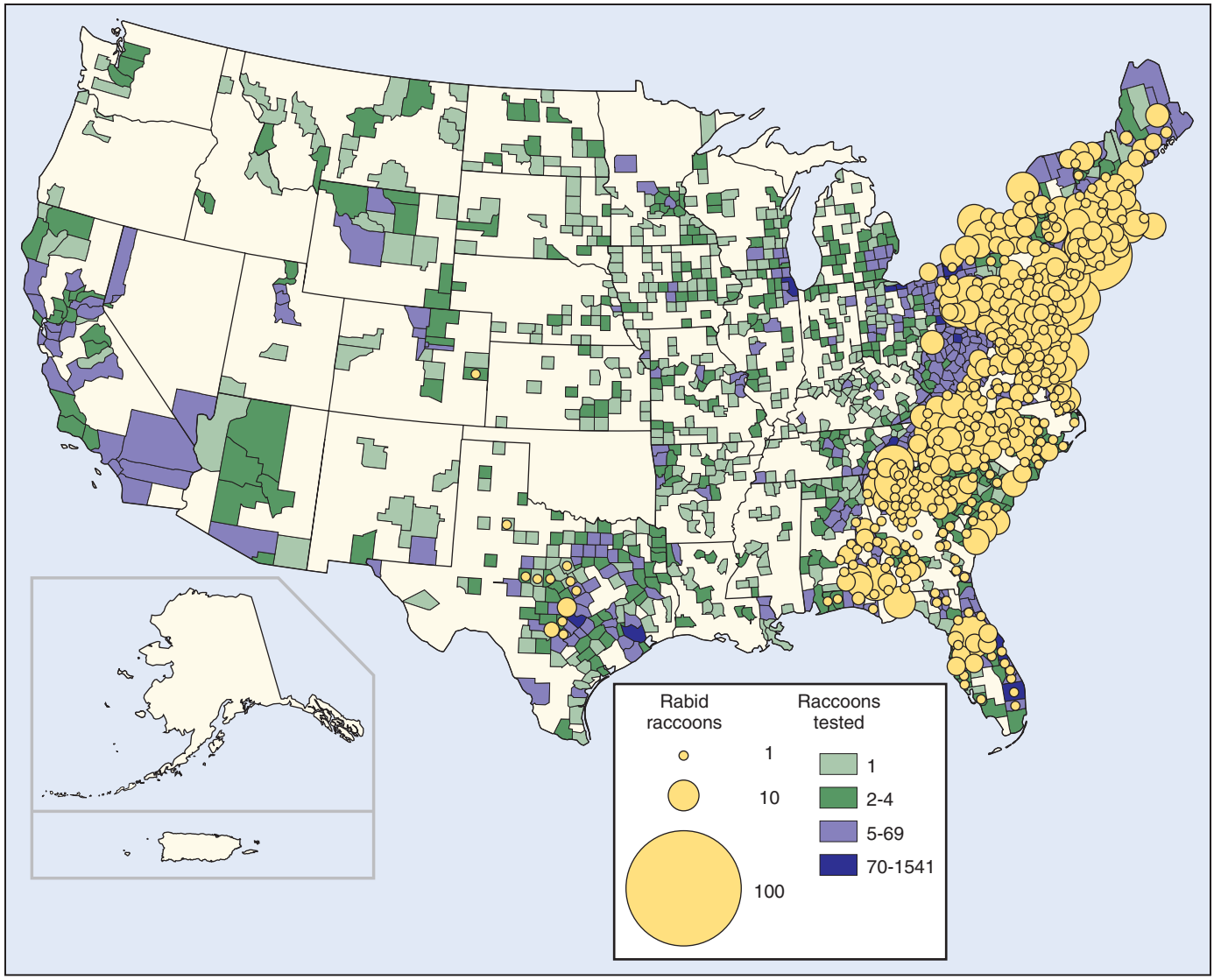

FIGURE 31-3 Rabid raccoons reported in the United States in 2008. *(From* http://www.cdc.gov/rabies/resources/publications/2008-surveillance/raccoons.html.*)*

resulting from bites by pets disappeared. Since 1966, all but 2 of the 19 human rabies infections resulting from exposures to rabid dogs were acquired outside the United States.[59,68,185]

Before 1965, the CDC had recorded no human rabies occurring within the United States that had been acquired outside the country.[185] Since then, however, the number of infections acquired outside the United States has been significant: 3 of 15 (20%) between 1965 and 1970, 6 of 23 (26%) in the 1970s, 7 of 10 (70%) in the 1980s, and 18 of the 63 cases (29%) since 1980. Lack of knowledge about the risk for rabies in developing countries has led some travelers to disregard animal encounters and not obtain rabies immunoprophylaxis, but some of these infections have been in children who did not inform their parents of the animal contact.

TABLE 31-5 Human Rabies Infections Identified in the United States and Puerto Rico, 2008

Domestic Animals (471)			Wild Animals (6369)		
Animal	**Total**	**Percentage**	**Animal**	**Total**	**Percentage**
Cats	294 (3)*	4.3%	Raccoons	2389	34.9%
Dogs	75 (11)*	1.1%	Bats	1806	23.2%
Cattle	59	0.9%	Skunks	454	6.6%
Horses/mules	20 (1)*	0.44%	Foxes	294	4.3%
Sheep/goats	12	0.18%	Mongooses	(42)*	0.61%
Other (llamas)	1	0.01%	Rodents/lagomorphs	34†	0.50%
			Other	97‡	1.42%

From Blanton JD, Robertson K, Palmer D, Rupprecht CE: Rabies surveillance in the United States during 2008, *J Am Vet Med Assoc* 235:676, 2009.
*Figures in parentheses are from Puerto Rico.
†31 groundhogs, 2 rabbits, and 1 beaver.
‡22 bobcats, 20 coyotes, 6 deer, 4 opossums, 1 otter, 1 coati, and 1 cougar.

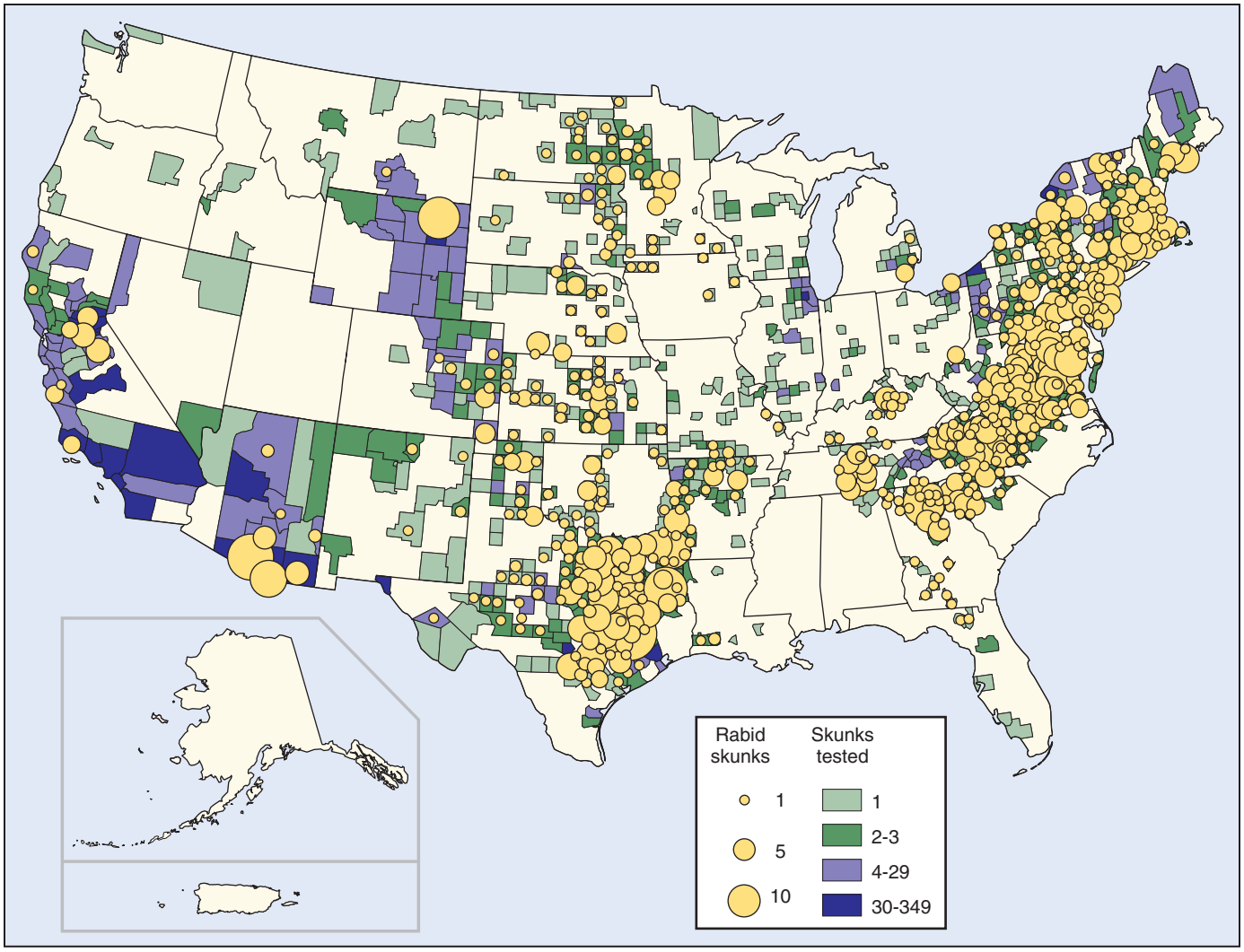

FIGURE 31-4 Rabid skunks reported in the United States in 2008. *(From* http://www.cdc.gov/rabies/resources/publications/2008-surveillance/skunks.html.*)*

Until the 1980s, identifying the source of a number of human rabies infections in the United States was impossible. For many infected persons, no animal exposure incident—even an opportunity for animal exposure—could be identified. An infectious source could not be found for 84 of 230 (35%) human rabies infections occurring in the United States between 1946 and 1961,[185] or for 6 of 38 (16%) human infections between 1960 and 1970.[57]

Only since the 1980s has monoclonal antibody typing or reverse transcriptase polymerase chain reaction (RT-PCR) nucleotide analysis allowed the source of human rabies infections to be determined when no animal exposure incident could be identified.[20,96,225] However, such studies have made it unmistakably clear that bats are now the major source of human rabies in the United States.

Of the 45 human rabies infections acquired within the United States since 1980, 42 are attributed to bats. A study of human rabies of bat origin in the United States and Canada from 1950 through 2007 identified 56 infections, of which 22 (39%) reported a bite, 9 (16%) had a direct contact but no bite, 6 (11%) found one or more bats in their homes (two in the room in which they slept), and 19 (34%) had no history of a bat contact.[93]

How the infection is transmitted has been uncertain. In 1956 and 1959, two men died of rabies after exploring Frio Cave near Uvalde, Texas. The walls and ceiling of that cave hold 300 to 400 bats per square foot. Neither man had been bitten, and the infections were attributed to aerosol transmission of the rabies virus. Subsequently, when experimental animals of various species were placed in the cave in cages that only allowed the virus to be transmitted as an aerosol, a significant percentage developed rabies.[91,92] Additionally, aerosol transmission of rabies to humans has occurred at least twice in laboratories.[27,267] The CDC recommends rabies vaccination for spelunkers.[63]

However, nursery caves, such as Frio Cave, contain an astounding number of bats. Saliva and urine constantly rain down on anyone entering the cave, and the blanket of guano on the floor ranges from several inches to several feet in thickness. In Frio Cave, air circulation is so poor that the bats warm the cave, the air is humidified by their respiration, and the concentration of ammonia from their urine is so high that the cave usually cannot be entered without respirators.[92] Similar infections in other caves have not been reported.

Unrecognized bites appear to be the source of infection for most individuals who have had no recognized bat encounters. Bat teeth are so small and sharp that a bite may not be felt. Even the recognized bites are not particularly painful, although at least one of the individuals known to have been bitten was intoxicated with ethanol at the time.[121] For centuries, South American vampire bats have been reported to bite sleeping victims without awakening them.

Limiting human rabies of bat origin is best addressed by informing the public of the risk.[198] Reducing the bat population is not an acceptable approach. Significant population reduction would be difficult and, if achieved, would be an ecologic disaster because bats play such a major role in insect control (Table 31-6).

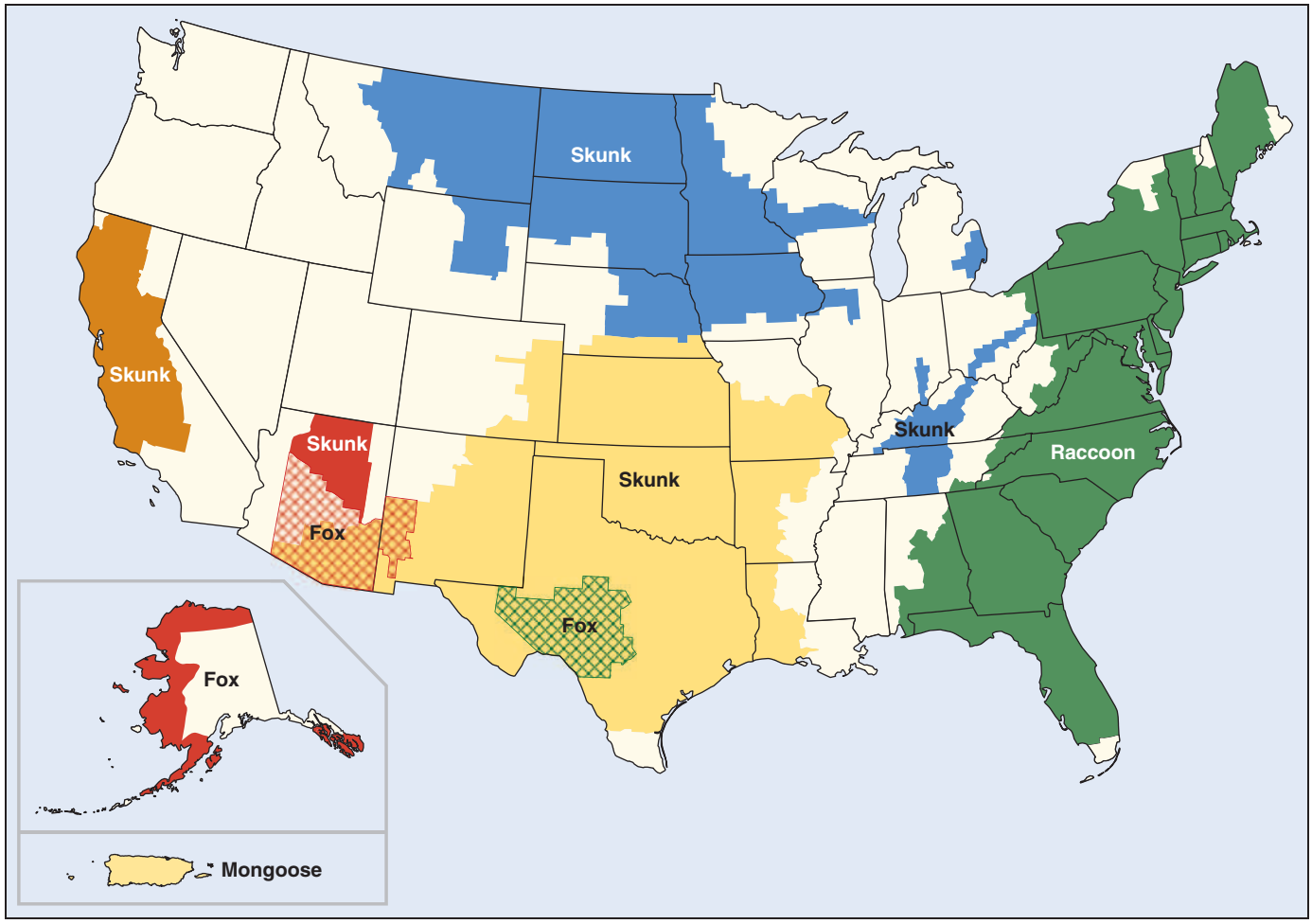

FIGURE 31-5 Terrestrial rabies reservoirs in the United States in 2008. *(From* http://www.cdc.gov/rabies/location/usa/surveillance/wild_animals.html.*)*

The CDC and other institutions now advocate the following measures:

- Dwellings should be "bat-proofed" by tightly covering all possible entrances, particularly roof ventilation openings, with wire screens. Protection from bats in unscreened dwellings or when sleeping outdoors can be achieved with mosquito netting.
- Contact with bats must be assiduously avoided, particularly bats that are behaving unusually. Bats are nocturnal, and any activity during daylight hours should be considered abnormal. Diseased bats often are unable to fly.
- Any person who has contact with a bat, regardless of whether a bite is thought to have been inflicted, should receive PEP unless the bat has been caught and examined for rabies.
- Any person, particularly a child, who awakens from sleep and finds a bat in the room should receive PEP unless the bat has been caught and examined. A number of the recent bat rabies victims have been children who experienced this type of exposure.

RABIES IN OTHER COUNTRIES

EPIDEMIOLOGY

Almost all deaths from rabies occur or are acquired in countries with inadequate public health resources to control canine rabies, and concomitantly have limited access to vaccine and rabies immune globulin (RIG) (Figure 31-7). These countries also have few diagnostic facilities and minimal rabies surveillance. More than 90% of human rabies exposure is through dogs (requiring PEP to avoid fatal infection), and canine rabies is the etiology for more than 99% of human rabies deaths worldwide.

Rabies is found throughout the world, and although more common in tropical or temperate climates, it is by no means limited to those areas (Figure 31-8). Arctic foxes with rabies have been found in Alaska, northern Canada, Greenland, Norway's Svalbard Islands, and much of Siberia. An epizootic in the Thule district of Greenland in 1958 and 1959 resulted in death from rabies of 50% of the sled dogs in that area. More than 1000 dogs in the Egedesminde district died in another epizootic in 1959 and 1960. For unknown reasons, transmission of rabies to humans is rare in these areas, even though exposures are common.[91] Perhaps the rabies variant is more infective for foxes and dogs.

Rabies is not found in a few areas of the world, all of which are landmasses or peninsulas isolated by water. Rabies does not occur in Hawaii (the only state in the United States where rabies is not found), some of the Caribbean islands, Pacific Oceania (including Australia [although Australian bat lyssavirus is found there] and New Zealand), or Antarctica.[125,180] The two human genotype 1 rabies infections that have occurred in Australia are thought to have been acquired outside that country[27,56,125] (see Figure 31-7).

Great Britain had been free of rabies since an extensive dog confinement and vaccination program was carried out in 1903, although concern about reintroduction of rabies was raised by the Channel Tunnel and reduction of border controls between members of the European Community.[84,243] A 55-year-old Scotsman with a fatal infection in 2002 was the first locally acquired lyssavirus infection on that island in 100 years, but the virus was not of genotype 1.[115]

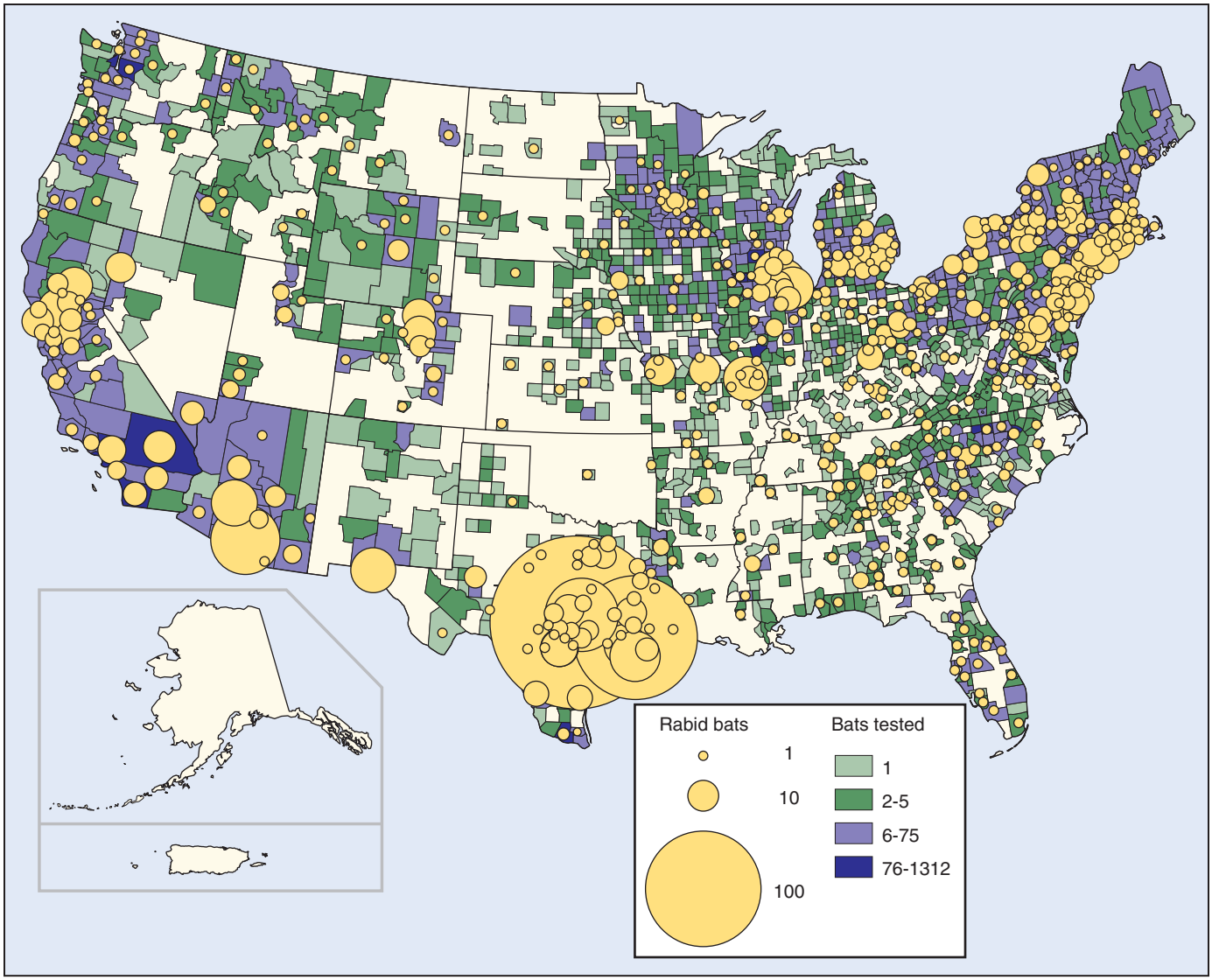

FIGURE 31-6 Rabid bats reported in the United States in 2008. *(From* http://www.cdc.gov/rabies/resources/publications/2008-surveillance/bats.html.*)*

Rabies has been endemic in Japan since the 10th century. However, following World War II, members of the U.S. Army Veterinary Corps determined that no reservoir of rabies existed in the wild animal populations of Japan, Taiwan, and the Philippines, perhaps in part because wild animals were hunted for food during the war. Extensive campaigns to eliminate stray dogs (which in some areas of Japan reduced the canine population by 70% to 80%) and to vaccinate those remaining succeeded in eradicating the infection from Japan and Taiwan. Endogenously acquired rabies has not occurred in those islands since the late 1950s.[5,228]

The success of canine rabies eradication programs depends on the society in which the programs are initiated. Such programs achieve little success in nations that are predominantly Hindu or Buddhist, because the people do not support elimination of animals that have no apparent owner. They often put out food for stray dogs. In contrast, Malaysia, a peninsula that is predominantly Muslim, has been largely free of rabies since the early 1950s.[28]

Elimination of stray dogs must be combined with vaccination programs. Dogs that are eliminated because they cannot be associated with human ownership are quickly replaced. The annual turnover of the dog population in developing countries has been found to range between 30% and 40%.[36]

Vaccination of domestic animals for rabies is limited largely to industrialized nations. In many developing countries, vaccination of animals is considered unaffordable, and rabies control resources are expended on postexposure immunoprophylaxis of humans. Even though rabies immunoprophylaxis is administered to 800 to 900 persons per 1 million inhabitants annually in such countries, the human death rate from rabies is still high, an average of almost five deaths for each 1 million population annually.[37] In the United States, that death rate would result in approximately 1500 rabies deaths a year.

The magnitude of the rabies threat in developing countries is illustrated by the experience in Thailand. Rabies has been of particular interest in that country since Princess Banlusirisarn was bitten by a rabid dog within the palace grounds near Bangkok in 1911 and subsequently died. No rabies vaccine was available in Thailand, then called Siam, at that time. The princess's death was instrumental in establishing the Institute Pasteur of Bangkok in 1913, which was renamed the Queen Saovabha Memorial Institute (QSMI) in 1922. The Institute, a WHO Collaborating Center for Research on Rabies Pathogenesis and Prevention, remains the site of many sophisticated rabies investigations.

In the 1990s, the Institute's postexposure rabies clinic treated about 18,000 patients with new animal bites each year, an average of almost 50 new patients a day. Furthermore, these

TABLE 31-6 Human Rabies Infections Contracted Within the United States Since 1980

Patient	Age	Gender	Onset Date	Location	Source
1	27	M	6/81	Oklahoma	Skunk
2	5	F	2/83	Michigan	Bat, Ln/Ps
3	20	M	9/84	Pennsylvania	Bat*
4	22	M	5/90	Texas	Bat, Tb
5	Adult	F	8/91	Texas	Dog*
6	Adult	M	8/91	Arkansas	Bat, Ln/Ps
7	Adult	F	10/91	Georgia	Bat, Ln/Ps*
8	11	F	7/93	New York	Bat, Ln/Ps†
9	82	M	11/93	Texas	Bat, Ln/Ps†
10	44	M	1/94	California	Bat, Ln/Ps†
11	41	M	10/94	West Virginia	Bat, Ln/Ps†
12	24	F	11/94	Alabama	Bat, Tb†
13	42	F	11/94	Tennessee	Bat, Ln/Ps†
14	14	M	11/94	Texas	Dog†
15	4	F	3/95	Washington	Bat, Msp
16	13	F	9/95	Connecticut	Bat, Ln/Ps†
17	74	M	8/95	California	Bat, Tb†
18	27	M	9/95	California	Bat, Ln/Ps†
19	42	F	9/96	Kentucky	Bat, Ln/Ps†
20	49	M	12/96	Montana	Bat, Ln/Ps†
21	65	M	12/96	Montana	Bat, Ln/Ps†
22	64	M	12/96	Washington	Bat, Ef†
23	71	M	10/97	Texas	Bat, Ln/Ps†
24	32	M	10/97	New Jersey	Bat, Ln/Ps†
25	29	M	12/98	Virginia	Bat, Ln/Ps†
26	49	M	9/00	California	Bat, Tb†
27	26	M	10/00	Georgia	Bat, Tb†
28	47	M	10/00	Minnesota	Bat, Ln/Ps†
29	69	M	11/00	Wisconsin	Bat, Ln/Ps†
30	28	M	3/02	California	Bat, Tb†
31	13	M	8/02	Tennessee	Bat, Ln/Ps†
32	20	M	9/02	Iowa	Bat, Ln/Ps†
33	25	M	3/03	Virginia	Raccoon†
34	66	M	9/03	California	Bat, Ln/Ps†
35	Adult	M	5/04	Texas	Bat, Msp
36	Adult	M	5/04	Texas	Bat/human‡
37	Adult	F	5/04	Texas	Bat/human‡
38	Adult	M	5/04	Texas	Bat/human‡
39	Adult	?	5/04	Texas	Bat/human‡
40	15	F	11/04	Wisconsin	Bat, Msp§
41	10	M	9/05	Mississippi	Bat¶
42	16	M	5/06	Texas	Bat, Tb†
43	10	F	9/06	Indiana	Bat, Ln/Ps†
44	46	M	9/07	Minnesota	Bat, Msp
45	55	M	11/08	Missouri	Bat, Ln/Ps†

Bat species: Ln/Ps, *Lasionycteris noctivagans* or *Pipistrellus subflavus*, silver-haired bat or the eastern pipistrelle bat; Tb, *Tadarida brasiliensis*, Brazilian (Mexican) free-tailed bat; Ef, *Eptesicus fuscus*, big brown bat; Msp, species unknown.
*No documented exposure; source of infection identified by monoclonal antibodies.
†No documented exposure; source of infection identified by RT-PCR.
‡Infection acquired through organ transplant from individual 35.
§Patient survived.
¶No documented exposure; source of infection based on history of bat exposure.

patients were only 28% of the estimated 64,000 Thais who receive postexposure therapy annually, many of whom were residents of rural or remote portions of Thailand and were treated by local physicians.[263] However, the number of human deaths from rabies in Thailand declined from about 400 a year in the 1970s to 70 in 1999, even though dog rabies has not been controlled.[83]

Other developing nations have similar rabies problems. WHO agencies have estimated that 87 countries and territories with a total population of about 2.4 billion people are afflicted with endemic canine rabies.[37]

SOURCES OF HUMAN INFECTION

Physical contact with wild animals should be avoided. If wild animals are observed, certain symptoms (which if lacking by no means excludes rabies) are indicative of rabies[179]:

- Unprovoked aggression ("furious" rabies). Some animals may attack anything that moves, or even inanimate objects.
- Unusual friendliness ("dumb" rabies).
- The animal may stumble, fall, appear disoriented or uncoordinated, or wander aimlessly.
- Paralysis, often beginning in the hind legs or throat. Paralysis of the throat muscles can cause the animal to bark, whine, drool, choke, or froth ("foam") at the mouth.
- Atypical vocalizations ranging from chattering to shrill screams.
- Nocturnal animals may become unusually active during the day.
- Raccoons walk as if on very hot pavement.
- Skunks, raccoons, foxes, and dogs usually display furious rabies. Bats often display dumb rabies and may be found on the ground, unable to fly. This can be very risky for children, who are more likely than adults to handle wild animals.

Although domestic animals are rarely the sources of human rabies in the United States and other developed countries, in developing countries the vast majority of human rabies—99% by some estimates—is the result of exposure to rabid dogs.[38,84,254,278] In Thailand, although rabies has been found in an array of exotic tropical animals, including tigers and leopards, between 1979 and 1985, 90.6% of human infections resulted from dog bites, and an additional 6% followed unknown events. The remaining 3.6% followed cat attacks.[214]

Other animals, particularly bats, transmit rabies. Hematophagous, or "vampire," bats are a major source of animal and human rabies in South and Central America, the only areas where such bats are found. Their range extends from northern Mexico to northern Argentina—basically between the Tropic of Cancer and Tropic of Capricorn—and fossils indicate vampire bats have inhabited those areas for 2.5 million years.[114] These animals consume 20 to 25 mL of blood at a feeding, and although cattle are their preferred food source, a study in Colima, Mexico, found human blood in the stomachs of 15.7% of 70 vampire bats.[16]

Human rabies of vampire bat origin was first recognized in 1929 in Trinidad when Negri bodies were found in the brains of 17 individuals, mostly school-age children, who died with acute ascending paralysis. Subsequently, small epidemics have been recognized almost every year in that country. Interestingly, almost all the rabies transmitted by vampire bats in Latin America is paralytic in type rather than furious.[257]

Human rabies resulting from vampire bat bites has been reported nearly every year from Mexico, but was first reported from South America in 1953 when 9 of 43 diamond miners who slept outdoors died of a mysterious illness. Autopsies of five of the miners disclosed rabies. In an outbreak in two rural communities in the Amazon Jungle of Peru during the first 4 months of 1990, 29 of 636 residents (4.6%) died after a rapidly progressive illness characterized by hydrophobia, fever, and headache. Rabies virus was isolated from the brain of the only individual on whom autopsy was possible. Of the 29 victims, 96% had a history of bat bites, although bats also had bitten 22% of unaffected community members.[6]

Human infection is not the only major problem resulting from rabies transmitted by vampire bats in Central and South America. Migrating epizootics of vampire bat–transmitted bovine paralytic rabies kill thousands of animals annually; the estimated cost in 1980 was $500 million.[6,83] Efforts to control these epizootics have included vaccination of cattle and attempts to limit the vampire bat population by administering anticoagulants, usually warfarin.

It is interesting to note that meat is often consumed from cattle slaughtered at the first, virtually pathognomic sign of disease, paralysis of the hindquarters. Even normal-appearing animals may have infected brains. Four of 1000 (0.4%) apparently healthy

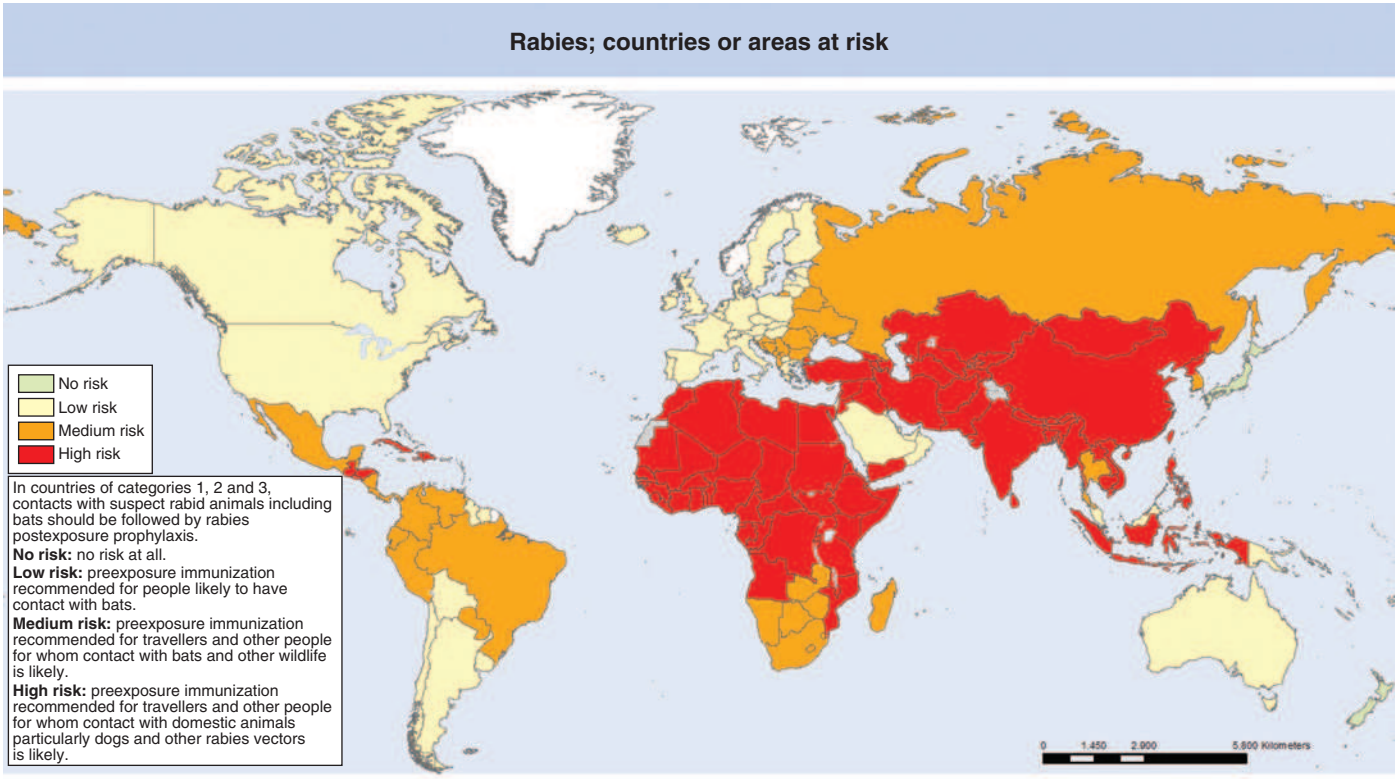

FIGURE 31-7 Global rabies risk. *(From World Health Organization ©2013.* http://gamapserver.who.int/mapLibrary/Files/Maps/Global_Rabies_ITHRiskMap.png?ua=1.*)*

cattle selected at random at the Mexico City slaughterhouse of Ferrería were found to be infected by rabies when investigated with fluorescent antibody staining and animal inoculation of brain tissue. However, no cases of human rabies from this source have been reported.[16] Human rabies has resulted from consumption of brain tissue from a rabid dog and a rabid cat in Vietnam.[259]

Mongooses are the major source of rabies in South Africa and in some Caribbean Islands, such as Puerto Rico.[17,105] The yellow mongoose is the main reservoir of rabies in South Africa.[278] The

FIGURE 31-8 Global *Lyssavirus* host animals. *(From Centers for Disease Control and Prevention.* http://blogs.cdc.gov/global/files/2013/09/photo1.png.*)*

small Indian mongoose, imported many years ago in an effort to control rodents,[131] is an important reservoir and vector of rabies in Cuba, the Dominican Republic, Grenada, Haiti, and Puerto Rico.[278] In Grenada, from 1968 to 1984, mongooses accounted for 787 (73%) of 1078 cases of animal rabies on the island. Of 208 human exposures requiring antirabies therapy, mongooses were responsible for 119 (57%). The possibility of eliminating the animals by hunting or trapping appears remote in view of the island's topography and the animal's skill at adapting to its surroundings. However, mongooses take oral bait, so oral vaccination appears feasible if an appropriate vaccine can be identified.[160] About 20% to 40% of mongooses have naturally acquired antirabies antibodies, possibly from having survived infection.[101]

At the Canadian International Water and Energy Consultants (CIWEC) Clinic in Kathmandu, Nepal, 51 travelers required immunoprophylaxis following rabies exposure during a 2-year period. Although 36 of these encounters were with dogs, 10 were with monkeys at Swayambhunath, the "Monkey Temple," a Buddhist shrine popular with tourists. The bites were inflicted when monkeys leaped for food carried by visitors.[219]

Human-to-human transmission of rabies is rare. Eight documented infections were in individuals who received corneal transplants (two from the same person) from individuals whose neuroparalytic disorder was not recognized as rabies.[52,113,135] In 1996, Fekadu and colleagues[109] reported two apparent cases of human-to-human rabies transmission in Ethiopia. A 41-year-old woman, who died of rabies 33 days after her 5-year-old son died of the same infection, had been bitten on a finger by her son. Another 5-year-old boy, who developed rabies 33 days after his mother died of that infection, had been repeatedly kissed on his mouth by his mother, apparently passing infected saliva to him. However, these infections were not confirmed by laboratory studies.

In July 2004, the CDC reported four cases of human rabies transmitted by organ transplants from a single donor. The male donor was hospitalized in Texas with "severe mental status changes," low-grade fever, and neurologic imaging findings indicative of subarachnoid hemorrhage. That lesion expanded rapidly in the 48 hours after admission and led to cerebral herniation and death. An autopsy was not performed. Only after the organ recipients' deaths from rabies was the donor's history of having been bitten by a bat discovered.

The donor's lungs were transplanted to a male who died of intraoperative complications. The liver and one kidney were transplanted to males, and one kidney was transplanted to a female, all of whom died of rabies 27, 37, and 39 days later. The fourth victim had a liver transplant from another donor, but a segment of iliac artery from the first (rabid) donor was inserted during the procedure. This recipient died of rabies approximately 1 month after the transplant.[67,69]

Also in 2004, three German individuals who had received a lung, a kidney, and a kidney/pancreas transplant from the same individual died of rabies. When the cause of their deaths was recognized, three additional transplant recipients who had received a liver and two corneas were given PEP and survived. Their corneas were removed. The donor had been scratched by a dog while visiting India and had not received postexposure therapy. The nature of her disease was not recognized until the three transplant recipients died.[144]

One case of human rabies appears attributable to transplacental infection. However, a number of mothers dying of rabies encephalitis have given birth to healthy babies, presumably because the virus travels through nerves—viremia has never been documented—and cannot reach the placenta or fetus.[110,135]

FEATURES OF HUMAN RABIES

MORTALITY

Rabies in humans, once it has become clinically apparent, is uniformly fatal. No other infection is so lethal or progresses so rapidly. In the 1970s, intensive support allowed three humans with clinical rabies to survive.[51,129,193] Three rabies survivors have been reported subsequently. The first five infections were vaccination failures, and four of the five survivors had severe residual neurologic deficits, severe enough to be fatal 34 months later in one person.[2,163] The rabies virus was not cultured from any of these patients, and at least one may have had a reaction to neural-derived vaccine rather than an actual infection.[142]

In October 2004, a 15-year-old female in Wisconsin became the first human to survive clinical rabies without vaccination. This young woman, who developed symptoms 1 month after she failed to report a recognized bite by a bat, was admitted 5 days later to the Medical College of Wisconsin. On the second hospital day, the CDC confirmed the presence of rabies virus–specific antibody in serum and cerebrospinal fluid (CSF). Because she had evidence of an adequate immune response, because brain pathology in humans succumbing to rabies largely reflects secondary complications rather than a clear primary process, and because clinical reports have included the hypothesis that death results from "neurotransmitter imbalance" and autonomic failure, her physicians, with her parents' approval, elected to treat her with antiexcitatory and antiviral drugs. Rabies vaccine and RIG were not administered.[68]

Coma was induced with ketamine and midazolam, the patient was intubated and maintained on a ventilator, and she received intravenous ribavirin and amantadine. Ketamine is a dissociative anesthetic, but it is also an *N*-methyl-D-aspartate (NMDA) antagonist, and the NMDA receptor has been speculated to be one of the rabies virus receptors. Later, she also was given benzodiazepines and supplemental barbiturates. She recovered slowly, was removed from isolation on the 31st day, and was discharged from the hospital on the 76th day. Attempts to isolate the rabies virus, detect viral antigens, or identify rabies RNA in two skin biopsies and nine salivary specimens were uniformly unsuccessful. Five months after her initial hospitalization, she was alert and communicative, but had choreoathetosis, dysarthria, and an unsteady gait. At 25 months after hospitalization, she continued to have fluctuating dysarthria and gait difficulties, as well as an intermittent sensation of cold feet. She had no difficulties with activities of daily living, including driving. In high school, she took college-level courses in English, physics, and calculus; scored above average on a national college achievement test; graduated in 2007; and planned to attend a local college. She had no problems with peer relations or mood disorders.[68,136,266]

At the time, hope was held that this therapy might be a breakthrough in the treatment of clinical rabies. However, a number of individuals have subsequently been treated by the same protocol, and none survived.[33,134,163]

In February 2009, a 17-year-old female presented to a community hospital emergency department (ED) with severe frontal headache of 2 weeks' duration, photophobia, vomiting, neck pain, dizziness, and paresthesia of her face and forearms. Two months earlier, she had come in contact with flying bats in a Texas cave, where several of the bats had hit her body, but she had not detected any bites or scratches. She had intermittent disorientation and a Glasgow Coma Scale score of 14, nuchal rigidity, and fever as high a 38.9°C (102°F). Her CSF had a white blood cell (WBC) count of 163 cells/mm^3 with 97% lymphocytes. Bacterial cultures of CSF grew no organisms. After 3 days, her symptoms resolved, and she was discharged.[72]

Six days later, this young woman presented to another hospital with photophobia, vomiting, and muscle pain. Her CSF showed a protein determination of 160 mg/dL (normal, 15 to 60 mg/dL) and WBC count of 185 cells/mm^3 (normal, <5/mm^3), of which 95% were lymphocytes and the rest macrophages. She was transferred to a tertiary care children's hospital.

Initially, she had decreased strength of the left lower and upper extremities, but that resolved. Four days later, she reported loss of sensation and strength of the right extremities, and vomiting increased. A lumbar puncture demonstrated increased intracranial pressure. The history of bat exposure was elicited that day. The following day, serum, CSF, saliva, and nuchal skin samples were submitted to the CDC for rabies testing. No rabies virus antigens or RNA could be identified in the skin or saliva, but four serum and CSF specimens contained rabies virus antibodies. Serum immunoglobulin G (IgG) reactivity increased to a

peak dilution of 1:8192 and immunoglobulin M (IgM) to 1:32. CSF IgG was positive to a dilution of 1:32.

After the initial results of testing were confirmed, the young woman received one dose of rabies vaccine and 1500 units of human RIG. To avoid potentiating the immune response, more vaccine was not given. She was managed supportively, never required intensive care, and was discharged 16 days later, after symptoms had resolved. Twelve days later, she returned to the ED with headache and vomiting, which resolved after a lumbar puncture. Her CSF pressure was still elevated. Subsequently, she did not return for follow-up.

Testing for evidence of 30 other causative agents of encephalitis or aseptic meningitis was uniformly negative. Her illness has been classified as presumptive abortive human rabies.[72]

Other than the 15-year-old from Wisconsin and the 17-year-old from Texas who received only a single dose of vaccine, no person who has not been vaccinated has survived clinically evident rabies. Subclinical human infections probably occur, as discussed later. The clinical phase of rabies encephalitis rarely lasts more than a few days to a few weeks, and infected persons are severely incapacitated.[3] The catastrophe of rabies is compounded by the young age of many victims; 40% to 50% are 15 years old or younger.[113]

INCUBATION PERIOD

For many years, some human rabies infections have been thought to follow prolonged incubation periods. In 1987, a 13-year-old boy who had immigrated from the Philippine Islands six years earlier died with rabies determined by nucleotide analysis to be of Philippine dog origin. He had not been out of the United States since he arrived.[55] The second documented Australian rabies patient, a 10-year-old girl of Vietnamese origin, had experienced no identifiable animal contact since she had left North Vietnam 6 years and 4 months earlier. She had spent some time in Hong Kong, and the virus responsible for her death was of an immunotype found in China, although the brain tissue was partially decomposed and nucleotide sequencing was limited.[27,125,145] Joshi and Regmi[148] have reported an individual who had an apparent incubation period of 1100 days (3 years). The first documented patient with rabies reported in Australia, a 10-year-old boy who died in 1987, probably resulted from a monkey bite inflicted in northern India 16 months earlier.[56] An 18-year-old Mexican man who died in Oregon in 1989 was infected with rabies virus of a strain to which he could not have been exposed for at least 10 months, although no history of any type of exposure could be obtained.[57] Even longer incubation periods of 10 years and 19½ years have been reported, but these occurred in areas where rabies is endemic, and a second exposure in the intervening period could not be ruled out.[225]

Confirmation of such prolonged incubation periods was achieved in three immigrants into the United States from the Philippines, Laos, and Mexico. Nucleotide analysis disclosed rabies viral amino acid compositions essentially identical to the patterns from rabies viruses isolated from dogs in their native countries and unlike rabies viruses found in the United States. These individuals had been in the United States for 6 years, 4 years, and 11 months before the onset of clinical disease.[225,229]

In 2004, a 22-year-old man from El Salvador who had been in Los Angeles for 15 months died of rabies that, by nucleotide analysis, was typical of rabies viruses found in dogs in El Salvador and unlike viruses found in the United States.[151]

Such prolonged incubation periods may explain the inability to recall any animal exposure by some patients. However, the possibility that in the past, rabies infections resulted from an unrecognized source, such as an undetected bite by a bat, cannot be dismissed.

Almost 99% of human rabies infections clinically manifest in less than 1 year, typically at 2 to 12 weeks.[18,27,113] The median incubation period in the United States for persons diagnosed between 1960 and 1990 was 24 days for those 15 years old and younger, and 43.5 days in those older than 15 years. Fixed (laboratory) strains of virus tend to produce shorter incubation periods than do wild or "street" strains. In 1960 in Brazil, 60 people were injected with vaccine that had been inadequately inactivated. Sixteen developed rabies, and the incubation period ranged from 4 to 16 days.[113]

The size of the viral inoculum clearly influences the incubation period. Experimental animals injected with large numbers of viruses develop clinical infections significantly faster than do those receiving small inocula. Small inocula resulted in greater central nervous system (CNS) histologic damage and more widespread infection outside the CNS, particularly in salivary glands.[104]

PATHOGENESIS OF CENTRAL NERVOUS SYSTEM INFECTION

Immediately after a bite (or investigational injection), rabies virus can be identified at the site with fluorescent antibodies and remains near the wound or injection site for hours to weeks, depending on the animal species. Viral antigen can be demonstrated in muscle, and viral particles budding into the sarcoplasmic reticulum and from the sarcolemma have been demonstrated on electron microscopy.[82] The virus appears to enter both motor and sensory nerves, probably through motor end plates and neuromuscular spindles.[14,210]

Passage of the virus through peripheral nerves was demonstrated in 1887 when rats[99] and rabbits[98] were protected from rabies after injection of the virus in their hind legs by sectioning the sciatic nerve. After entry into peripheral nerves, the virus travels at a rate of about 5 to 10 mm per hour to neuronal cell bodies such as dorsal root ganglia.[18,82] Replication can begin at this site, and prolonged ensconcement there has been suggested as one explanation for prolonged incubation periods.[210]

On reaching the CNS, the virus is widely disseminated with extreme rapidity, almost simultaneously with entry, but the manner in which the virus disseminates throughout the CNS is not known. Viremia has not been documented. Plasma membrane budding from infected to uninfected neurons and dissemination through intercellular spaces or CSF have been suggested. Clusters of viral particles at neuromuscular junctions, reduction of viral infectivity by nicotinic acetylcholine receptor competitors, and other data suggest that the virus recognizes cholinergic binding sites and perhaps enters peripheral and central nerve fibers through these sites. The large numbers of muscle cholinergic binding sites in foxes, which are exquisitely sensitive to rabies, and the small number of such sites in opossums, which are highly resistant to rabies, support this hypothesis and possibly explain the mechanism of sensitivity or resistance.[18] The glycoprotein that coats the viral particle is a major determinant of neuroinvasiveness, and alteration of this protein can greatly alter the kinetics of CNS viral spread.[14]

Viruses can be isolated from CSF. A significant antibody concentration in CSF is considered diagnostic of CNS rabies infection, and spread by this route may be quite rapid.[217] Additionally, rabies virions have been identified in intercellular spaces in the CNS on electron microscopy. Rabies antigen can be found in essentially all parts of the CNS and, although limited mostly to neurons, can also be found in oligodendrocytes.[140]

The rabies virus can infect a wide variety of cells in culture; no explanation for its localization to neurons in vivo has been found.[150]

After wide CNS involvement, the virus passes centrifugally through neural axoplasm to a wide variety of tissues, including salivary glands, corneas, and skin of the head and neck, sites at which identification of the virus may aid in the diagnosis of clinical illnesses. The route of spread to the periphery was demonstrated more than 90 years ago, when Bartarelli[25] sectioned nerves to salivary glands and found that the glands subsequently did not contain rabies virus. Even within the salivary gland, the virus appears to spread by neural networks and not between adjacent epithelial cells.[82]

An element of immunopathology is produced by disseminated rabies infection. Among persons exposed to rabies, those immunized with early vaccines who subsequently developed infections did so more rapidly than did unvaccinated individuals, a phenomenon termed "early death." Experimental confirmation of this feature has been achieved by injecting mice with a lethal quantity

of rabies virus and immunosuppressing a portion of them. The immunosuppressed animals survived 20% to 25% longer than did unsuppressed animals, but their survival was shortened to that of the control animals when injected with antirabies antibody. Additionally, cytolytic T cells appear to be a significant component of the protective response to rabies virus. Avirulent strains of rabies virus induce rabies-specific cytolytic T cells, but virulent strains do not.[176]

Pathologic alterations in the CNS infected by rabies are surprisingly mild, unless supportive care has kept the patient alive for several weeks, which allows much more extensive, necrotic lesions to develop.[198,210] Leptomeningeal congestion is the only grossly visible change typically found. Mild edema may be present if the patient has been hypoxic. Pressure grooves are rare. The meninges may be cloudy if severely inflamed.[189]

Typical histologic features are perivascular cuffing by mononuclear inflammatory cells, microscopic collections of reactive glial cells known as Babes nodules (named for the man who first described them in 1892[9]), and areas of neuronal degeneration and neuronophagia. Some leptomeningeal inflammation is usually present. Spongiform degeneration similar to that found in prion diseases has been described in animals, particularly in skunks.[82]

Van Gehuchten and Nelis[245,246] described a striking proliferation of the capsular cells surrounding ganglionic neurons that pushed these cells apart and separated them by a dense cellular layer. The neurons also contained degenerative changes. Subsequent studies have found the Van Gehuchten–Nelis changes to be present in almost everyone dying with rabies—and to be a much more consistent and reliable diagnostic feature than viral inclusions.

Negri bodies are the best-known histologic feature of rabies and were the first viral inclusions to be found (Figure 31-9). Negri[177] described these cytoplasmic inclusions in 1903 and considered them parasites that caused the disease. Entirely independently, Bosc[39,40] described identical inclusions in two separate papers published the same year, but he is rarely recognized. Negri bodies are eosinophilic cytoplasmic inclusions. Some contain a small, basophilic inner body, or *innerkörperchen*, and are known as "lyssa bodies." They are found almost entirely within neurons; although most common in Ammon's horn and Purkinje cells of the cerebellum, they may be seen in any part of the CNS, particularly in humans. Inclusions may also be seen in other tissues, such as the salivary gland, skin, cornea, and pancreas, but are not seen in the ependyma and choroid plexus.

The appearance of the inclusion bodies varies in different animal species, and uninfected animals, such as cats, usually contain cytoplasmic inclusions that easily could be confused with rabies bodies.[235]

On electron microscopy, three types of bodies have been identified: one composed of a granular matrix of viral protein and typical virus particles, a second composed of matrix and tubular structures, and a third composed of matrix alone. Invaginations of cytoplasm into the inclusion give rise to the *innerkörperchen*, indicating that Negri bodies and lyssa bodies are both diagnostic of rabies.[189]

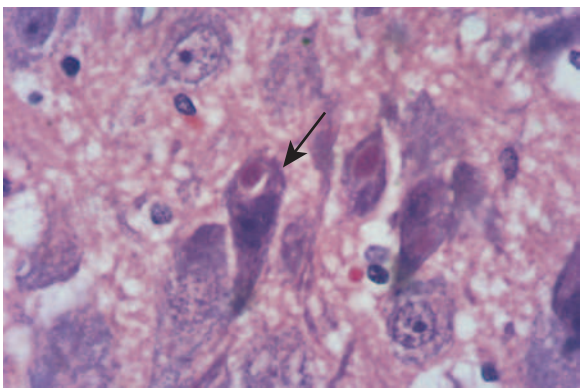

FIGURE 31-9 Negri bodies (*arrow*) in the cytoplasm of neurons in the hippocampus of a dog. (Hematoxylin-eosin, ×1000.) *(Courtesy Mérieux Institute.)*

CLINICAL FEATURES

Although the clinical features of classic rabies are said to be too well known to require description, few clinicians practicing outside the tropical endemic zone have ever seen the disease, and the rare cases presenting in Europe and North America are often misdiagnosed.[257]

After exposure to rabies, the incubation period is usually 20 to 60 days, with onset of disease within 3 months in 85% of cases. During the incubation period, it is suggested that the virus is probably sequestered in skeletal muscle at the bite site and amplified, while the exposed person remains asymptomatic.[220]

Clinical presentation is extremely variable, with symptoms first occurring as early as 5 days or as long as more than 6 years after transmission. Initial symptoms of rabies mimic other systemic viral infections: fever, headache, and malaise. Pain, paresthesias, or symptoms such as burning, itching, or numbness at the site of the bite or in the bitten limb are the most common early symptoms. Paresthesias may result from proliferation of rabies virus in the spinal cord at the level at which the nerves enter from the bite site.[113] In Thailand, this initial symptom often takes the form of severe itching that can lead to frenzied scratching and extensive excoriations.[257] This symptom is so well known among the Thai people, and animal bites are so common in that country, that any cause of itching or dysesthesia, even contact dermatitis, can lead to anxiety months to years after an animal exposure.[263] Additional symptoms that could manifest are anorexia, nausea, and vomiting. This prodromal period typically lasts 4 to 10 days.

Systemic symptoms usually develop later and are largely nonspecific. Local symptoms may not appear at all. One-third or less of all patients initially have symptoms that suggest the etiology of their infection to physicians who do not usually encounter the disease. Complaints include malaise, chills, fever, or fatigue. Symptoms that suggest an upper respiratory infection are common and include sore throat, cough, and dyspnea. Gastrointestinal symptoms include anorexia, dysphagia, nausea and vomiting, abdominal pain, and diarrhea. Headache, vertigo, irritability, or anxiety and apprehension suggest CNS involvement. However, even advanced rabies often has nonspecific features.[59,185] Hypoventilation and hypoxia are common during the prodrome and early acute neurologic phase, but their cause is not understood. Cardiac involvement is common and manifested by tachycardia out of proportion to the fever; hypotension, congestive failure, or even cardiac arrest may ensue.[113]

Two clinical forms of human rabies are recognized. The furious, encephalitic, or agitated form that is associated with periodic episodes of hyperactivity, restlessness, or agitation is considered most typical. This form of rabies is characterized by periodic opisthotonic spasms or convulsions, particularly in response to tactile, auditory, visual, or olfactory stimuli (aerophobia and hydrophobia). Episodes of disorientation, sometimes with hallucinations or violent behavior, often alternate with periods of lucidity, which can be particularly horrifying because the patient recognizes the nature of his or her illness. The terror associated with hydrophobia has been labeled "powerful but indescribable." Episodes of priapism, increased libido, insomnia, nightmares, and depression may suggest a psychiatric disorder. Patients maintained with supportive therapy progressively deteriorate, become comatose, lose peripheral nerve function, lose brainstem function, and die.[113,257]

Hydrophobia has been described in only 32% of recent U.S. patients,[113] although one recent U.S. rabies victim, an 11-year-old boy, was so afraid of water he would not even take a bath.[62] Experienced observers in Thailand have described hydrophobia as a violent, jerky contraction of the diaphragm and accessory muscles of inspiration that is triggered by attempts to swallow liquids and by other stimuli. Usually, it is not associated with neck or throat pain or with laryngopharyngeal spasms. It has

been likened to respiratory myoclonus (Leeuwenhoek's disease). When patients lapse into coma, hydrophobia is typically converted into cluster breathing with long apneic periods.[257]

The variability of the clinical manifestations of rabies may result from heterogeneity in wild or "street" rabies viral populations (as contrasted with "fixed" viral strains maintained in laboratories), even in the viruses infecting a single animal. Rabies viruses isolated from a boy who died after being bitten by a fox and propagated by intracerebral inoculation of white mice produced three distinctly different forms of disease in the mice.[126]

The second clinical form of rabies, the paralytic, dumb, or Guillain-Barré–like form, is characterized by progressive paralysis without an initial furious phase. Even though the paralytic form of the disease does not appear to be as familiar to some health care providers, 20% to 30% of human rabies patients present in this manner.[3,263] Other animals also have furious or dumb rabies presentations.[181] Paralytic rabies is more common after rabid vampire bat bites, in persons injected with fixed virus strains, and in persons who have received postexposure vaccination.[113] Distinction from Guillain-Barré syndrome may be difficult, although individuals with that disorder usually do not have urinary incontinence, which is common in rabies-infected persons.[141]

Individual case reports make clear that every patient is different. The most common misdiagnoses are psychiatric or laryngopharyngeal disorders.[141] Physicians at QSMI, who have vast clinical experience, consider inspiratory spasms to be the most reliable clinical sign of rabies, particularly in comatose patients, regardless of whether the disease was initially furious or paralytic. Such respirations also have been described as rapid, irregular, or jerky, termed *apneustic*.

In addition, most of the QSMI patients have myoedema, particularly in the region of the chest, deltoid muscles, and thighs.[263,278] However, the phenomenon of a brief, unpropagated, and localized muscle contraction that appears in response to percussion with a tendon hammer has not been confirmed as an important sign of paralytic rabies.[141]

Because the signs and symptoms are so nonspecific and often are rather mild at onset, many patients with rabies are not hospitalized the first time they are seen by a physician. Two patients who died in the United States, one between 1960 and 1980 (the year of death was not stated) and the second in 2008, were never hospitalized.[37] When admitted, most patients have a fever, which may be mild, but typically is above 39.4°C (103°F). Of the 38 individuals who died of rabies in the United States between 1960 and 1980, 24 (63%) had difficulty swallowing, but only half of those had definite hydrophobia or aerophobia; 27 (72%) manifested excitement or agitation; 24 (63%) had paralysis or weakness; and 12 (32%) had hypersalivation. Dysesthesias at the exposure site were described by 19 (79%) of the 24 individuals who had an identifiable bite or similar exposure.[3]

Of the 28 patients diagnosed before death, 26 had a history of an animal exposure. Only four of eight patients diagnosed after death had this history. All 12 patients with hydrophobia were diagnosed before death.[3]

The duration of illness for patients not given supportive care averages 7.3 days and ranges from 2 to 23 days. For patients who are given supportive care, the average duration of illness is 25.3 days, with a range of 7 to 133 days.[3,235]

Even with advanced supportive care, the case fatality rate is essentially 100% within 2 weeks of coma onset. Consequently, management approaches generally focus on palliation. As described earlier, however, in 2004 a 15-year-old female treated with a novel protocol became the first person to survive documented clinical rabies without previous vaccination (see also Therapy, later). In 2009, another unvaccinated adolescent female with a history of bat exposure, symptoms of encephalitis, and positive rabies virus serology recovered from a presumed rabies infection after receiving only basic supportive care. Similarly, a third, unvaccinated, 8-year-old female recovered from clinical rabies in the United States. All patients had evidence of rabies virus–specific antibodies in their serum and CSF at clinical presentation, but no viral antigen or RNA was identified.[79]

The WHO Expert Committee on Rabies[278] reported:

> The following [therapeutic] measures have . . . been tried in clinical rabies, but without any evidence of effectiveness: administration of vidarabine; multisite intradermal vaccination with cell-culture vaccine; administration of α-interferon and rabies immunoglobulin by intravenous as well as intrathecal routes; and administration of anti-thymocyte globulin, high doses of steroids, inosine pranobex, ribavirin and the antibody-binding fragment of immunoglobulin G.

In a review of the management of rabies in humans, Jackson and associates[142] suggested a combination of some specific therapies, pointing out that essentially no individuals with clinical rabies survive, and the best therapy often is palliative.

SUBCLINICAL RABIES

Although clinical rabies in humans is a uniformly lethal infection with only a handful of recognized exceptions, subclinical infections probably occur. Low titers of rabies virus–neutralizing antibodies have been found in Canadian Inuit hunters and their wives, as well as in unimmunized students and faculty members of a veterinary medical school.[141] In Nigeria, 28.6% of 158 healthy individuals who had no history of exposure to rabies or any antirabies prophylaxis were found to have serum-neutralizing antibodies against rabies. Antibodies against Mokola virus (genotype 3) and Lagos bat virus (genotype 2) also were found in 7.5% and 2.5% of these individuals. The investigators suggested that these individuals had been infected, but the infection had been halted before the virus had entered nerves. An attenuated strain of rabies virus also has been suggested as the cause of such antibodies, but an as-yet-unidentified virus of the *Lyssa* group, or even some other cross-reacting infectious agent, could be responsible.[184] Among 48 family members of Peruvians who died following rabid vampire bat bites in 1990, seven had antirabies antibody levels that ranged from 0.14 to 0.66 international unit (IU). These antibodies could not be related to exposure to bats, exposure to other animals, or to other epidemiologic events.[6]

Some animals, including dogs, have significant amounts of nonspecific virus-neutralizing antibodies in their sera. Up to 20% of raccoons in Virginia and Florida[213,268] and 20% to 40% of mongooses on Grenada have antirabies antibodies, which may be evidence of nonfatal infections.[101] Up to 80% of bats in crowded nurseries may have rabies antibodies.[20] The only finding considered diagnostic of prior rabies infection is antibodies in CSF.[106,107]

Even clinical rabies is not always fatal in animals. Pasteur observed that some dogs recovered from early symptoms of rabies and subsequently could not be infected by rabies virus injections.[187] Recovery from infections that produced paralysis has been described in two dogs.[108] Recovery from clinical rabies has also been described in mice, donkeys, bats,[16] and pigs.[19]

UNDIAGNOSED RABIES

Clearly, many rabies infections are not diagnosed in developing countries. Several considerations suggest that in industrialized countries a number of human rabies infections also are not diagnosed, and that the true incidence of this infection is higher than reported. The clinical manifestations usually are nonspecific, and many infections are diagnosed late in the course of illness as a result of testing for any identifiable cause of encephalitis, or subsequently by autopsy examination of the CNS. Of the 38 human rabies infections in the United States in the 1960s and 1970s, eight (21%) were diagnosed after death. Subsequently, the percentage of infections diagnosed postmortem has been higher.[57,258]

In recent years in the United States, most individuals with rabies have no recognized exposure to potentially infective animals, yet an account of animal exposure often is the only stimulus for laboratory identification of rabies as the cause of encephalitis.[57]

The significance of undiagnosed human rabies is uncertain. When the diagnosis is made, members of the patient's family and all health care personnel who have had a significant exposure

to the patient are given postexposure immunoprophylaxis. However, human-to-human transmission of rabies has been reported only after tissue or organ transplantation, except in two individuals in Ethiopia.[109]

BASIC TRANSMISSION

Rabies is most frequently transmitted to humans by the saliva of an infected animal during a bite. Immediately after infection, the virus enters an eclipse phase, during which it replicates in nonnervous tissue and is not easily detected. Following this phase, the virus invades motor and sensory nerves. Neurologic disease is preceded by an incubation period of several days to more than 6 years; the median incubation time is 1 to 2 months.[273]

The virus moves centripetally from the periphery to the dorsal root ganglia and spinal cord, resulting in nerve dysfunction manifested as a prodrome of neuropathic pain. When rabies has invaded the nerve cell body in the spinal cord, acute neurologic symptoms evolve into encephalitis.

After dissemination within the CNS, the virus is mainly concentrated in nerve tissues, salivary glands, saliva, and CSF. Other body fluids and intact organs are thought to be at low risk for carrying the virus; however, several cases of rabies have been reported in tissue (specifically corneal) transplant recipients; other transplanted tissues have also transmitted rabies.[231]

Needles or other sharp objects can transmit virus if they have passed through infected nervous tissue and thus carry the virus. Feces, blood, urine, and other body fluids are not considered to contain infectious virus.[80]

Not all rabid animals transmit virus to other animals they bite. Virus shedding is estimated to occur in 50% to 90% of infected animals. The amount of virus in saliva varies between animals and is unknown for most.[75] Shedding in animals can begin before onset of clinical signs. Cats have been reported to excrete virus 1 to 5 days before signs appear, dogs from 1 to 5 days, cattle from 1 to 2 days, skunks for up to 14 days, and bats for up to 2 weeks.[78] Human saliva also contains rabies virus, and transmission between people is theoretically possible but has not been documented. It is not known how long humans can shed virus before becoming symptomatic. The CDC recommends PEP for anyone who has had at-risk contact with a person during the 14 days before onset of clinical symptoms.

Risk Factors Associated with Disease Transmission

The risk of developing rabies after exposure to an infected animal depends on several factors. The amount of viral inoculum is fundamental; the extent of exposure to saliva is directly related to rapidity of the disease course.[260] Direct exposure to infected saliva affects disease transmission; bites involving exposed skin are associated with a greater probability of rabies developing than those occurring through thick clothing that protects the skin from the animal's saliva. The risk of rabies transmission is higher in cases of multiple bites and in bites occurring on the face rather than the extremities. Disease transmission can occur via aerosolized virus exposed to mucous membranes or the respiratory tract.[92]

LABORATORY DIAGNOSIS OF RABIES

Conventional laboratory procedures are not helpful in establishing a diagnosis of rabies. CSF protein and leukocyte counts may be modestly elevated, but these changes are nonspecific.

Currently available techniques for a definitive laboratory diagnosis of rabies usually are nondiagnostic in the early days of infection and become useful only 1 week or more after the onset of illness. The diagnosis of rabies should be confirmed as early as possible so that the number of persons exposed to the infection can be limited and therapy for those exposed can be initiated promptly. In industrialized nations, the number of persons exposed to a hospitalized rabies patient can number in the hundreds.[196,241]

If rabies is suspected, a complete set of samples should be collected for testing by all currently available diagnostic procedures. Consultation is available from the CDC 24 hours a day, 7 days a week, and should be obtained (877-554-4625; http://www.cdc.gov/rabies/). However, samples taken antemortem cannot definitively rule out rabies. If infection is seriously suspected, repeated sampling is needed.[241] Samples can be transported overnight to the CDC or to state laboratories.

The rabies virus is systemically disseminated shortly after CNS infection and often can be detected with labeled antibodies or by RNA extraction. Currently, detection of rabies RNA in saliva after RT-PCR amplification appears to be the most reliable procedure. Saliva should be collected with a sterile eyedropper or pipette and placed in a small sterile container that can be sealed securely. No preservative or other material should be added. Tracheal aspirates and sputum are not suitable for diagnostic testing.

A 5- or 6-mm punch biopsy of hair-bearing skin with at least 10 hair follicles from the nape of the neck is typically used for immunohistochemical staining for rabies virus. The specimen should be placed on sterile gauze, moistened with sterile water or saline, and placed in a sealed container with no other fixative or preservative.

At least 0.5 mL of serum (not whole blood) is needed to test for antibodies by immunofluorescence and virus neutralization. If no vaccine or rabies immune serum has been administered, the presence of antibodies is diagnostic and testing for CSF antibodies is not needed. At least a similar volume of CSF is needed for antibody studies. The rapid fluorescent focus inhibition test (RFFIT) is the reference standard serologic test for neutralizing antibodies. Some patients have detectable antibody by day 6 of clinical illness, 50% by day 8, and virtually all by day 15.[170] Highly sensitive serologic methods used for serum and CSF samples are immunofluorescent antibody tests that detect rabies virus–specific IgM and IgG antibodies against rabies virus, primarily to the virus ribonucleoprotein.[183]

Rabies virus can sometimes be found in imprints from the cornea, although this procedure is infrequently used now. An ophthalmologist should prepare the smears after consultation with the rabies testing laboratory to avoid damaging the cornea. RT-PCR with nucleotide analysis and immunostaining are used to identify the viral antigens.

Brain biopsies should not be routinely performed because human rabies is so rare in industrialized countries and no effective treatment is available. If a biopsy is performed to rule out another condition, it can also be examined for rabies.[241]

Rabies virus often can be isolated from body fluids, particularly saliva and CSF. The murine neuroblastoma cells used for isolation of rabies are more susceptible to that virus than any other cell line tested, and culture on such cells can usually provide a diagnosis within 24 hours. Mouse inoculation may take 15 to 30 days, although the time can be shortened by sacrificing mice starting 5 days after inoculation and examining the brains with fluorescent antibodies.[235,278] In industrialized nations, facilities for such studies can be found in local, state, and national public health laboratories. In developing countries, they often are unavailable.

Postmortem testing is best done using nervous tissue; brain is the ideal tissue to test for rabies antigen. Immunohistochemistry methods or direct fluorescent antibody (DFA) tests can be used to provide sensitive and specific means to detect rabies tissues.[76]

RABIES IN ATTACKING ANIMALS

Before 1903, the diagnosis of rabies in attacking animals was based entirely on the clinical features of the disease or on the presence of unusual material in the stomach of an animal that evidenced bizarre behavior. The dog that attacked Joseph Meister, the first recipient of Pasteur's antirabies vaccine, was diagnosed as rabid because it had hay, straw, and wood in its stomach.[9] In 1903, Negri and Bosc described the typical neuronal cytoplasmic inclusions, and for many years the laboratory diagnosis of rabies in animals depended on the detection of such bodies. However, only 60% to 80% of infected animals have identifiable inclusions.[240] For example, typical inclusion bodies are scarce in Arctic foxes.[91]

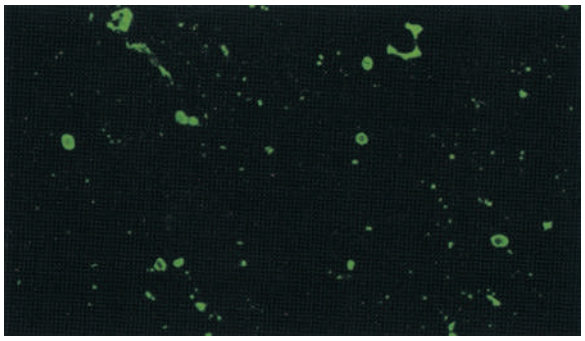

FIGURE 31-10 Fluorescence-labeled, rabies-specific antibody staining of a smear from the brain of a rabid Canadian fox. (×400.) *(Courtesy Centers for Disease Control and Prevention.)*

Immunofluorescent detection of rabies antigen in smears of cerebral tissues, which was introduced in 1958 and became widely used in the early 1960s,[122] is much more reliable in experienced hands (Figure 31-10). Comprehensive analyses of the performance on survey examinations established that in major U.S. public health laboratories, the sensitivity of fluorescent antibody examination is almost 100%. Fluorescent antibodies are used to identify rabies antigen in tissue culture (see later) because the rabies virus produces few cytopathogenic changes.

The major shortcoming of the procedure is its reduced sensitivity for rabies antigen in decomposed brain tissue. Some investigators have concluded that failure to identify rabies antigen with fluorescent antibodies in partially decomposed brain tissue cannot justify withholding postexposure therapy for exposed individuals.[240]

A procedure to confirm negative diagnoses is essential. Rabies diagnosis by intracerebral mouse inoculation was introduced in 1935 and demonstrated that only 85% to 95% of rabies infections could be identified by examination for inclusion bodies alone.[232] Eventually, most laboratories, even those in developing countries, adopted adult or suckling mouse inoculation. Tissue culture inoculation began with inoculation of chick embryo cells in 1942.[235] Currently, tissue culture isolation on mouse neuroblastoma cells is used, is much faster, and is the most sensitive technique for confirming negative immunofluorescence examination results, at least in laboratories with suitable facilities and appropriate personnel.[41,207,235] The rabies virus does not produce cytopathic changes in tissue culture, and fluorescent-labeled antibodies must be used to diagnose the infection.

THERAPY

There is no proven antiviral therapy for rabies. Development of effective treatment for rabies in humans is urgently needed. Even in cases of comprehensive intensive care, rabies is almost invariably fatal, with death occurring within several days to weeks of disease onset. To date, there are only three documented cases of survival following rabies infection. All three patients presented with rabies virus–specific antibodies in serum and CSF, while lacking viral antigens or RNA, which suggests these findings may be biomarkers of a promising prognosis.

A now disproven treatment protocol that is not routinely recommended is the Milwaukee protocol (www.mcw.edu/Pediatrics/Infectious Diseases/PatientCare/Rabies.htm). This experimental protocol, originally applied to a 15-year-old girl from Wisconsin who presented with signs and symptoms of rabies 1 month after being bitten by a bat, involves inducing coma by placing the patient into electrographic burst suppression with ketamine and midazolam, followed by antiviral therapy with ribavirin and amantadine.[266] This patient was not administered rabies vaccine or rabies immune globulin, because an immune response was present in both serum and CSF. After 76 days of hospitalization, she was released home, and she remained well with only mild neurologic sequelae.[136] Despite her survival, the Milwaukee protocol is no longer recommended because of subsequent reports of deaths in rabies patients treated with this experimental regimen.[7,70,71]

Future research efforts should focus on advancing understanding of rabies virus pathobiology and pathogenesis, as well as developing clinically relevant animal models to aid in rational design of antiviral therapies.[116] In the absence of effective antiviral therapies, individuals considered to be at high risk for exposure to rabies virus should take appropriate prophylactic measures.

PREEXPOSURE PROPHYLAXIS

Given the lack of an effective rabies therapy, preexposure prophylaxis is critical for individuals at high risk of exposure to rabies virus, such as veterinarians, laboratory technicians who work with rabies virus, cavers, and deployed military troops or travelers in rabies-endemic countries with poor medical care infrastructure (Table 31-7). Before travel, international travelers

TABLE 31-7 CDC Guidance on Rabies Preexposure Prophylaxis by Risk Category

Risk Category	Nature of Risk	Typical Population	Preexposure Recommendations
Continuous	Virus present continuously, often in high concentrations Specific exposures likely to go unrecognized Bite, nonbite, or aerosol exposure	Rabies research laboratory workers; rabies biologics production workers	Primary course Serologic testing every 6 months; booster vaccination if antibody titer is below acceptable level
Frequent	Exposure usually episodic, with source recognized, but exposure also might be unrecognized Bite, nonbite, or aerosol exposure	Rabies diagnostic laboratory workers, spelunkers, veterinarians and staff, animal control and wildlife workers in rabies-enzootic areas All persons who frequently handle bats	Primary course Serologic testing every 2 years; booster vaccination if antibody titer is below acceptable level
Infrequent	Exposure almost always episodic with source recognized Bite or nonbite exposure	Veterinarians and terrestrial animal control workers in areas where rabies is uncommon to rare Veterinary students Travelers visiting areas where rabies is enzootic and immediate access to appropriate medical care, including biologics, is limited	Primary course No serologic testing or booster vaccination
Rare (population at large)	Exposure always episodic with source recognized Bite or nonbite exposure	U.S. population at large, including persons in rabies-epizootic areas	No vaccination necessary

Modified from http://www.cdc.gov/rabies/specific_groups/travelers/pre-exposure_vaccinations.html.
CDC, U.S. Centers for Disease Control and Prevention.

should consult the CDC website for current rabies preexposure prophylaxis recommendations (wwwnc.cdc.gov/travel/diseases/rabies). Although preexposure rabies vaccination, comprising a three-shot series (days 0, 7, and 21 or 28) administered before travel, does not preclude the need for immediate medical attention after suspected exposure, it decreases the number of vaccine doses required after exposure (injections at days 0 and 3) and eliminates the need for administering RIG. For individuals at high risk for rabies exposure, booster doses every 2 to 3 years are recommended if titer levels are known or suspected to be low. In the United States, an adequate antibody response is classified as complete neutralization at the 1:5 serum dilution level (0.1 IU/mL) using the RFFIT, whereas the WHO recommends a less conservative antibody titer concentration (0.5 IU/ml).

POSTEXPOSURE PROPHYLAXIS

Given that animal rabies is relatively common in the United States, appropriate PEP measures are important to mitigate disease transmission (Figure 31-11). PEP for individuals in contact with suspected rabid animals is given to a total of 16,000 to 39,000 individuals per year in the United States[74] and incurs a cost of approximately $290 million.[149] The CDC Advisory Committee on Immunization Practices (ACIP) advises PEP guidelines based on the type of animal responsible for the bite and whether the animal shows signs of rabies (Table 31-8).

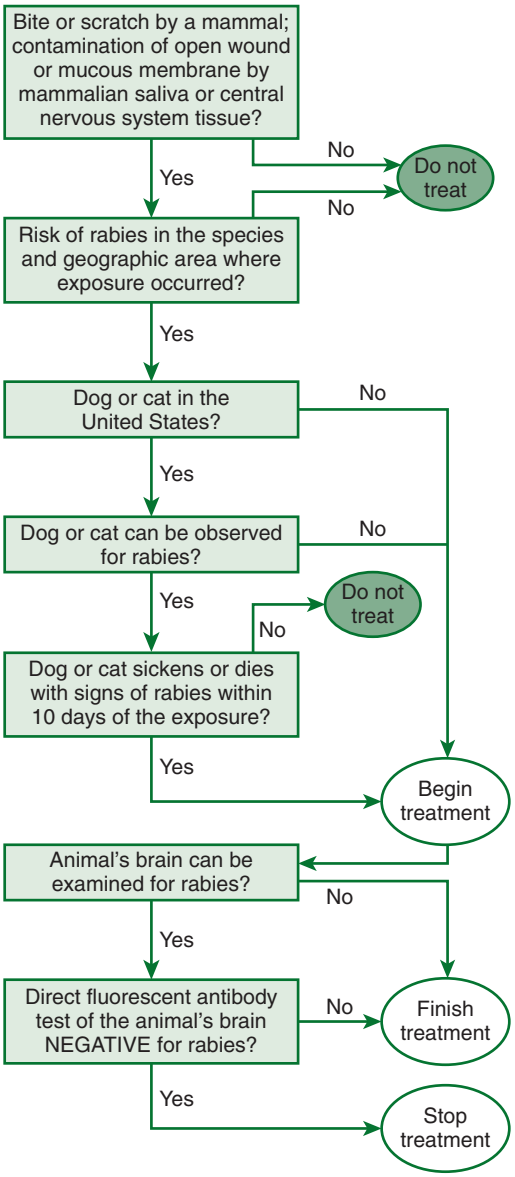

FIGURE 31-11 Decision tree for human rabies postexposure prophylaxis (PEP). *(From Bennett JE, Dolin R, Blaser MJ, editors:* Mandell, Douglas, and Bennett's principles and practices of infectious diseases, *8th ed, Philadelphia, 2015, Elsevier.)*

Postexposure treatment for humans consists of reducing the viral inoculum by cleansing the wound as thoroughly as possible, administering antiserum to help control viral reduplication and spread (passive immunization), and administering rabies vaccine to establish immunity to the virus before signs of infection appear (active immunization). "Rabies vaccination is a race between the active immunity induced by vaccination and the natural course of infection."[249]

Identifying Exposure

Exposure to rabies is divided into bite and nonbite categories. A bite is considered a significant exposure if it penetrates the skin. Scratches that break the skin are also considered significant exposures because the claws could be contaminated by saliva. Unprovoked attacks are more likely to have been inflicted by a rabid animal than are provoked attacks, but determining whether a dog or cat bite has been provoked is frequently difficult. Bites that occur while feeding or handling apparently healthy animals are generally regarded as unprovoked, but some animals, particularly dogs, may bite anyone walking by or riding a bicycle.

Nonbite exposure consists of contamination of cutaneous wounds—including scratches, abrasions, and weeping skin rashes—with saliva, CSF, or brain tissue from a rabid animal. If the material is dry, it is considered noninfectious.[42] Contamination with urine from a rabid animal or person is not considered an exposure, even though rabies viruses have been isolated from kidneys and urine. A laboratory technician cut by a broken specimen container was given postexposure therapy.[83]

It is important to note that the rabies virus passes through intact mucous membranes, and that any mucous membrane contact, particularly membranes of the oral cavity or conjunctiva, with saliva or other infectious material from a possibly rabid animal is considered an exposure.

Exposure of medical personnel or family members caring for patients with rabies is a significant problem. "High-risk contact" is defined as a percutaneous (through needlestick or open wound) or mucous membrane contact with saliva, CSF, or brain tissue. Such contact is considered essentially the same as bite and nonbite exposures to rabid animals. Individuals who have had a high-risk contact should receive postexposure immunoprophylaxis. However, routine infection isolation procedures, including respiratory precautions, minimize the risk for medical personnel caring for patients with rabies.[42]

Individuals who have not had a high-risk contact do not need postexposure immunoprophylaxis, although such treatment is sometimes administered to allay anxiety.

In areas where canine rabies is not enzootic, which includes all U.S. regions except for the area along the border with Mexico (particularly southern Texas), a healthy domestic dog or cat that bites a person should be confined and observed for 10 days, particularly if the animal has been previously vaccinated. A veterinarian should evaluate any illness during confinement. If rabies is suspected, the animal should be humanely killed and its head should be shipped to a qualified laboratory.[63] The head must be refrigerated during shipping. Examinations for rabies cannot be reliably performed on decomposed brain tissues.[241]

Such confinement and observation were judged safe for exposures to ferrets in 1998. Scientific evidence that the same quarantine period would be adequate for wolf hybrids does not exist, because studies of pathogenesis and virus shedding have not been performed. Hybrids that bite humans should be euthanized immediately, and their heads should be shipped to reliable laboratories.[181]

The significance of the laboratory's qualifications was emphasized by the death from rabies of a U.S. citizen in 1981 after he was bitten by a dog in Mexico. The dog's head was shipped to a Mexican laboratory, where it was examined with Sellers' stain instead of a fluorescent antibody technique. Because no evidence

TABLE 31-8 Rabies Postexposure Prophylaxis (PEP) Guidance Based on Type and Disposition of Animal Causing Bite

Animal Type	Evaluation and Disposition of Animal	PEP Recommendations
Dogs, cats, and ferrets	Healthy and available for 10 days' observation	Persons should not begin prophylaxis unless animal develops clinical signs of rabies.*
	Rabid or suspected rabid	Immediately begin prophylaxis.
	Unknown (e.g., escaped)	Consult public health officials.
Skunks, raccoons, foxes, and most other carnivores; bats†	Regarded as rabid unless animal proven negative by laboratory tests‡	Consider immediate prophylaxis.
Livestock, small rodents (rabbits, hares), large rodents (woodchucks, beavers), and other mammals	Consider individually	Consult public health officials.
		Bites from squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other small rodents, rabbits, and hares almost never require antirabies PEP.

Modified from Centers for Disease Control and Prevention: Human rabies prevention—United States, 2008: Recommendations of the Advisory Committee on Immunization Practices, *MMWR* 57:1-27, 2008.

*During the 10-day observation period, begin PEP at the first sign of rabies in a dog, cat, or ferret that has bitten someone. If the animal exhibits clinical signs of rabies, it should be euthanized immediately and tested.

†PEP should be initiated as soon as possible after exposure to such wildlife, unless the animal is available for testing and public health authorities are facilitating expeditious laboratory testing, or it is already known that brain material from the animal has tested negative. Other factors that might influence the urgency of decision making regarding initiation of PEP before diagnostic results are known to include the species of the animal, general appearance and behavior of the animal, whether the encounter was provoked by the presence of a human, and severity and location of bites. Discontinue vaccine if appropriate laboratory diagnostic test (i.e., direct fluorescent antibody test) is negative.

‡The animal should be euthanized and tested as soon as possible. Holding for observation is not recommended.

of rabies was found with this less sensitive technique, he was not given PEP.[186] In a Thai investigation, 13 of 404 rabid animals diagnosed with fluorescent antibodies did not have Negri bodies identifiable with Sellers' stain.[224]

Any stray or unwanted animal should be killed immediately and its head submitted for rabies examination. Euthanasia does not need to be delayed for further development of the infection in an attacking animal for a reliable diagnosis to be made.[241]

No person in the United States has died of rabies when the attacking dog or cat has been healthy after 10 days of observation.[225] However, dogs injected with an Ethiopian strain of rabies virus excreted virus in the saliva up to 13 days before signs of disease were observed,[105] and dogs that have recovered from experimental rabies excrete virus in saliva for as long as 6 months after recovery.[110]

If an attacking dog or cat is rabid or is suspected to be rabid, PEP should be initiated at once. However, a reliable determination of the presence or absence of rabies in animals can usually be completed in less than 1 day.[241] If the dog or cat escapes and is not suspected to be rabid, the ACIP of the U.S. Department of Health and Human Services recommends that local public health officials be consulted.[63]

In a study of PEP practices in EDs of a number of U.S. university hospitals, the most frequent inappropriate administration of therapy was for animals that could be observed for 10 days. The most common failure to administer PEP was for animals that could not be observed. The investigators emphasized that physicians often failed to use the expert consultative services available 24 hours a day from their local health departments or the CDC.[171]

In the United States, any exposure to a skunk, raccoon, bat, fox, or other carnivore, including bears and cougars, should be considered a rabies exposure. Treatment should be initiated immediately, except when the exposure has occurred in a part of the continental United States known to be free of rabies, and when the results of immunofluorescence testing will be available in 48 hours. If the animal is captured, it should be killed and its head shipped to a qualified laboratory immediately. The signs of rabies in wild animals, including wolf hybrids, are not consistent enough or sufficiently well known for a 10-day observation period reliably to determine whether the animal was rabid.[63]

Small rodents (squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice) and rabbits are rarely found to be infected with rabies and have not been known to produce rabies in humans. ACIP recommends that local health officials be consulted after a bite by a rodent or rabbit.[63]

Initial Wound Management

Immediate and thorough cleansing of bite wounds with soapy water to reduce the viral inoculum is an essential and highly effective component of postexposure therapy. Fishbein,[113] former Chief of the Viral and Rickettsial Zoonoses Branch of the CDC, has stated, "Local treatment is perhaps the single most effective means of preventing rabies." Also, "In some groups exposed to a single rabid animal and many laboratory investigations, local wound care alone has been found to be as or more important than vaccine alone." Vodopija and colleagues[251] have declared, "Washing the wound with soap and water or with other substances that are lethal to rabies virus may be crucial for survival, irrespective of subsequent immunization." Fangtao,[102] who has had extensive experience with rabies in China, asserts, "The protective effect of each (wound care, immune globulin, and vaccine) should be considered equivalent." Neglect of the wound or inadequate wound care has resulted in rabies in individuals who received ideal immunotherapy.[27,63]

Many experimental studies have shown that the duration of the incubation period after rabies exposure is inversely proportional to the size of the viral inoculum. A large inoculum produces generalized infection in a much shorter time than does a small inoculum.[82] If rabies vaccine is to induce immunity before infection appears, it must have sufficient time. After a severe rabies exposure, such as a bite about the head or neck, or multiple bites, a major reduction in the number of virus organisms introduced may be essential to allow time for immunization.

In experimental studies, the best results have been obtained by thoroughly cleaning the wound with soap and water and then irrigating it with a virucidal agent such as povidone-iodine or a 1% solution of benzalkonium chloride (Zephiran). Soap neutralizes benzalkonium chloride and must be completely rinsed from the wound before it is irrigated with the detergent. With deep wounds, only virucidal substances, such as benzalkonium chloride or povidone-iodine, have been found to be effective. If neither of these agents is available, 70% alcohol (ethanol) or iodine, either tincture or aqueous solution, can be instilled in the wound. The best cleansing agent that can be obtained immediately must be used.[42,278] If these measures are painful, which is often the case when they are carried out with appropriate vigor, the area can be anesthetized with a local anesthetic. Avoid directly touching the wound(s) with bare hands.

This vital procedure is often neglected, particularly in developing countries. In a study of 250 patients with rabies seen at the Sassoon Hospital in Pune, India (the eighth-largest city in

India, with a population over 3.5 million), the wound had been washed with soap and water for only nine patients.[218]

Appropriate measures to prevent bacterial infection, including antibiotics if indicated, and tetanus prophylaxis should also be instituted.[42,205] The WHO Expert Committee and others recommend that bites not be sutured.[42,48,63,278]

Further PEP Measures Following Wound Care

Following immediate wound cleansing, health care providers should consult public health officials for guidance on whether to treat with specific PEP measures, such as RIG plus active vaccine, or vaccine alone.[164] Exposure history, including the animal species responsible and the patient's prior rabies vaccination history, is integral to making PEP recommendations. In cases of suspected rabies in a healthy-appearing biting dog or cat in a country with low rabies incidence, the patient is administered PEP only if the animal shows signs or symptoms of rabies within a 10-day period of observation. Specific PEP is almost always indicated with exposure to wild mammals, especially if they exhibit unusual behavior. PEP can be discontinued if the animal is available for pathologic examination, and if no evidence of rabies virus infection exists in the brain. PEP is safe for administration to pregnant women.[86]

In cases of exposure in individuals lacking prior vaccination, PEP should include administration of passive antibody (RIG) in addition to vaccine (Table 31-9). Rabies immune globulins, available in human (HRIG) and equine (ERIG) forms, are purified from the sera of hyperimmunized donors. HRIG is currently available in the United States as Imogam Rabies-HT (Sanofi Pasteur, Swiftwater, Pennsylvania) and HyperRAB S/D (Grifols Therapeutics, Research Triangle Park, North Carolina). HRIG is administered as a single dose of 20 IU/kg body weight (40 IU/kg for ERIG), regardless of the patient's age. This recommended dose should not be exceeded because RIG can partially suppress active production of antibody. Current WHO and ACIP guidelines advise HRIG to be infiltrated into the wound.[74] Any additional remaining dose not infiltrated into the wound should be injected intramuscularly (IM) at a site remote from the active vaccine injection site. Note that rabies vaccine should never be administered in the gluteal area, to avoid potential inadequate immune response.[272] Infiltration of the wound with RIG before surgical closure appears to be a critical part of successful PEP application, because failure to do so is associated with development of rabies even in cases of otherwise appropriately applied PEP.[261] Generally, HRIG is administered when active vaccine is initiated; however, HRIG remains effective if given by the seventh day of the PEP series.[74] Clinical studies suggest a cocktail of antirabies monoclonal antibodies show great promise in replacing RIGs as safer and more easily produced alternatives.[23,31,175]

Rabies Immune Globulin

Although proposed and investigated by Babes[8] and colleagues over a century ago, the benefit of hyperimmune serum immediately after rabies exposure was established only about 55 years ago. The most dramatic study was initiated by Koprowski and carried out in Iran in 1954. Of 29 persons bitten by a single rabid wolf, 13 with bites about the head were treated with antiserum and neurally derived vaccine; only one died. Five individuals with similar bites received vaccine alone; three died.[22,23,25]

Similar results were demonstrated in China with a much more effective cell culture vaccine by Lin and associates, who suggested that immune serum might be effective because it stops virus from entering susceptible cells (nerves).[103] The need for immune serum with human diploid cell vaccine (HDCV) has been demonstrated by the death from rabies in a 29-year-old female U.S. citizen in Rwanda who received prompt therapy with HDCV but not with hyperimmune serum.[94]

Measurements of the antibody response to earlier rabies vaccines demonstrated that immune serum reacted with the vaccine and limited the antibody response in the first 7 to 10 days of administration. These data were considered evidence of passive immunity that was essential for early control of the rabies virus, particularly when the viral inoculum was large and the incubation period before the development of clinical rabies was likely to be short.[22] However, with contemporary cell culture vaccines that have a concentration of 2.5 IU/mL, such inhibition of the serum-neutralizing antibody response is not seen.[251]

The only rabies immune globulin licensed for use in the United States is HRIG, which is prepared by cold ethanol fractionation from plasma from hyperimmunized human donors and is virtually free of significant side effects.[264]

In developing countries, immune serum is rarely administered because it is expensive or unavailable. Only about one-third of the immune serum required for rabies postexposure therapy is

TABLE 31-9 Rabies Postexposure Prophylaxis (PEP) Schedule Based on Vaccination Status—United States, 2010

Vaccination Status	Intervention	Regimen*
Not previously vaccinated	Wound cleansing	All PEP should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent (e.g., povidone-iodine solution) should be used to irrigate the wounds.
	Human rabies immune globulin (HRIG)	Administer 20 IU/kg body weight. If anatomically feasible, the full dose should be infiltrated around and into the wound(s), and any remaining volume should be administered at an anatomic site (intramuscular [IM]) distant from vaccine administration. Also, HRIG should not be administered in the same syringe as vaccine. Because RIG might partially suppress active production of rabies virus antibody, no more than the recommended dose should be administered.
	Vaccine	Human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV), 1.0 mL, IM (deltoid area†), 1 each on days 0,§ 3, 7, and 14¶
Previously vaccinated**	Wound cleansing	All PEP should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as povidine-iodine solution should be used to irrigate the wounds.
	HRIG	HRIG should not be administered.
	Vaccine	HDCV or PCECV, 1.0 mL, IM (deltoid area†), 1 each on days 0§ and 3

Data from Use of a reduced (4-dose) vaccine schedule for post-exposure prophylaxis to prevent human rabies: Recommendations of the Advisory Committee on Immunization Practices, *MMWR* 59(RR-2), 2010. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5902a1.htm.
*These regimens are applicable for persons in all age groups, including children.
†The deltoid area is the only acceptable site of vaccination for adults and older children. For younger children, the outer aspect of the thigh may be used. Vaccine should never be administered in the gluteal area.
§Day 0 is the day dose 1 of vaccine is administered.
¶For persons with immunosuppression, rabies PEP should be administered using all 5 doses of vaccine on days 0, 3, 7, 14, and 28.
**Any person with a history of preexposure vaccination with HDCV, PCECV, or rabies vaccine adsorbed (RVA); prior PEP with HDCV, PCECV or RVA; or previous vaccination with any other type of rabies vaccine and a documented history of antibody response to the prior vaccination.

being produced. Travelers who have received postexposure therapy usually are not given immune serum unless they know enough about rabies PEP to demand its administration.

When immune serum is given, it is usually of equine origin, which costs only about 10% as much as HRIG.[262] However, contemporary highly purified ERIG is not associated with the 15% to 46% incidence of serum sickness typical of older equine antirabies serum.[48] In 3575 individuals treated at QSMI, ERIG from Pasteur Vaccins of France, Sclavo of Italy, and the Swiss Serum and Vaccine Institute produced allergic reactions in 0.87%, 3.58%, and 6.19% of the recipients, respectively. The reactions were uniformly mild and lasted less than 1 week with appropriate therapy. Only 9 of the 66 patients with reactions required corticosteroid therapy; the remainder were satisfactorily treated with analgesics and antihistamines. ERIG is also produced in developing countries, but the purification procedures and potency criteria have not been published, and these products may be associated with a higher incidence of adverse reactions.

At QSMI, an initial intradermal injection of horse serum is administered, and individuals who present with sensitivity are treated with HRIG. One 17-year-old male did not react to the intradermal injection, but with subsequent injections, he had an anaphylactic reaction that was successfully treated with epinephrine, hydrocortisone, and chlorpheniramine.[262,264]

Equine $F(ab')_2$ fragment rabies immunoglobulin is also used. In a study of 7660 patients in the Philippines, of 151 patients with laboratory-confirmed exposure, two died of rabies: a 4-year-old girl who had multiple deep lacerations on the nape, neck, and shoulders, and an 8-year-old boy who only received PEP on the day of exposure. Local adverse reactions were documented in 35 individuals (0.46%) and systemic adverse reactions in 104 (1.36%). Only two patients had documented local adverse reactions within 30 minutes of immunization, and 11 with systemic adverse reactions were documented as having possible allergic reactions.[195]

The dose of immune globulin is 20 IU/kg for HRIG or 40 IU/kg for ERIG. Larger-than-recommended doses should not be administered because the immune globulin neutralizes vaccine given simultaneously. Immune globulin should be administered as soon after exposure as possible but is clearly beneficial when administered within 7 days. In view of the long incubation period for some human rabies infections, immune globulin administration may be advisable regardless of the interval after exposure.

Currently, all agencies recommend injection of as much immune globulin as possible around the bite site.[264,278] For bites on the fingers and similar locations where only a limited amount of globulin can be injected locally, the remainder should be injected IM.[42] For individuals with multiple bites, which is common with rabid dog attacks in developing countries, the immune globulin may have to be diluted with saline to achieve uniform injections. The syringe used to inject immune globulin must not be used to inject vaccine, which would be inactivated by residual antiserum.

Rabies Vaccines

Louis Pasteur revolutionized rabies therapy and all medicine on July 7, 1885, when he began administering rabies vaccine to Joseph Meister, a 9-year-old boy who had been bitten 14 times by a dog that was killed and diagnosed as rabid because its stomach contained hay, straw, and fragments of wood.[250,252] Although the rabies diagnosis in this animal may be suspect, and the boy may not have developed a clinical infection, Pasteur in 1886 observed only a single failure in a series of 688 treatments, many of whom must have been exposed to rabid animals and would have been expected to die without therapy.[9] Meister's only employment as an adult was as a security guard for the Pasteur Institute.[232]

Pasteur's first rabies vaccine was produced from rabid rabbit spinal cords that were allowed to dry to attenuate the virus. After 15 days, the cords were noninfectious, so the first injections were made with 14-day-old spinal cords, and subsequent injections were made with cords that had been dried for shorter times.[237,249] Roux[204] and Callmette[49] demonstrated that desiccated rabbit spinal cords retained appropriate virulence when preserved in glycerin, which greatly facilitated the production and storage of such vaccine. Although other vaccines were soon developed, the Pasteur rabbit spinal cord vaccine was administered at the Pasteur Institute of Paris as recently as 1953.[249]

Subsequently, similar vaccines have been prepared in brain tissues from various animals, particularly goats and sheep, containing virus killed with formaldehyde, phenol, or β-propiolactone.[132,237] These preparations are collectively known as *Semple vaccines* or *neural tissue vaccines,* and Semple's introduction of such vaccines in 1911 was a significant advance. In 1955, Fuenzalida and Palacios in Chile introduced the use of suckling mice less than 3 days old for the preparation of neurally derived vaccines. Such animals have little cerebral myelin and are thought to yield a product that contains less myelin basic protein. Currently, animals no older than 1 day are used. In Thailand, this vaccine has been found to be as poorly immunogenic and to be associated with as many side effects as are other similar vaccines,[117,263,278] but other investigators have found the incidence of neural reactions to be lower.[250] At present, neural tissue vaccines are still employed for a large percentage of all postexposure rabies therapy worldwide because they are inexpensive. Of 50 million doses of rabies vaccine administered worldwide each year, 20 million are still neural tissue vaccines.[44]

Such animal brain vaccines have been described as the crudest biologic material administered to humans. These vaccines have low immunogenicity, and as many as fifteen 5-mL injections of a 5% to 10% suspension of brain tissue are required to produce satisfactory antibody titers. Intense local reactions are common, and many patients abscond from treatment.[44] In Taiwan between 1952 and 1955, 55% of individuals who began rabies vaccination failed to complete treatment.[255] In one study, 20 of 681 persons bitten by dogs that proved to be rabid refused therapy because they had witnessed the side effects of vaccination in other villagers. Nine (45%) died of clinically diagnosed rabies. Another 62 persons received Semple vaccine, even though the dogs to which they were exposed were not rabid, presumably because the dog-testing results were not accepted as valid.[224]

The potency of these vaccines is highly variable. Some batches are known to have been ineffective. After 15 years of observations, the Pasteur Institute of Iran, a branch of the Pasteur Institute in Paris and a WHO Collaborating Center for Reference and Research in Rabies, concluded that rabies vaccines prepared in animal brains were totally ineffectual for preventing rabies in individuals bitten about the head or neck who would be expected to develop encephalitis within a short time after exposure.[24] Pasteur observed that his treatment was not always successful, particularly after bites around the face.[232] In Bangkok, 11% of a group of patients who died of rabies encephalitis had received complete courses of the vaccine starting soon after they were bitten.[248] The vaccine appears to be beneficial for less severe exposures.[247]

Since the time of Pasteur, the failure of immunoprophylactically treated persons to develop clinical rabies has been attributed to the vaccine, and some of these individuals produced antirabies antibodies. However, many, perhaps most, individuals attacked by rabid animals do not develop clinical rabies. In fact, humans are considered to have a low susceptibility to rabies.[106] Citing the 1912 studies of Babes, which now could not be repeated, Baer[12] has emphasized that only about 15% of individuals bitten by rabid dogs and not vaccinated develop rabies[210] (Table 31-10). The absence of rabies infection in many individuals treated with Semple vaccine undoubtedly is a reflection of failure to transmit the infection by attacking animals, and not of vaccine effectiveness.

The neuroparalytic reactions associated with Semple rabies vaccines are the most serious neurologic complications that follow any vaccination[133] and were reported only 4 years after Pasteur introduced his vaccine.[24] Remlinger[197] reported 26 cases between 1888 and 1905. Even dogs vaccinated with this product developed anorexia, as well as "depression, nervous symptoms, a morbid desire to bite," or paresis of the hind limbs.[46] Of the patients receiving such vaccines, 15% develop electroencephalographic abnormalities, and 5% develop measurable antibodies against brain tissue. About one-fourth of the severe neurologic reactions are fatal, and an additional one-third cause permanent

TABLE 31-10 Estimates of Mortality Among Unvaccinated Persons Exposed to Animals Assumed To Be Rabid (Babes, 1912)

Attacking Animal	Location of Exposure	Type of Exposure	Likelihood of Mortality (%)
Wolf	Face	Bites, multiple, severe	80-100
Cat	Face	Bites, multiple, severe	70
Dog	Face	Bites, multiple, severe	60
Dog or cat	Other part of head	Bites, multiple, severe	50
Wolf	Neck or arm	Bites, multiple, severe	40
Wolf	Face	Bite, single	40
Cat	Face	Bite, single	40
Dog	Face	Bite, single	30
Wolf or cat	Fingers or hand	Bites, severe	20
Dog	Fingers or hand	Bites, severe	15
Wolf	Trunk or legs	Bites, severe	15
Wolf, cat, or dog	Face	Bites, superficial	10
Wolf, cat, or dog	Hands	Bites, superficial	5
Wolf	Face	Scratches	5
Wolf, cat, or dog	Trunk or legs	Bites, severe, through clothes	3
Wolf, cat, or dog	Hands or exposed skin	Bleeding superficial wound	2
Wolf, cat, or dog	Clothing covered skin	Bleeding superficial wound	0.5
Wolf, cat, or dog	Recent wounds in contact with saliva	—	0.1
Wolf, cat, or dog	Wounds older than 24 hours in contact with saliva	—	0.0

Data from Babes V: Traité de la rage. *Paris: Bailliere et Fils,* 81, 1912; cited by Baer.[13]

damage.[17,22,180] An incidence of neuroparalytic reactions of approximately 1 in 1200 patients seems to be generally accepted, but much higher rates of 1:400, 1:220,[117] 1:142,[224] or even 10 times higher at 1:120 have been reported.[236] Probably the most accurate evaluation of the frequency of such complications is that the incidence is not known. The countries that have a high incidence of rabies, which are the countries that use neural-derived vaccines for PEP, also have very poor or no programs for reporting complications.[237]

Recently, the specter has been raised of transmission to humans of spongiform encephalopathies caused by prions from infected sheep by neural tissue vaccines derived from sheep brains.[44]

Because so many problems were associated with Semple vaccines, a safer vaccine was developed with viruses grown in duck embryos. This vaccine was not as immunogenic as contemporary vaccines, and 14 to 23 injections were required to produce satisfactory antibody titers. In addition, this vaccine also had a significant incidence of adverse side effects. Reactions to duck embryo vaccine in one retrospective analysis of 424,000 persons consisted of 22 cases of anaphylaxis, four cases of transverse myelitis, five cases of cranial neuropathy, two cases of nonfatal encephalopathy, and two cases of fatal encephalopathy that may actually have been fatal rabies infections.[206] Immunization with vaccine grown on duck embryos has failed to prevent rabies, but for many of the failures, a prolonged interval separated the exposure and immunoprophylaxis.[2]

Human Vaccination

Postexposure prevention of human rabies by immunization is unique in the therapy of infectious diseases and is possible only because the moment of exposure can be vividly remembered and the incubation period is relatively long. For 30 years, the recommended procedure for producing active immunity in the United States has consisted of five vaccine injections into the deltoid muscle of 1.0 mL of vaccine on days 0, 3, 7, 14, and 28 after animal exposure. This schedule is known as the "Essen scheme" in recognition of the contributions of Ernst Kuwert of the Essen Institute of Medical Virology and Immunology.[250] Immunoprophylaxis is most effective when begun within 24 hours of exposure, but the average delay after animal exposure in the United States and in Nepal has been 5 days.[219] Since the incubation period for rabies may be prolonged, no upper limit can be set for the time after a potential rabies exposure at which postexposure vaccine therapy should be given.[27,278]

In 2010, a number of investigators and the ACIP, after a review of rabies virus pathogenesis, experimental animal models, human immunogenicity studies, prophylaxis effectiveness in humans, documented failures of prophylaxis in humans, and vaccine safety, recommended that postexposure vaccination be reduced to four injections given on days 0, 3, 7, and 14.[73] A detailed review of the evidence supporting a four-dose schedule for human PEP had been previously published.[209]

The recommendations for wound irrigation and passive immunization with immune globulin remain unchanged. Three vaccine injections are still recommended for preexposure vaccination, and two injections are needed after a rabies exposure for previously immunized individuals. Immunocompromised individuals should still receive five injections and should be tested afterward to determine whether they have developed a protective antibody response. The report warned that manufacturers of the vaccine do not plan to change the recommendation in the package insert.

An alternative treatment schedule, termed the "2-1-1 regimen," was first developed in Yugoslavia. On day 0, two 1-mL doses of vaccine are injected into the left and right deltoid muscles. Additional 1-mL injections are given on days 7 and 21. This schedule was originally intended for use only after severe exposures, when the incubation period could be expected to be short. However, in a number of countries, it is used routinely because it produces antibody levels just as high as does the Essen scheme, and only three clinic visits are required.[251]

The only rabies vaccines licensed for use in the United States are prepared from viruses grown in cell cultures and inactivated with β-propiolactone. HDCV, the first to be licensed and the gold standard against which other vaccines are compared, was made possible by development of the WI 38 cell line of diploid human fibroblasts by Hayflick and Moorhead and by adaptation of the Pitman-Moore strain of rabies virus to growth in such cells by Wiktor, Plotkin, and Koprowski at the Wistar Institute in Philadelphia.[232,250] The virus used to prepare this vaccine was originally isolated in 1882 by Pasteur from a cow bitten by a rabid dog and was maintained by serial passage in rabbit brain before it was adapted to cell culture.[211,250] The HDCV available in the United States is produced in cultures of human diploid cells by Sanofi Pasteur. This vaccine was introduced in December 1974 and was licensed for general use in the United States on June 9, 1980.[53] A single-dose vial containing lyophilized vaccine that is reconstituted in the vial to a final volume of 1.0 mL, Imovax Rabies is

licensed for postexposure and preexposure intramuscular (IM) vaccination. The unreconstituted vial must be refrigerated; it cannot be carried into remote areas in first-aid kits.

Because HDCV is expensive and cannot be produced in sufficient quantities to supply worldwide demands, a number of cell culture vaccines have been developed. These vaccines, when produced according to accepted standards, are all considered equally effective.[42] These vaccines are much more immunogenic than earlier products, and protective antibody levels are routinely achieved with only four or five injections.[63,249] A "protective level" is defined as either an antibody concentration that will completely neutralize rabies viruses at a dilution of 1:5, as determined by the rapid fluorescent focus inhibition test, or 0.5 IU/mL. These vaccines are so effective that measurement of postvaccination antibody levels is recommended only for individuals who are immunodeficient because of disease or therapy.

The effectiveness of HDCV was dramatically demonstrated during 1975 and 1976 in Iran by complete prevention of rabies in 45 persons attacked by dogs or wolves subsequently proved to be rabid.[22] Between 1980 and 1982, all 511 individuals bitten by rabid animals in the United States and treated with five doses of HDCV and with HRIG survived.

In the United States, two other cell-cultured vaccines have been licensed. Rabies Vaccine Adsorbed (RVA) was prepared from viruses grown on fetal rhesus lung diploid cell cultures, concentrated by adsorption to aluminum phosphate, and produced in a liquid form. RVA was licensed on March 19, 1988. It has been used to vaccinate humans allergic to HDCV but has been unavailable for a number of years.[212]

At least in part because the raccoon rabies epizootic had increased consumption of rabies vaccine so dramatically, the U.S. Food and Drug Administration (FDA) licensed purified chick embryo vaccine (PCEV) in October 1997. This vaccine (RabAvert) has been widely used worldwide. It is thought to produce fewer allergic reactions because it does not contain human albumin altered by β-propiolactone. All three preparations are considered equally efficacious and safe for postexposure therapy and preexposure IM vaccination.[63]

The WHO has approved HDCV and PCEV, as well as purified Vero cell rabies vaccine (PVRV or Verorab), which is widely used in developing countries. This vaccine is produced in continuous culture and is less expensive to produce, but has not been licensed for use in the United States or Canada.[275,277]

In its 1992 Eighth Report, the WHO Expert Committee on Rabies[278] made a remarkable statement, "Prompt and thorough cleansing of the wound, and administration of purified equine or human rabies immunoglobulins and cell-culture rabies vaccine immediately after exposure virtually guarantee complete protection. . . . Pregnancy and infancy are never contraindications to post-exposure rabies vaccination." Although some antigens, particularly surface glycoprotein antigens, vary widely in different viral strains, standard vaccines have provided effective protection against all wild, or "street," rabies viruses. These vaccines also appear to be effective against other lyssaviruses, except Mokola and Lagos bat virus, although no alternative vaccines are available.[258,278]

Occasional failures with cell culture vaccines have been reported, but in essentially every case, treatment has not been administered correctly. Many of the individuals did not receive immune globulin.[42,180,278] Some have had the vaccine injected into gluteal muscles, which is thought to be the cause of these failures.[17,42,54,63,133] Hepatitis B vaccine gluteal injections have been found to be less consistently effective than injections in the deltoid.[17] All injections of rabies vaccine must be made in the deltoid muscle, or in the quadriceps muscle for small children.

Approximately 18,000 persons receive preexposure vaccination and an additional 23,000 receive postexposure immunoprophylaxis each year in the United States, but reactions of any type are very uncommon.[34] Reactions after HDCV administration during the first 46 months of use (and reported to the CDC) occurred in 108 individuals, a rate of 11 per 10,000 vaccinees. Few patients required hospitalization, and no fatal reactions were reported. Of these reactions, nine (1 in 10,000) were immediate hypersensitivity reactions that occurred within minutes to hours after injection and were characterized by bronchospasm, laryngeal edema, and generalized pruritic rash, urticaria, or angioedema. All nine reactions followed postexposure immunization of unvaccinated persons or preexposure vaccination.

Eighty-seven delayed reactions appeared 2 to 21 days after injection and were characterized by a generalized pruritic rash or urticaria. Some of the individuals also had arthralgias, arthritis, angioedema, nausea, vomiting, fever, and malaise. Twelve reactions were classified as indeterminate. Unlike the immediate reactions, 81 (93%) of the delayed reactions followed booster injections for individuals who had been vaccinated previously. Most patients improved in 2 to 3 days when treated with antihistamines, but a few required systemic corticosteroids and epinephrine.[53]

The reactions are attributed to β-propiolactone–altered albumin in the vaccine.[203] HDCV vaccine that is free of β-propiolactone was developed by Connaught Laboratories but was not licensed in the United States.[30] PCEV and RVA are not made with albumin. Further rabies booster immunizations are not recommended for individuals who have had this type of reaction, but exposure to rabies should be treated in the usual manner.[53]

Neurologic reactions after HDCV administration have been extremely rare. After millions of vaccinations worldwide, three Guillain-Barré–type paralytic reactions have been described, and all three individuals recovered. Other neurologic disorders have occurred at the time of vaccination, but a definitive causal relationship has not been established.[30,203]

Immunocompromised Individuals

Immunosuppression resulting from such therapy as corticosteroids, chemotherapy, antimalarials, or other agents, or the result of illness, particularly human immunodeficiency virus (HIV) infection, may interfere with the immune response to vaccines. If the condition is transient, preexposure vaccination can be postponed until therapy has been completed. If delaying therapy is not feasible, a rabies antibody titer should be obtained after vaccination has been completed, even though such determinations are not needed for individuals who are not immunocompromised. If antibody levels are not high enough to be protective, ACIP recommends that individuals who do not seroconvert should be managed in consultation with their physician and appropriate public health officials.[165] Immunocompromised persons must be particularly careful to avoid rabies exposure, even avoiding travel to areas where rabies is endemic.

In one investigation of the response to vaccination, normal controls, asymptomatic individuals with HIV infection, and symptomatic persons with HIV infection were given a five-dose simulated postexposure vaccination. Seroconversion occurred in 100% of the controls, 76% of the asymptomatic patients, and 57% of the symptomatic patients. However, rabies virus–neutralizing antibodies could not be detected in 40% of the symptomatic individuals with CD4+ T cell counts below 400/μL.[43]

However, in another investigation, 18 individuals with CD4+ cell counts less than 200/μL and 9 individuals with CD4+ counts above 200/μL received eight 0.1-mL intradermal inoculations of PCEV each day on days 0, 3, 7, 14, and 30. By day 14, all patients in both groups had protective rabies-neutralizing antibody concentrations. No significant differences between the two groups developed in the following year.[223]

Thirty HIV-infected adults who had been treated for almost 4 years with highly active antiretroviral therapy (HAART) and had median CD4+ T cell counts of 537/μL received two rabies vaccinations within 3 months. The HIV-infected patients had lower antibody levels than normal controls, but the levels were protective. Five years after vaccination, 63% of the HIV-infected individuals still had protective antibody levels.[120]

No documented failures of rabies postexposure vaccination in HIV-infected individuals have been reported.[63]

PREEXPOSURE VACCINATION

Preexposure vaccination can be achieved with three deltoid or quadriceps IM injections of 1.0 mL of cell culture vaccine on days 0, 7, and 21 or 28.

Preexposure vaccination with 0.1 mL of HDCV injected intradermally on the same schedule was approved by the FDA in April 1987. However, intradermal vaccination does not result in antibody levels as high as those produced by IM injections, and antibodies do not last as long. Some investigators have recommended that only IM injections should be administered.[44] In the United States, the question is moot because the raccoon epizootic on the East Coast has increased vaccine utilization so much that syringes with 0.1 mL of the vaccine are not being produced.

After a rabid animal bite, previously vaccinated individuals need only IM injections of 1.0 mL of cell culture vaccine on days 0 and 3. Immune serum is not needed, a major consideration for travelers in developing countries where immune serum may not be available. The additional two injections are essential. Fatal rabies encephalitis developed in a 23-year-old female Peace Corps Volunteer in Kenya who had previously been vaccinated for rabies, but did not report a bite by a pet puppy too young to have been vaccinated, and did not receive PEP.[185]

Chloroquine interferes with the response to rabies vaccine; vaccination should be completed before malarial chemoprophylaxis with chloroquine is begun. Whether other agents used for malarial chemoprophylaxis interfere with the response to rabies vaccine has not been ascertained.[44]

The ACIP divides individuals for whom preexposure vaccination is recommended into three groups. Group one consists of workers in rabies laboratories and others who may unknowingly be exposed to rabies, for whom vaccination followed by evaluation of antibody titers every 6 months is advised. Boosters are needed if antibody concentrations fall below a titer of 1:5 or higher by the RFFIT, or 0.5 IU/mL or greater.

Group two includes spelunkers, veterinarians in areas where rabies is endemic, animal control workers, and fish and game wardens, for whom vaccination followed by serologic testing or a booster every 2 years is recommended.

Group three consists of veterinarians and animal control workers in areas of low rabies endemicity, travelers to foreign rabies-epizootic areas who are staying 30 days or more, and veterinary students, for whom vaccination but no subsequent serologic testing or boosters is advised. Vaccination is not recommended for the U.S. population at large.[63]

In 1990, investigators at the CIWEC Clinic in Nepal found the incidence of animal exposure requiring immunoprophylaxis in travelers to be quite low, approximately 1 in 123,000 days (337 years). They disagreed with the recommendation that travelers to foreign rabies-epizootic areas staying 30 days or more be vaccinated, because the cost of immunization is high, and because the incidence of allergic reactions to booster immunizations is significant.[219] However, investigators from the QSMI in Bangkok subsequently surveyed 1882 departing English-speaking travelers in the Bangkok air terminal and determined that 1.2% had been bitten by a dog and 8.7% had been licked by a dog during their stay. These investigators recommended that all travelers be routinely vaccinated for rabies and that the vaccine be inoculated IM. The CIWEC Clinic now recommends that most travelers to Nepal be preimmunized.[192]

In a review of immunizations for travelers, Ryan and Kain[216] state:

> Optimal post-exposure prophylaxis against rabies (including rabies immune globulin and tissue-culture–derived vaccines) is often unavailable in many developing countries. Vaccination against rabies before travel should be considered for long-term travelers to the developing world, those who will have unavoidable direct contact with animals, *those who may be unable to receive timely post-exposure prophylaxis, and those (such as young children) who may be unable to report possible exposure* [emphasis added].

Several of the recent American victims of rabies acquired outside the United States, and the only genotype 1 rabies victims in Australia, were children who, perhaps in fear of punishment, did not tell their parents about bites they had received. The problem of protecting children, who run the highest risk for animal bites, may not be widely recognized.[203] Children who cannot understand the hazard of rabies in developing countries probably should be routinely vaccinated; they must also be closely observed so that postexposure booster vaccination can be administered.

The effectiveness of preexposure vaccination is documented by the fact that no one residing in the United States who has received preexposure vaccination with a modern cell culture vaccine has contracted rabies.[42]

In June 2007, Sanofi Pasteur began renovating its rabies vaccine production facility in France to maintain compliance with the requirements of the U.S. FDA and the French regulatory body, Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS). The company had accumulated a store of rabies vaccine that it thought would last through the renovation, but estimates of demand proved low. As a result, vaccine for preexposure vaccination became unavailable. In 2008, the shortage of vaccine was one of the considerations leading to changing the recommendations for postexposure therapy to four doses instead of five. The facility is now operational, and limits on vaccine for preexposure vaccination were lifted in August 2009.

RABIES THERAPY IN DEVELOPING COUNTRIES

Rabies therapy in developing countries must be modified by financial considerations. The cost for such therapy for a typical laborer could be devastating.[224] At least four different measures have been taken to reduce the costs of postexposure rabies therapy and increase the availability of reliable cell culture vaccines. The simplest has been the transfer of cell culture vaccine–manufacturing technology to developing countries, but despite support by WHO and other agencies, progress has been slow. Local manufacturers in Latin America and Asia are producing Vero cell rabies vaccine "copies" and primary hamster kidney cell rabies vaccines. Because some of these vaccines do not adhere to the strict standards imposed by the FDA or the European Pharmacopeia, they are less expensive to produce.

The substitution of ERIG for HRIG, which results in a 90% cost savings, is discussed earlier.

A third approach has been the use of small-volume intradermal vaccine injections instead of larger-volume IM injections. The Warrells, Phanuphak, and their co-workers at QSMI pioneered the use of intradermal vaccination for postexposure immunoprophylaxis because a smaller volume of vaccine would be required. The regimen developed by the Warrells consisted of intradermal injections of 0.1 mL of HDCV at eight different sites on postbite day 0, injections at four sites on day 7, and injections at one site on days 28 and 90, which reduced the vaccine expense to 30% of the cost of five 1.0 mL IM injections.[256,263] Phanuphak intradermally injected 0.1 mL of PVRV at two sites on days 0, 3, and 14 and at one site on days 30 and 90. This regimen reduced the expense for PVRV, which is already much less expensive than HDCV, by an additional 68%.[190,191]

One hundred Thai patients, who had injuries severe enough to produce active bleeding inflicted by animals proved rabid by fluorescent antibody testing, were treated according to the schedule developed by Phanuphak and colleagues in a prospective study. This procedure is now known as the Thai Red Cross intradermal postexposure rabies treatment schedule, or TRC-ID. All were uniformly protected from rabies. Since 1987, the TRC-ID regimen has been routinely used for PEP of more than 1000 patients a month at QSMI, with only one failure, a 53-year-old alcoholic patient with cirrhosis who did not report for treatment until 6 days after his exposure.[87]

An anticipated problem with intradermal injections was the inadvertent subcutaneous injection of part or all of the vaccine. This has not been a problem at QSMI, but the staff there is highly experienced.[87] Nonetheless, deliberate subcutaneous injections have been found to produce antibody titers just as high as intradermal injections.[191]

The fourth measure has been development of reliable nonhuman cell culture vaccines. Production of HDCV is characterized by "a demanding technology, low virus yield, and enormously high production costs per unit of vaccine."[251] It is not suitable for large-scale human rabies prevention. A variety of nonhuman cell cultures has been used to produce rabies vaccines: primary cell cultures (hamster kidney, dog kidney, or chick embryo

fibroblast), diploid cell lines (human or rhesus monkey), and continuous cell lines (Vero and baby hamster kidney cells). Those made according to FDA standards are considered as effective as HDCV for PEP and for IM preexposure vaccination.[29,63,251]

The PVRV vaccine is produced in cultures of kidney cells from African green monkeys by Sanofi Pasteur in France and by other agencies and is extensively used at QSMI and other institutions.[47,128,263] This vaccine can be prepared in continuous cell lines cultured in suspension on microcarrier beads in biofermenters with a capacity of up to 1000 L, which allows production of vaccine on an industrial scale at greatly reduced cost.[234,250,257]

Nonhuman cell culture vaccines are less satisfactory than HDCV in one respect. Approximately one-third of recipients reported pain at the injection site, and two-thirds of vaccinees given PVRV boosters developed local erythema. Approximately 5% to 10% of recipients had systemic reactions, such as fever, headache, malaise, or urticaria.[250] In terms of safety and antigenicity, HDCV and the vaccines grown in other cell cultures are identical.

RABIES CONSIDERATIONS FOR TRAVELERS

Rabies is a definite risk for travelers, as illustrated by the 32-year-old female American traveler who was bitten on the hand while petting a stray dog in Kathmandu, Nepal. She missed at least three opportunities to obtain treatment in Nepal, Thailand, and Australia, as well as any number of opportunities after returning to the United States, and died of rabies 75 days later.[26] Of the 63 human rabies infections in the United States since 1980, 18 were acquired in other countries, although most of those infections were in immigrants. The United Kingdom, which has been free of rabies since 1919, encountered 23 rabies infections acquired outside the British Isles from 1946 to 2005. Sixteen originated in the Indian subcontinent. From 1981 to 2005, four of the nine rabies infections diagnosed in Germany were acquired elsewhere.[144]

Probably the major problem in preventing rabies in travelers is their uninformed status. In a study of 300 French travelers, only 6.7% knew that the risk for rabies was significant, and 40.1% considered it moderate or low. The danger of dog bites appeared well known, but the risk for scratches (0.7%) and licks (10%) was not known. The danger of cat, fox, monkey, and bat bites was not well known. Only half the travelers knew about preexposure vaccination, and 57.6% of travelers going to rabies-endemic countries presented to travel clinics too close to their travel departure date for vaccination to be completed. Immediate washing of bite wounds was described by only 3% of those questioned, although 21.3% mentioned disinfection with antiseptics.[1]

Information about rabies is not widely disseminated in developing countries. Travelers must know about this hazard before they depart.

According to WHO estimates, 99% of rabies infections are the result of dog bites.[168] However, monkeys are a significant threat around some of the temples in parts of Asia, such as the Swayambhunath and Pashupatinath temples in Nepal. Most monkey bites result from attempts to snatch food carried or being eaten by travelers, which visitors to temples must avoid.[88,214] Among foreign travelers in Nepal treated at the CIWEC Clinic, dog bites accounted for about 75% of reported exposures, and monkeys inflicted 20% of the bites.[219]

In areas where canine rabies is endemic, which includes essentially all of Latin America and Africa and most of Asia, PEP should be initiated immediately after a bite by a dog or cat, but can be terminated if the animal remains healthy during a 10-day observation period. The vaccination status of the biting animal must be ignored. Vaccines used for animals in developing countries are not as reliable as U.S. vaccines, and fatal rabies has been reported in U.S. citizens and in others who were bitten by "vaccinated" dogs in developing countries and did not obtain prompt PEP.[56,264] In the United States, rare rabies infections are found in dogs or cats that have been vaccinated.[174]

In developing countries, except for those few areas where rabies does not occur, all attacking animals should be considered rabid if they escape.

WOUND CLEANSING

Because wound cleansing is such a vital element of postexposure therapy, travelers should be prepared to carry out this procedure in an optimum manner. The best soap to use is a liquid antibacterial preparation; if this is not available, soap of some type can usually be obtained. More important, virucidal agents such as povidone-iodine (Betadine) are rarely available unless the traveler's group had a well-stocked first-aid kit. Travelers could carry a 3- or 4-oz bottle of one of these agents, and it should be reserved solely for cleansing animal bites, not for routine scrapes and cuts. Povidone-iodine preparations are easy to keep on hand because they can be stored in plastic bottles.

IMMUNE GLOBULIN

In developing countries, immune serum is rarely administered, because it is expensive or is unavailable. Only about one-third of the immune serum required for rabies PEP worldwide is being produced. In many areas, it cannot be obtained.

Even in areas where immune serum is available, travelers who receive PEP often are not given immune serum. Investigators in France found that of 261 travelers exposed to rabies, only 24% were given immune globulin. Of the travelers who did not receive RIG, 43% received a first dose of vaccine more than 7 days after return and before presenting to a clinic in their home country.[119]

As discussed earlier, when immune serum is given, it is usually of equine origin, the cost of which is only about 10% of the cost of HRIG.

If RIG is not available for immediate administration, it may be given through day 7 following the administration of the first dose of a tissue culture vaccine.

VACCINE

At present, neural tissue vaccines are still employed for a large percentage of all postexposure rabies therapy worldwide because they are considered inexpensive. Travelers must not allow themselves to be treated with neural tissue vaccines. Cell culture vaccines can be obtained in most developing countries, although travel to a major city may be required to obtain them.

PREEXPOSURE VACCINATION

If postexposure immunization is to be effective, it must be available on an urgent basis and must include access to contemporary tissue-culture vaccines and either HRIG or purified ERIG. Although access to prompt PEP may be available in major cities, it cannot be found in rural or wilderness areas where rabies is endemic. In determining whether preexposure vaccination (discussed earlier) should be administered, travelers and travel medicine consultants must consider the location, the purpose and duration of the trip, lifestyle, activities, and access to health care or repatriation.

Investigators at the CIWEC clinic in Kathmandu, Nepal, have found that trekkers do not have a greater risk for being exposed to rabies. However, canine rabies exists in popular trekking areas, and trekkers and participants in similar activities are much farther from medical care than are individuals who remain in cities. For trekkers and climbers in the Mt Everest area of Nepal, it can take days to reach the site of the aircraft landing strip, and additional days elapse before good weather allows aircraft to land. Furthermore, aircraft landings and takeoffs from this site are usually filled to capacity, so an unscheduled traveler may have difficulty boarding a departing flight. WHO recommends that individuals who spend a lot of time outdoors, particularly in rural areas, receive preexposure vaccination.[276]

CHILDREN

Children are considered to be at higher risk for rabies exposure for several reasons: their small stature makes extensive bites more likely, bites occur higher on the trunk or on the face, children are attracted to animals, and they may be less likely to report an

exposure for fear of punishment.[214] Preverbal children cannot report such events. Children must be carefully monitored and not allowed to play with dogs (even puppies) or cats in rabies-endemic areas.

In children, the dose of vaccine for preexposure immunization or postexposure therapy is the same as that for adults: 1.0 mL injected IM. Only the dose of RIG for PEP is based on body weight.

OBTAINING MEDICAL CARE

In foreign countries, American embassies and consulates are reliable sources of help. The U.S. Department of State's Bureau of Consular Affairs website states, "If an American citizen becomes seriously ill or injured abroad, a U.S. consular officer can assist in locating appropriate medical services and informing family or friends. If necessary, a consular officer can also assist in the transfer of funds from the U.S." The website provides important information in case of emergencies and crises abroad, including the telephone number to contact the State Department's overseas American Citizens Services (from outside the U.S., 202-501-4444).[244]

Travelers should obtain travel insurance before going to other countries. Medicare does not cover the cost of medical treatment outside the United States; other insurance agencies have varying policies. Payment for unplanned transport back to the United States usually is covered only by travel insurance.

The following WHO Rabies Collaborating Centers are available for consultation, and if unavailable, citizens should seek their embassy or consulate for possible treatment if needed:

- WHO Collaborating Centre for Control, Pathogenesis and Epidemiology of Rabies in Carnivores Centre of Expertise (COFE) for Rabies, Ottawa Laboratory Fallowfield (OLF), Canadian Food Inspection Agency, Nepean (Ontario), Canada
- WHO Collaborating Centre for Reference and Research on Rabies, Rabies Section Division of Viral and Rickettsial Diseases (DVRD), Viral and Rickettsial Zoonoses Branch, National Center for Infectious Diseases (NCID), Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, United States
- WHO Collaborating Centre for Reference and Research on Rabies, The Wistar Institute, Philadelphia, Pennsylvania, United States
- WHO Collaborating Centre for Neurovirology, Department of Immunology and Microbiology, Thomas Jefferson University, Philadelphia, Pennsylvania, United States
- WHO Collaborating Centre for Reference and Research on Rabies, Pasteur Institute of Iran, Tehran, Islamic Republic of Iran
- WHO Collaborating Centre for Rabies Surveillance and Research, Institute of Epidemiology, Federal Research Institute for Animal Virus Diseases, Wusterhausen, Germany
- Centre collaborateur de l'OMS de Référence et de Recherche pour la Rage, Unité de la Rage, Institut Pasteur, Paris, France
- WHO Collaborating Centre for the Characterization of Rabies and Rabies-related Viruses, Veterinary Laboratories Agency, Weybridge Department of Virology, New Haw, Addlestone, Weybridge, Surrey KT15 3NB, United Kingdom
- WHO Collaborating Centre for Reference and Research in Rabies, Department of Neurovirology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India
- WHO Collaborating Centre for Rabies Epidemiology, National Institute of Communicable Diseases (NICD), New Delhi, India
- WHO Collaborating Centre for Research on Rabies Pathogenesis and Prevention, Queen Saovabha Memorial Institute, The Thai Red Cross Society, Bangkok, Thailand

OTHER LYSSAVIRUSES

With RT-PCR amplification and nucleotide analysis, seven rabies virus genotypes have been recognized. Genotypes other than genotype 1 cause very few human infections. Genotype 2, Lagos bat virus, has not produced a recognized human infection. However, these additional genotypes are a source of considerable concern, particularly in Europe, where bats infected by genotypes 5 and 6 are common. Treatment of humans infected by viruses of these genotypes with the immune serum and vaccine used for genotype 1 appears to be effective, with the exceptions of genotypes 2 and 3. These two genotypes are so different from the others that specific antisera can be prepared for them; identification of the other genotypes is based almost entirely on nucleotide sequence analyses. True vaccine failure occurs when animals vaccinated with rabies vaccines are exposed to Mokola and Lagos bat viruses.[83,115,141,227,258] Therefore, genotypes 2 and 3 have been classified as phylogroup 2, and the other genotypes have been lumped into phylogroup 1.

- Genotype 1 contains the viral strains that produce almost all recognized infections in humans and terrestrial mammals, many bat infections, and the fixed viral strains found in laboratories.
- Genotype 2 (Lagos bat virus) was first isolated from fruit-eating (frugivorous) bats on Lagos Island, Nigeria, in 1956. It is not known to infect humans, but it is found in bats and cats in Africa.
- Genotype 3 (Mokola virus) was isolated from mice in the Mokola district of Ibadan, Nigeria, in 1968. In 1971, it was recovered from a 6-year-old girl who had a nonlethal infection that was not clinically typical of rabies. Subsequently, a lethal human infection more typical of rabies has been recognized. This virus is found in shrews and cats in Africa.
- Genotype 4 (Duvenhage) was isolated in 1970 from a 31-year-old man with that name who died of the infection in Pretoria, South Africa, following a bite on the lip by a bat. It is found in insect-eating (insectivorous) bats in Africa.
- Genotype 5 (European bat lyssavirus—EBLV—types 1a and 1b) has produced lethal infection in two Russian girls, a 15-year-old bitten on her finger by a bat, and an 11-year-old bitten by a bat on her lip. This virus is found in insectivorous bats in much of Europe.
- Genotype 6 (EBLV types 2a and 2b) has produced lethal infections in two people, a 30-year-old male zoologist in Finland and a 55-year-old male bat handler in Scotland. It is also found in insectivorous bats throughout most of Europe.
- Genotype 7 (Australian bat lyssavirus—ABLV) was isolated from a 39-year-old female in 1996 and a 37-year-old female in 1998 after both had died in Australia of rabies-like illnesses. It is found in insectivorous and frugivorous bats (flying foxes) in Australia. Bats with antibodies to this virus have also been found in the Philippine Islands.

Four other distinct lyssaviruses have been isolated in recent years. An application has been submitted to the International Committee on Virus Taxonomy to have them declared distinct species, although some investigators think they should be considered distinct genotypes.

- The Aravan virus (ARAV) was isolated from the lesser mouse-eared bat in Kyrgyzstan in 1991.[4]
- The Khujand virus (KHUV) was isolated from the whiskered bat in Tajikistan in 2001.
- The Irkut virus (IRKV) was isolated from the greater tube-nosed bat in Russia (East Siberia) in 2002.
- The West Caucasian bat virus (WCBV) was isolated from the Schreiber's bent-winged bat in Russia (West Caucasus) in 2002. Bats with antibodies to this virus have been found in Kenya.[156]

No human infections by these viruses have been identified. Bats with antibodies to Irkut, Aravan, and Khujand viruses, as well as the Australian bat lyssavirus (genotype 7), have been found in Thailand.[162] These viruses are pathogenic for laboratory mice, hamsters, and bats by intracranial and IM injection routes, except for WCBV, which is pathogenic for mice only by the intracranial route. WCBV has been found to be pathogenic for nonhuman primates by both routes. All produce acute progressive fatal encephalitis essentially identical to rabies. All produce intracytoplasmic inclusions (Negri bodies).When groups of nine Syrian hamsters were treated with various vaccines and challenged with injections of the different viruses, the results shown in Table 31-11 were obtained.[157] Genome sequencing of the *N*, *P*, and *G* genes has indicated that ARAV, KHUV, and IRKV are

TABLE 31-11 Results of *Lyssavirus* Injections

	WCBV	ARAV	IRKV	KHUV	Rabies
Human diploid cell vaccine	4/9*	5/9	6/9	8/9	9/9
Veterinary vaccine	2/9	9/9	8/9	9/9	9/9
Recombinant vaccine	1/9	4/9	5/9	9/9	9/9
Unvaccinated controls	2/9 p <0.01	0/9 p <0.01	0/9 p <0.001	1/9 p <0.001	0/9

*Numerator indicates the number of survivors.
ARAV, Aravan virus; *IRKV,* Irkut virus; *KHUV,* Khujand virus; *WCBV,* West Caucasian bat virus.

related to genotypes 4, 5, and 6, and these viruses manifest as a solid phylogroup of Old World bat lyssaviruses. WVBV is more divergent than the other genotypes, with only limited relatedness to genotypes 2 and 3.[154,155]

CURRENT RABIES DEVELOPMENTS

RABIES ERADICATION IN WILD ANIMALS

Attempts to destroy wild animals that provide a reservoir for rabies have been made, but these pursuits are expensive and largely ineffective, with the possible exception of a program to eliminate striped skunks in Alberta, Canada. Even if such attempts were cost-effective, the consequences are considered unacceptable, namely, increased populations of animals that had been prey (e.g., rodents) for the destroyed animals.[202,278] Eradication of rabies in wild animal populations by oral vaccination was first suggested by Baer, and a program using baits distributed by aircraft was initiated in Canada in the early 1980s. Foxes were the targets of the early studies because they are particularly susceptible to rabies, and an effective oral vaccine could be produced.

The most striking successes in vaccinating wild animal populations have been achieved in Western Europe and in Texas. In Europe, the only significant wild reservoir for rabies is the red fox. A wave of fox rabies began on the Polish-Russian border after World War II and swept over most of central Europe.[32] The increased incidence of rabies in this species, and an economically distressing rise in the number of secondary rabies infections in livestock, principally sheep and cattle, led to efforts to control that source of infection.

After extensive trials to demonstrate its safety, particularly for humans, vaccination of foxes was achieved with an oral attenuated–live-virus vaccine, starting in 1978 in areas of Switzerland, and later in parts of Germany. The vaccine first was placed in capsules attached to chicken heads. Subsequently, a specially designed bait of fishmeal and fat, the "Tübingen fox bait," was developed. The baits included tetracycline as a marker, and fluorescence microscopy of mandible or canine tooth sections from foxes that were subsequently killed or found dead was used to determine the number of animals that had been immunized. Because dentine is deposited daily, the date of bait uptake could be calculated by counting the increment (von Ebner) lines between the pulp cavity and the tetracycline deposit.[146,147,253] Baits were uniformly distributed throughout the test areas by hand or by helicopter. Immunization campaigns were carried out in the spring and fall, the latter particularly to vaccinate young foxes that could not take the baits during the spring. Follow-up studies of tetracycline labeling indicated that 75% to 80% of the foxes had consumed the vaccine, an adequate number to interrupt the spread of infection within the fox population.

The attenuated live virus used for the initial vaccinations in Switzerland and Germany retains pathogenicity for rodents and can revert to virulence. In addition, this attenuated virus cannot be used in North America because it is pathogenic for striped skunks and ineffective for raccoons. Starting in 1990, a vaccinia-rabies recombinant vaccine that expressed the G glycoprotein was used in Belgium and France.[45,278] In the areas where the vaccine has been distributed, genotype 1 rabies has largely been eradicated in all terrestrial animals, not just foxes.[180] The incidence of rabies in livestock reported from the Belgium test area has fallen from more than 80 cases a year to none.[45,265]

As a result of this program, Finland and The Netherlands were declared free of terrestrial rabies in 1991, Italy in 1997, Switzerland in 1998, France in 2000, Belgium and Luxembourg in 2001, and the Czech Republic in 2004. Bats in those countries are infected with lyssaviruses of genotypes 5 and 6, and these infections have not been controlled.

An epizootic of rabies in raccoon dogs, which apparently had originated in the USSR, was detected in southern Finland, and in the autumn of 1988 a field trial of oral immunization of these dogs and foxes was initiated. Rabies was eliminated from these populations within 12 months.[278]

An epizootic of rabies in coyotes in southern Texas originated in unvaccinated Mexican dogs that crossed the Rio Grande River. The epizootic spread to domestic dogs and resulted in two human rabies infections and more than 2000 PEP courses. Control by dropping baits containing oral rabies recombinant vaccine from aircraft has grown to the largest aerial vaccination program ever attempted (2.6 million vaccine/bait units over a 42,000 square mile region during 1997). The rabies baits contain markers such as tetracycline. In 1997, 87% of coyotes manifested tetracycline fluorescence, more than enough of the population to stop the epizootic, which has disappeared. In 2001, only one infection by the dog/coyote rabies variant was found; in 2002 none was encountered.[153]

A similar program has been used in Ohio to stop the spread of the raccoon rabies epizootic from Pennsylvania on the state's eastern border.

Rare human vaccinia infections have been attributed to contact with the recombinant vaccine baits.[208]

Although such programs are expensive, they are considered less costly than the alternatives: treating humans, diagnosing animals, vaccinating domestic animals, compensating farmers for culling infected livestock, culling wild foxes, and paying the salaries of individuals who carry out these alternatives.[45,180] Additionally, once rabies has been eliminated in a geographic area, it can be kept out by establishing buffer zones in which oral vaccination campaigns are carried out regularly. Vaccination campaigns for the entire area can be carried out less frequently or possibly eliminated entirely.[278]

In North America, control of rabies in wild animals is much more complex, because this infection is enzootic in a variety of animals: skunks, raccoons, foxes, and bats. These animals vary considerably in their sensitivity to different strains of the rabies virus and vaccines prepared from those strains, they respond differently to the rabies virus sachet, and they have widely differing ranges (9.5, 2.5, 1.5, 0.8, and 0.037 km^2, respectively, for coyotes, raccoons, red foxes, striped skunks, and mongooses). Furthermore, these animals have widely varying population densities, and they prefer different habitats.[159] Even though North America contains vast sparsely populated areas, many of the animals live in urban areas. A 60-km^2 (23.1-$mile^2$) area of Toronto with a perimeter of 28 km (17.4 miles), in which 252,000 humans lived, also had a population of approximately 1540 skunks, 3510 raccoons, and 70 red foxes from 1987 to 1991.[201] The entire city of Toronto is estimated to have a red fox population of approximately 1000 animals.[200] A program to trap, vaccinate by injection, and release animals in this area was effective and cost $27,000 to $69,000 (Canadian) a year. That sum was considerably less than the $100,000 spent annually to treat humans exposed to rabid animals in Toronto.[201]

Although these programs control rabies in the target species, the ecologic effects of increasing the animal population by eliminating a significant cause of mortality are almost entirely unknown.[32,253]

VACCINE DEVELOPMENTS

Killed-virus vaccines are used for human and most domestic animal vaccinations. Attenuated live-virus vaccines have been used only to vaccinate animals. The first vaccine used orally to vaccinate wild red foxes in Europe was a live-attenuated vaccine.

Subunit vaccines contain only one of the viral structural proteins. Since these vaccines contain only an antigenic portion of the virus and not the entire organism, they can induce immunity but are incapable of producing infection. The rabies-vaccinia recombinant vaccine that produces only the G surface protein of the rabies virus has proved to be noninfective, immunogenic, and very effective for vaccinating foxes in Europe.[278] However, this recombinant vaccine cannot be used for humans because much of the world's population has been vaccinated with vaccinia to prevent smallpox, and vaccinia can produce disseminated infections in humans.[45]

Some orthopoxviruses cannot completely replicate in mammalian cells and therefore cannot produce infections, but they can abortively replicate, so that proteins expressed by the virus are presented to the immune system. A recombinant with canarypox virus that expresses the G glycoprotein has been developed at Sanofi Pasteur; it has been found to be safe and effectively produces a neutralizing antibody response in a variety of animals and humans. This vaccine is currently licensed for vaccinating cats in the United States.[44] Orthopox vectoring may permit incorporation of several antigens, such as measles, mumps, rubella, rabies, and pertussis, in a single vaccine, which would greatly facilitate and reduce the cost of human immunization.[278]

Adenoviruses replicate on mucosal surfaces and could be ideal vectors for oral and intranasal vaccines. Recombinant human adenovirus type 5, into which complementary DNA for glycoprotein (G protein) has been inserted, has been shown to elicit protective levels of neutralizing antibodies in skunks and foxes when administered orally. Deleted replication-defective recombinants have produced high titers of rabies virus–neutralizing antibody in dogs and have provided 100% protection against a lethal rabies challenge in mice. A vaccine containing an adenovirus recombinant that expressed G protein was protective for dogs when injected subcutaneously. These developments appear to hold promise for development of an oral vaccine for dogs.[95,137,238] Baits containing this adenovirus recombinant were aerially distributed in Southwest Ontario, Canada, and successfully immunized raccoons and skunks.[199]

DNA vaccines based on plasmid vectors expressing the rabies G protein offer promise because they are easy to construct, manipulate, and produce. Such vaccines have produced high titers of virus-neutralizing antibody in mice, dogs, and nonhuman primates. They appear to be effective in much younger animals. In a field trial, a DNA vaccine injected into dogs' ears with a jet injector was much more efficient for inducing long-lasting high titers of virus-neutralizing antibodies than was cell culture vaccine.[21] DNA vaccines have not proved as effective for PEP, because the antibody response to such vaccines is slow. Efforts to accelerate the antibody response appear to be effective.[44,95]

Incomplete rabies viruses that cannot replicate have been investigated as rabies vaccines. One of these experimental viruses lacks the P, or phosphoprotein, gene. (The P and L genes are responsible for viral replication.) The P gene–deficient virus is apathogenic in mice, even when inoculated intracranially. It induced a high titer of virus-neutralizing antibody and protected the mice from lethal challenges with rabies virus.[172]

The rabies matrix (M) protein plays an important role in assembly and budding of progeny viruses. M gene–deficient viruses failed to generate progeny viruses, and mice inoculated intracerebrally developed no signs of disease. IM injection of these viruses induced formation of neutralizing antibodies. Intranasal installation resulted in almost the same antibody response.[139] In a comparison of M gene–deficient and P gene–deficient viruses as vaccines, the M gene–deficient virus induced a more rapid response and a fourfold higher virus-neutralizing antibody response in rhesus macaques than did a commercial vaccine. The M gene–deleted vaccine has the potential for replacing current preexposure and postexposure rabies vaccines.[50]

Transgenic maize has been employed to produce rabies G protein. The amount of G protein produced was approximately 1% of the total soluble plant protein. Transformed kernels were given orally to mice. When challenged 90 days later with a lethal dose of a vampire rabies virus, the edible vaccine had induced viral neutralizing antibodies that 100% protected mice.[161] Transgenic tomatoes have been employed to produce full-length rabies nucleoprotein genes. When injected intraperitoneally or administered orally, a protein extract induced production of antibodies. However, intraperitoneal injections were only partially protective, and oral injections were not protective.[188]

REPLACEMENTS FOR RABIES IMMUNE GLOBULIN

DNA recombinant technology has been used to express three human rabies virus–neutralizing monoclonal antibodies in a rhabdovirus vector. Growth of the recombinant in cell culture produced high yields of three monoclonal antibodies that differed in epitope recognition. A "cocktail" of these antibodies neutralized several fixed and street rabies viruses. Mice and hamsters treated with this cocktail after infection with a lethal dose of rabies virus were protected. The protection was comparable with that provided by HRIG. Notably, such cocktails could help compensate for inadequate RIG production that now prevails in developing nations.[173,194] A number of such products have been used to treat humans.[21,124] However, industrial production and widespread use of such products has yet to be initiated.

SIMPLER LABORATORY TESTS FOR RABIES

In countries where rabies infection is endemic, funds and infrastructure often are insufficient to allow employment of the direct fluorescent test, which is the gold standard. Therefore, efforts are being made to develop simpler laboratory procedures for rabies testing. An example is the immunochromatographic test kit, which is both simple and rapid and does not need a cold chain for transportation or sophisticated training for personnel. The kit with two monoclonal antibodies has achieved sensitivity of 93.2% and specificity of 100%.[182]

RABIES REMAINS A NEGLECTED GLOBAL PUBLIC HEALTH CRISIS

Despite that rabies is preventable, it is an ongoing, global public health threat that is relatively neglected compared to other viral infectious diseases associated with lower morbidity and mortality. For example, as of January 2015, the largest outbreak of Ebola on record reported just over 21,000 cases and 8429 deaths.[269] Highly pathogenic avian influenza (H1N5) from 2003 through 2014 resulted in just under 700 cases and 402 deaths.[270] The immediate and concerted response by global public health officials to address these viral disease outbreaks successfully controlled and contained disease spread. A similarly organized and aggressive campaign to suppress the global burden of rabies is urgently needed. Successful programs suggest this would also be cost-effective.[215,221]

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CHAPTER 32

Bear Behavior and Attacks

LUANNE FREER

Bears are widely distributed throughout the world; at least one of the eight bear species currently exists in Asia, Europe, North and South America, and the Arctic (Table 32-1). Bears became extinct in Africa several million years ago. Australia and Antarctica are the only continents where bears have never existed. The koala bear of Australia is a marsupial and not a true bear.

Bears occupy a wide variety of habitats, including tropical forests, polar ice sheets, swamps, barren ground tundra, bamboo jungles, alpine meadows, and coniferous and deciduous forests. Their range extends from sea level up to about 6100 m (20,000 feet).

Bears are carnivores. Although some bear species practice specialized feeding in response to their habitat, all bears are omnivores and retain the ability to feed on a variety of food types, including vegetation, insects, and meat.

Modern bears have larger brains than did their extinct ancestors,[37,52] and the relative brain size of bears is larger than that of other carnivores.[24] This greater brain size probably resulted from a need to increase sensory and perceptual capacities for locating an omnivore food base with both seasonal and annual variations in distribution and abundance.[11,16,44] The larger brain size reflected the increased intelligence required by bears to develop a complex foraging strategy. Increased intelligence also allowed them to develop individual behavior, shaped by both experience and memory. Thus, bears possess a wide variety of behaviors, some distinct to their subspecies, and have been described as playful, lazy, doleful, entertaining, intelligent, caring, powerful, aggressive, terrifying, and vicious.[59]

The image of bears as "man-eaters" ignites our fear of them. Human injury and deaths from natural phenomena, especially wild animal attacks, are sensationalized. Bear attacks are rare, but the psychological impact of widespread media coverage inflates the perception of their frequency and significance.[13,40] Every bear attack is traditionally referred to as a *mauling,* regardless of the extent of injuries. This term contributes to the emotional response regarding such attacks and leads to "bearanoia" in many people who visit bear country. This fear of bears may affect how people use wilderness areas that have bear populations and how they view the conservation of bears and their habitat. Better understanding of bears and their behavior helps reduce bear-human conflict, assists health care providers in treating bear attack victims, and promotes conservation of bears.

An international organization composed of wildlife experts and social scientists was formed in 2009 to coach communities through reducing conflict between bears and humans, with the goal of creating sound public policy while conserving bear populations.[69]

NORTH AMERICAN BEARS

Grizzly bears (*Ursus arctos horribilis*) are larger and more heavily built than most other ursids, with adults weighing 147 to 386 kg (325 to 850 lb) (Figure 32-1).[6] Polar bears (*Ursus maritimus*) are similar in size and weight but are more elongated in shape (Figure 32-2). Black bears (*Ursus americanus*) have the same general shape of grizzly bears but are typically smaller than both polar and grizzly bears (Figure 32-3). Weights for black bears range from 64 to 136 kg (140 to 300 lb) for adult females and 113 to 295 kg (250 to 650 lb) for adult males.

Dentition in these three species is bunodont and reflects their omnivorous diet, although polar bears are the most carnivorous of the three (Figure 32-4). Their canine teeth are sturdy and can reach a length of 7 cm (2.75 inches). Their legs are of approximately equal length and taper to large, plantigrade feet. The foreclaws of a grizzly bear are heavier, longer, and straighter than those of a black bear and can reach a length of 8.75 cm (3.5 inches) measured along the external curvature (Figure 32-5).[60] A large, muscular hump overlies the scapulae of grizzly bears, giving additional strength to the forelimbs for digging (Figure 32-6). The face of a brown bear tends to be more dish-shaped (concaved) than that of a black bear (Figure 32-7). The guard hairs on brown bears can be lighter in color and lend a "grizzled" appearance. Black bears can be many colors, ranging from white to black, cinnamon, brown, or "blue."[18]

The physical strength of bears is tremendous, and they can run at speeds up to 65 km/hr (40 miles/hr) over irregular terrain. They have a keen sense of hearing and an even keener sense of smell. Their eyesight has been described as poor,[30] although many field researchers believe that bears can see as well as humans and are especially adept at detecting movement. Evidence also suggests that grizzly bears have good night vision.[22]

Grizzly and black bears hibernate for about 5 months during winter, an evolutionary adaptation to reduced food availability. Hibernation of polar bears is slightly different because their primary food (seals) is available during winter.[49] Adult male polar bears tend to hibernate for short periods each winter in response to severe storms, whereas pregnant females have more extended hibernation. During the active (nondenning) season, all bear species wander throughout a general home range in search of seasonal foods.

GRIZZLY BEARS

The grizzly bear symbolizes wilderness in North America (Figure 32-8). In certain respects, "grizzlies" define the "wild" in wilderness. They range from Alaska through western Canada and into the lower 48 U.S. states in remnant populations, primarily located in undeveloped federal lands in the northern Rocky Mountains.

Attacks by grizzly bears are relatively rare and sporadic. A total of 162 bear-inflicted injuries (including deaths) were reported from 1900 through 1985 in Canadian and North American national parks.[30,31] In the Canadian province of Alberta, there were 29 documented serious or fatal injuries caused by grizzly bears during the period of 1960 through 1998.[33] From 1980 to 1994, 21 grizzly bear attacks, including two deaths, occurred in Yellowstone National Park.[29] During the following decades, one or two people were injured by grizzly bears in Yellowstone each year, with two additional deaths in 2011. In Alaska, the number of people injured by grizzly bears has increased in recent times, most likely as a result of increased recreational use of grizzly bear habitat.[45,55]

Calculation of an accurate injury rate remains elusive. Earlier records were incomplete, and it has always been difficult to define and quantify those at risk. Injury rates are based on total visitation days to national parks in Canada and the northern United States.[31] The average number of grizzly bear–inflicted injuries ranges from a high of 1 in 317,700 visitors in Kluane National Park to a low of 1 per 6,693,859 visitors in Banff. During this same period, the grizzly bear–inflicted injury rate for Yellowstone National Park was 1 in 1,543,287 visitors and for Glacier National Park, 1 in 848,180 visitors.

Not every visitor to a national park is exposed to the same risk of being attacked by a grizzly bear. To obtain an injury rate that more accurately reflects the risk for visitors with higher and

TABLE 32-1 Distribution of Bear Species

Common Name	Scientific Name	Distribution
Panda bear	*Ailuropoda melanoleuca*	Eastern rim of China's Tibetan Plateau
Spectacled bear	*Tremarctos ornatus*	Andes Mountains in South America
Sloth bear	*Melursus ursinus*	Nepal, Bangladesh, Bhutan, northern India, Sri Lanka
Asiatic black bear	*Ursus thibetanus*	Southern Asia from Pakistan across northern India and into China and southeast Asia; separate populations in eastern Russia, Korea, Taiwan, and Japan
Sun bear	*Helarctos malayanus*	Borneo, Burma, Java, Malaysia, Sumatra, Thailand
American black bear	*Ursus americanus*	Alaska, Canada, most of continental United States
Brown bear	*Ursus arctos*	Eurasia, Alaska, Canada, northern Rocky Mountain states (including Wyoming, Montana, Idaho, and Washington)
Polar bear	*Ursus maritimus*	Arctic circle (circumpolar)

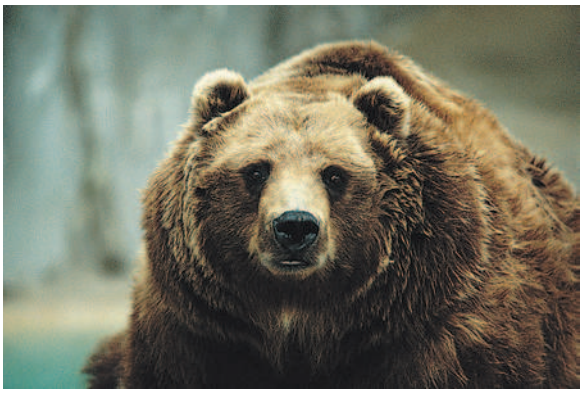

FIGURE 32-1 Grizzly bear. *(Courtesy Marilynn G. French.)*

FIGURE 32-2 Polar bear. *(Courtesy Steven D. Evans.)*

FIGURE 32-3 American black bear. *(Courtesy Marilynn G. French.)*

FIGURE 32-4 Grizzly skull, demonstrating canine teeth. *(Courtesy Marilynn G. French.)*

FIGURE 32-5 Grizzly paw with claws. *(Courtesy Marilynn G. French.)*

FIGURE 32-6 Alaskan coastal brown bear, demonstrating muscular back hump. *(Courtesy Luanne Freer.)*

FIGURE 32-7 Silhouette of brown bear, demonstrating hump and "dished" face. *(Courtesy Timothy Floyd.)*

more uniform exposure, the incidents among registered backcountry users have been reported. However, this method provides an inaccurate injury index because some parks do not register backcountry use and others generally underestimate it. Also, it is significant to note that most backcountry use (and therefore exposure) is by unregistered day hikers.

The number of bear attacks (both black and grizzly) increases in months when more people seek recreation in grizzly bear country. For national parks, the incidence of bear attacks increases during peak tourist season, July and August. For surrounding national forests, another peak occurs during hunting season, September to November. The state of Wyoming has reported a trend of increasing grizzly bear–human conflicts as the grizzly bear population hovers at an all-time high for this century.[47] With more people seeking recreation in bear country, greater opportunity exists for human-bear encounters.

Native peoples and grizzly bears occupied the same land for thousands of years in North America in what was probably a neutral coexistence, as neither had a profound influence on the other. However, the European expansion into the American West after Lewis and Clark's expedition in the early 1800s tipped the scales heavily in favor of humans, both in sheer numbers and technology, such as guns, traps, and poisons. Bears were killed in large numbers, out of fear and hatred and to protect life and property. Most of their original habitat was occupied by people or livestock or was dramatically altered by ranching and agricultural development.

Selection pressures that began with European expansion into the grizzly bear habitat have probably been altering their behavior. Since that early period, and even today in protected areas such as national parks, aggressive bears have been removed at a higher rate than nonaggressive bears. Bears that were curious about humans and human developments and those that did not readily flee the presence of humans were also removed at a higher rate. Therefore, bears that avoided humans survived at a higher rate than did other bears and probably passed that trait on to their offspring through genes and learning.

A built-in safety factor exists for people entering grizzly country, because the vast majority of bears now avoid a confrontation if given the opportunity, which probably explains why grizzly bear attacks on humans are so rare. Unfortunately, available information on grizzly attacks does not always yield an accurate account of the cause-and-effect relationship. The specific sequence of events is not always known and is subjectively reconstructed, although case histories reveal certain patterns.

A sudden and close encounter with a grizzly bear is the primary event leading to human injury. From 1980 to 1994, of 21 people injured by grizzlies in Yellowstone National Park,[29] 18 injuries resulted from people surprising a grizzly at close quarters. These attacks were often brief, and the bear generally left the area soon after the attack. Although injuries were typically described as a mauling, they were usually much less severe than the bear had the potential to inflict (Figure 32-9), and victims were rarely killed. This suggests that the bear's behavior in response to a close encounter was to remove a perceived threat.

A close encounter with a female with cubs is considered more dangerous, because she is considered to be more aggressive in defense of her young (Figure 32-10). Evidence to support this hypothesis is strong. Females with young represent about 20% of a bear population but account for more than 80% of bears involved in human injury. Another explanation, however, is that females with young are more likely to be active during daylight hours when humans are active, whereas males are active primarily in the predawn hours and after dusk.[22]

Grizzly bear attacks sometimes occur near a carcass on which the bear has been feeding. The bears may be more aggressive under these circumstances in defense of the carcass. Grizzly bears of all ages and either gender, however, may readily exit when they sense people approaching.[22] When a grizzly bear injures

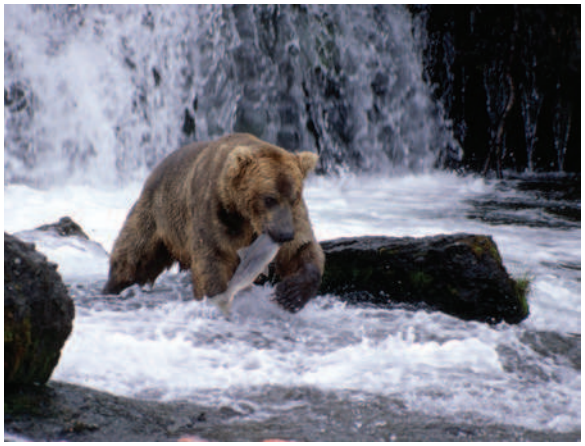

FIGURE 32-8 Grizzly bear encounters have become popular events for wildlife photographers. *(Courtesy Timothy Floyd.)*

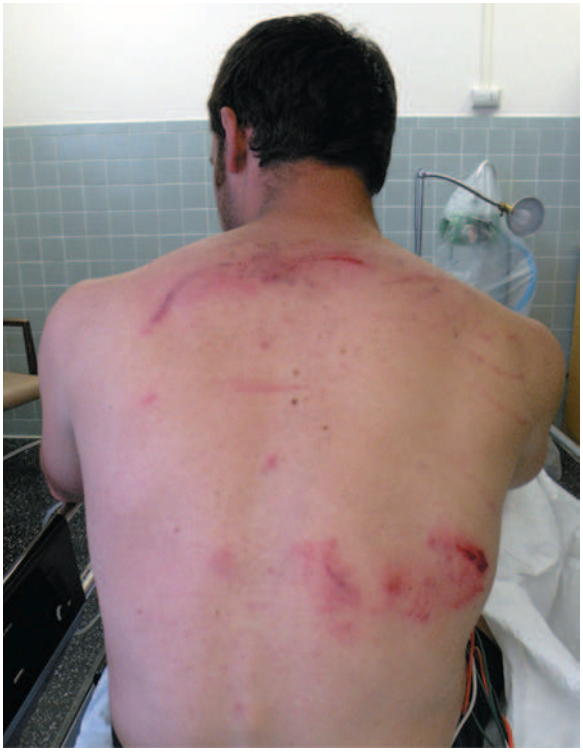

FIGURE 32-9 When surprised at close quarters, grizzly bears, which have the potential to do much more harm, often inflict relatively minor injuries and then flee. This victim of a bear attack stumbled upon a surprised bear that was trapped by fire lines. *(Courtesy Luanne Freer.)*

FIGURE 32-10 Brown bear sows with cubs are notoriously aggressive in protection of their young. *(Courtesy Luanne Freer.)*

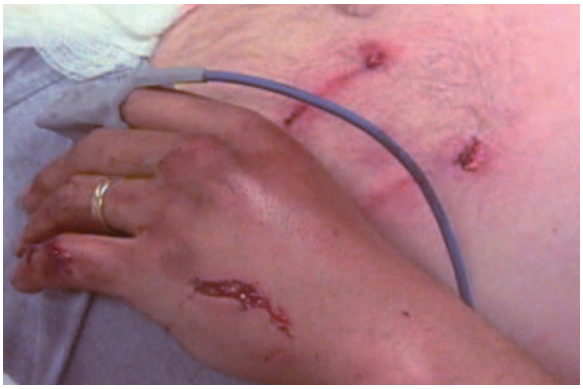

FIGURE 32-12 Hunter attacked by grizzly bear. *(Courtesy Luanne Freer.)*

someone near a carcass, the precipitating event may simply be a close encounter with a preoccupied bear.

Another class of attacks results from provocation, most often when a grizzly bear is wounded with a gun. Once the bear is injured, its behavioral response is no longer to remove a threat but to fight for its life. These attacks tend to be more prolonged and aggressive, resulting in more severe injuries than those resulting from a close encounter. Provoked bear attacks can result from direct harassment by aggressive photographers (Figure 32-11). Although such incidences are rare, these attacks tend to resemble the response of an injured bear rather than one responding to a close encounter. The injuries tend to be more severe, and a disproportionate number of photographers are killed. Up to 1985, at least 10 photographers were injured, one fatally, and from 1986 to 1992, at least four were injured, two fatally.[30]

Most people attacked by grizzly bears are injured but not killed; again, the intent of the bear is simply to remove a perceived threat, not to prey on the individual (Figure 32-12). From 1900 to 1979, 19 human deaths resulted from grizzly attacks documented in the national parks in North America, and 22 deaths occurred in Alaska outside the parks.[30,40] A Wikipedia file tracking human deaths in North America from grizzly bear attacks cites 10 deaths in the 4-year period from June 2010 through October 2014; all these citations are verifiable, but this list may not be complete.[68] Some fatalities were victims of defensive attacks, whereas others were probably the result of predation. It is important to ask why grizzly bears do not prey on humans more often. As a potential prey species, humans are predictable and abundant, easy to catch and kill, and easy for a grizzly bear to consume.

Historical evidence suggests that grizzly bears did not routinely prey on humans except in unusual circumstances. In 1860, a smallpox epidemic struck a small band of Stoney Indians (Assiniboine tribe) camped in the Yarrow Creek drainage in Alberta, Canada.[56] Grizzly bears began scavenging on the dead left on the ground as the tribe moved to the next drainage. The bears followed them to their next encampment and began preying on survivors. For years, the Indians avoided this area for fear of being eaten by bears that had "learned" to prey on humans.

Since about 1900, when reasonably accurate records were first kept, predatory attacks on humans by grizzly bears generally have been rare, sporadic, and isolated events.[6] However, a disturbing trend was first recognized in the 1960s. Between 1967 and 1986, 12 deaths were inflicted by grizzly bears in Banff, Glacier, and Yellowstone national parks. In each case, the bear was conditioned to humans' food (regularly seeking out and obtaining it) or habituated to human presence (not readily fleeing). Nine of the victims were partially consumed, and eight deaths were classified as predatory events.[30] During the same period, however, many bears with these same behavioral traits did not prey on humans. Conditioned and habituated behavior may predispose some grizzly bears to prey on humans under certain but poorly understood circumstances. The relationship between conditioning and habituation appears strong but is not conclusive. The bear involved was not always known, and the terms *conditioned* and *habituation* are both borrowed from learning theory and have never been precisely defined by wildlife biologists. This potential relationship, however, has significantly influenced grizzly bear management. Currently, the primary thrust is to prevent bears from obtaining human foods and from routinely being around people and human developments.

Grizzly bears may also mistakenly perceive a person as one of their normal prey species. Five such incidents have been documented. Two victims were killed by grizzly bears while making prey calls to lure in other predators. Two victims were attacked while field-dressing a game animal, and the fifth was attacked while carrying the hide of a deer draped over his shoulder. Clearly, persons should not look, smell, or sound like a prey species when in grizzly bear country.

FIGURE 32-11 Photographers dangerously close to bears in the wild. *(Courtesy Luanne Freer.)*

BLACK BEARS

Black bears are the most numerous and widely distributed of all North American bears (Figure 32-13). They occur in more than 30 of the lower 48 states, from Maine to Florida and from California to Washington. Recently, a black bear was recovered in Nebraska, where none had been seen in more than 100 years, adding to the growing numbers of large carnivores reoccupying previously native territory in the Great Plains.[35] Black bears also occur throughout Canada and Alaska, extending up to the tree line below the Arctic Circle. They are well adapted to an arboreal habitat and prefer to eat vegetation, carrion, and mast (nuts, acorns), with small mammals and insects accounting for less than 5% of their diet.[18] Black bears have been filmed fishing in southeast Alaska,[5] and I have observed them fishing in Yellowstone

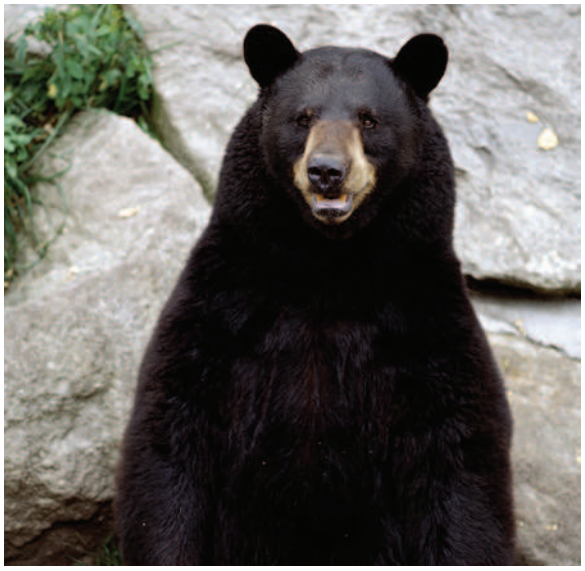

FIGURE 32-13 Black bear. *(Courtesy Timothy Floyd.)*

National Park, evidence of their ability to adapt to available food sources.[20,21]

A trend of increasing black bear–human conflicts in New Jersey prompted lawmakers to introduce legislation to prohibit homeowners from putting their food waste or other bear-attracting refuse at the curb without a bear-resistant container. A year earlier, the New Jersey Division of Fish and Wildlife reported a 58% increase in the number of bear complaints from the previous year, most involving bears rummaging through trash.[17] Colorado reported increases in black bear–human conflicts from 1986 to 2003, and several municipalities now require bear-resistant waste containers for home use.[3]

Between 1960 and 1980, more than 500 people were injured by black bears, but at least 90% of these episodes resulted in minor scratches or bites inflicted by bears that were either conditioned to human foods or habituated to human presence.[30] The number of victims of black bear attacks has declined significantly during the past 25 years, largely because of aggressive bear management in and around national parks that discourages the feeding of black bears and removes those bears that seek out human foods. Injuries as a result of close encounters are extremely rare, and in contrast to female grizzly (brown) bears, female black bears display little aggression in defense of their young and rarely cause injury. They have short, sharp radial claws better adapted for climbing trees than for attacking humans. They often retreat rather than attack, even in defense; thus hunters using dogs can "tree" black bears.[18]

Whereas grizzly (brown) bears sometimes prey on humans at night, black bears occasionally prey on humans during the daytime. In North America, from 1900 to 2009, at least 63 people were killed by black bears, with predation considered the motivation in many cases, and a male (bear) involved in 92% of attacks.[34] In many cases, attacks occurred in remote areas outside park boundaries; experts conclude that neither conditioning nor habituation was a major factor.

In recent years, black bears have attempted to prey or have preyed on humans; some attacks occurred at night while the victims were asleep. In one case, the bear broke into a camper and pulled the victim out, and in another the bear entered a wooden teepee ("wickiup") and dragged the victim out by her foot.[51] In most attacks, the black bears were driven away by aggressive actions by the victims and their companions, such as yelling and throwing objects.

POLAR BEARS

Polar bears are distributed in a circumpolar fashion around the Arctic Circle and subsist almost exclusively on a diet of seals (see Figure 32-2). In winter, these bears feed primarily while foraging on ice-covered polar seas. Some southern populations live on land during the summer in a state of waking hibernation and starvation. Polar bear–inflicted injuries are much less frequent than those by grizzly (brown) or black bears, primarily because the remote and harsh environment of polar bears is infrequently visited by humans. From 1973 to 1987, three people were injured (one fatally) in Norway,[25] and from 1965 to 1985, 20 people were injured (six fatally) by polar bears in Canada.[31] In 2009, a polar bear attacked a woman at the Berlin Zoo after she climbed a fence and jumped into its habitat during feeding time; the attack and rescue were broadcast on television and online (Figure 32-14).[12] The number of injuries in the wild would probably be much higher except that most people in polar bear habitat are armed, and in the majority of aggressive encounters the bear is killed before causing injury.

Polar bear–inflicted injuries have been classified into two general categories. The major one is predation, primarily by young adult and adult males. In these cases, five of the six victims who died were probably killed instantly. The other category is injury by adult females defending their young. These episodes are typically brief and nonfatal, which supports the theory that the bear is removing a perceived threat. In more than 90% of aggressive encounters with polar bears, an attractant, such as food, garbage, or carcasses, was considered contributory.[31]

BEARS ON OTHER CONTINENTS

Available data on attacks by bears on other continents are much less complete than those for North American bears. In Europe the brown bear has coexisted with humans much longer than those in North America. (In some parts of North America, the brown bear is called a grizzly bear, but they are genetically the same species.) As a result, its behavior is less aggressive and more like that of black bears. Numbers of European brown bears are extremely low; the animals are highly cryptic and nocturnal and thus are rarely seen or encountered. In Scandinavia, human injuries and fatalities coincide with bear den entry (October and November), when they are known to be more aggressive.[57] In Turkey, more than two-thirds of close encounters between brown bears and humans resulted in no harm to bear or human, and bear attacks were rare and only occasionally led to nonfatal injuries.[1] Human injury by brown bears in Europe was almost nonexistent until 2004, when a rabid brown bear killed two and injured six persons in Romania.[4]

The brown bears in the former Soviet Union live in vast, relatively undeveloped areas and appear to have aggressive responses against humans similar to those of North American brown bears. Many human injuries from brown bear attacks, including deaths, may be related to bears injured by sport hunters.[10]

The panda bear (*Ailuropoda melanoleuca*), commonly known as the giant panda (Figure 32-15), lives in the temperate climate

FIGURE 32-14 This woman had jumped into the polar bear exhibit at a zoo in Germany but was fortunately rescued, although she sustained significant injuries from the bear's attack. *(Courtesy B.Z./WENN.com.)*

FIGURE 32-15 Panda bear.

of the bamboo jungles distributed along the eastern rim of China's Tibetan Plateau. It is one of the most recognized bears in the world, with a distinctive white and black coloration. It is a relatively poor climber but will climb trees on occasion to avoid danger. During winter months, the panda bear migrates to lower elevations where food remains plentiful, thus avoiding the need to hibernate.

The panda bear is primarily a vegetarian. About 99% of its diet consists of stalks, leaves, and shoots of only two bamboo species.[58] The panda has an enlarged wrist bone that serves as an opposable digit, much like a thumb. This evolutionary adaptation enables the panda to efficiently hold and strip bamboo stalks. Because bamboo is a poor-quality food, the panda must compensate by eating large amounts. Each day it feeds up to 12 hours. The panda bear is shy and reclusive, representing a minimal threat to human safety in the wild.

The spectacled bear (*Tremarctos ornatus*) lives in the tropical climates of the Andes Mountains along the northwest border of South America. It is one of two bear species that live below the equator. The spectacled bear has a distinctive white coloration around its eyes. It is an excellent climber and spends most of its time in trees eating fruit; it often builds nests and rests in trees as well. Because its source of nutrition is abundant year-round, it does not hibernate. Spectacled bears are relatively small and shy. Encounters have been described as extremely rare and usually pose minimal threat to human safety. A survey of Columbian government officials reported 66 attacks or depredation by Andean bears, which the authors explained as being caused by recent increases in the level of human activities in that region.[38]

The sloth bear (*Melursus ursinus*) lives in the subtropical forests of Nepal, Bangladesh, Bhutan, India, and Sri Lanka (Figure 32-16). It has a disheveled appearance because of its long, shaggy fur coat. In some of its range, the sloth bear coexists with elephants, wild boars, leopards, tigers, greater one-horned rhinoceri, and Asiatic black bears.

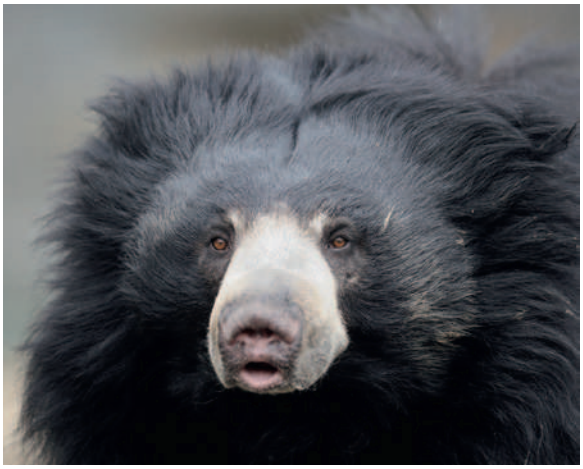

FIGURE 32-16 Sloth bear.

The sloth bear is a special type of insectivore, termed *myrmecophagous,* because it feeds primarily on ants and termites. It is uniquely adapted for this feeding behavior. Without the two upper incisors, and with an elongated and raised hard palate, mobile lips, and nearly naked snout, the sloth bear can blow away dust to expose termites and create a strong sucking force to feed. It can dig out insect burrows with its long claws, and its coat protects it from insect stings.

After the Russian brown bear, the sloth bear may be the most dangerous bear species in Europe or Asia. Approximately one person is seriously injured or killed by a sloth bear in Chitwan National Park in Nepal each year.[23] In the remote regions of western Nepal, at least one villager is seriously injured by a sloth bear every other year. Most of these injuries are the result of a close encounter, and the victims receive wounds to the head and neck. No predatory behavior has been reported.

In the North Bilaspur Forest of India, 137 attacks by sloth bears (including 11 fatalities) occurred between April 1998 and December 2000. Most (54%) incidents took place during the monsoon season, with 45% in early morning. Victims sustained multiple injuries in most cases (52%), but solitary injuries to leg (25%), hand (12%), and head (8%) regions were also recorded.[2]

Sloth bear researchers in Nepal work exclusively while riding elephants because of their concern about attacks from rhinoceri, sloth bears, and tigers, in that order.[39]

Asiatic black bears (*Ursus thibetanus*), also known as Tibetan black bears or Himalayan black bears, occupy the broad-leafed forests throughout a large portion of southern Asia, from Pakistan across northern India and into China and Southeast Asia (Figure 32-17). Separate populations also occur in eastern Russia, Korea, Taiwan, and Japan. Some of their range overlaps with those of brown bears, sloth bears, and sun bears. The Asiatic black bear

FIGURE 32-17 Asiatic black bear. *(Courtesy Marilynn G. French.)*

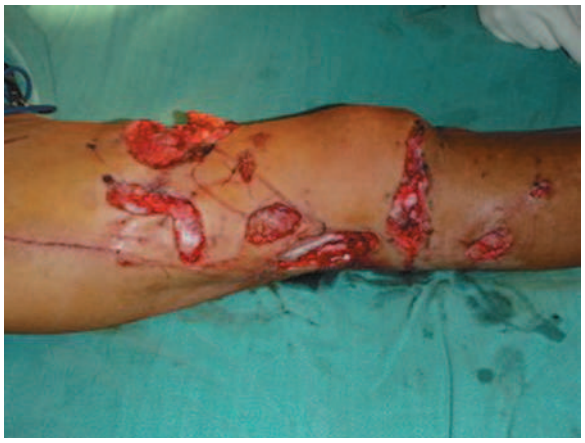

FIGURE 32-18 Himalayan black bear injury to Bhutanese farmer, who disturbed the bear feeding on a calf. The patient sustained an open fracture/dislocation of the knee and multiple lacerations. *(Courtesy Sam Baker.)*

is sometimes called the "moon bear" or the "white-breasted bear" because of the crescent-shaped white coloration on its chest.

The Asiatic black bear is a dietary generalist and feeds on a wide variety of plants, insects, and animal matter. It is a good climber and often forages and rests in trees. Unlike pandas and spectacled bears, these bears hibernate during the winter months. They are hunted extensively for illegal trade of bear parts and have been declared a threatened species; as such, they rarely come into human contact. A recent decrease in natural habitat, however, has increased the chances of bear-human interaction, resulting in human injury (Figure 32-18). One report documented five cases of serious injuries requiring hospitalization that occurred during a 1-year period.[66] In Kashmir, India, between 1990 and 2007, 417 cases of Asiatic black bear attack were recorded. The victims were predominantly young to middle age (96.8% of cases) and predominantly male (80.33%). Incidence of attack was highest during July to November (76.82%), and most of the attacks (97%) occurred during daytime hours when the victims were tending agricultural crops or livestock or gathering firewood.[64] The face (80.57%) was the most common body part injured (Figure 32-19), followed by the head (54.67%), and the mortality rate was 2.39%.[53] Another source quoted approximately 150 bear attack reports per year to tertiary care hospitals in Kashmir, a state with a population of 5.4 million persons.[15]

The sun bear (*Helarctos malayanus*) is the smallest of all bear species, rarely weighing more than 45 kg (100 lb) (Figure 32-20). It occupies tropical regions in Borneo, Burma, Java, Malaysia,

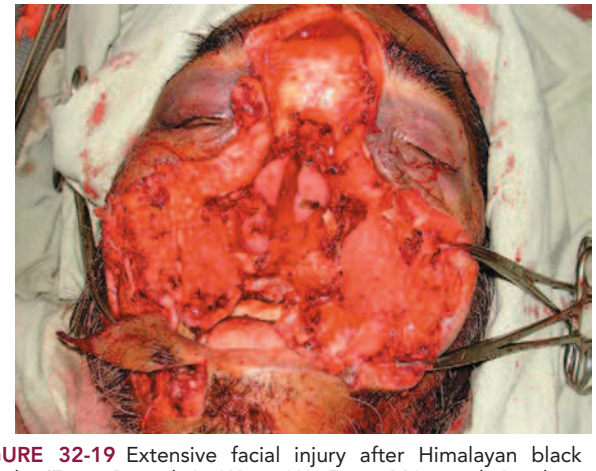

FIGURE 32-19 Extensive facial injury after Himalayan black bear attack. *(From Rasool A, Wani AH, Darzi MA, et al: Incidence and pattern of bear maul injuries in Kashmir,* Injury *41:116, 2010.)*

FIGURE 32-20 Sun bear. *(Courtesy Marilynn G. French.)*

Sumatra, and Thailand. As with the spectacled bear, the sun bear is equatorial because part of its range extends below the equator. It has a white to cream-colored, horseshoe-shaped marking on its chest, providing its common name. In some localities it is called the honey bear. It has a long, slender tongue, an adaptation for extracting honey from beehives. Its claws are long and more sharply curved than those of other bears, enabling it to be a proficient tree climber, where it can easily hang upside down from a branch. The sun bear is rarely seen and represents almost no threat to humans.

PREVENTION AND RISK REDUCTION

Much literature about safety in bear country involves feedback from attack victims,[13,30,31,40,45] who are generally unfamiliar with bear behavior and whose interpretations of events may reflect cultural biases. In several cases, circumstances surrounding the attack changed significantly with each telling, usually reducing the victim's culpability. Because of potential litigation, some victims have told their stories only through an attorney. Caution must be used when compiling and analyzing such "data."

Recommendations for avoiding bear attacks have been drawn primarily from what attack victims did "wrong." Because most people who live, work, and regularly vacation in bear country are never injured, it is equally important to understand what they have done "right." Unlike bear attack victims, these people have successfully navigated grizzly country without being injured. Although this information is not as readily available as are attack records, it is critical to our knowledge of grizzly bear–human interactions. Box 32-1 lists website resources for how to prevent bear attacks.

From 1900 to 1985, 115 human injuries were reported from black, polar, and grizzly bear attacks in Alaska, but only two victims were natives,[45] which suggests that people's behavior is important in determining how to coexist safely with bears. Safety in bear country involves four levels of interaction: (1) avoiding an encounter, (2) reducing the chances of being attacked after an encounter, (3) reducing the severity of injuries received if attacked, and (4) reducing the chances of becoming prey to a bear.

AVOIDING AN ENCOUNTER

The following actions can significantly reduce the chances of having a close encounter with a bear:

1. Make noise so the bear knows a person is present. This requires only casual conversation to prevent startling a bear at close range. The voice may have to be amplified somewhat while traveling along a noisy stream or a windy ridge. Foghorns have been used successfully in Alaska; commercially marketed "bear bells" may not be sufficiently loud (Figure 32-21).
2. Remain alert in bear country, and be aware that the terrain and environment may hamper a bear's ability to detect a

BOX 32-1 Website Resources for How to Prevent Bear Attacks

The Essentials for Traveling in Bear Country
http://www.wildlife.alaska.gov/index.cfm?adfg=bears.bearfax

If You Encounter a Bear?
http://www.bear.org/website/
(North American Bear Center, nonprofit website with education about North American black, brown and polar bears)

Encountering a Bear
http://fwp.mt.gov/recreation/safety/wildlife/bears/bearEncounter.html

What If I See a Black Bear?
http://fwp.mt.gov/recreation/safety/wildlife/bears/bearEncounter.html

Spray More Effective Than Guns Against Bears
http://www.bear.org/website/bear-pages/pepper-spray.html

Andean (Spectacled) Bears
http://www.andeanbear.org/
(Ecuadoran nonprofit website providing education about Andean bears, avoiding conflict, and preserving the population)

I Want To Know More About Avoiding Close Encounters with Polar Bears
http://www.polarbearsinternational.org/about-polar-bears/essentials/attacks-and-encounters
(Nonprofit website provides education about polar bears, including conflict avoidance)

human by sight, smell, or sound. The terrain and environment may also hamper your ability to see or hear a bear before it discovers you. An "upwind bear" is more likely to be surprised, as is one in heavy forestation or near loud rushing water, in the rain, or in fog. Avoid ripened berry patches, streams with spawning fish, and elk calving grounds.[18] A flock of ravens may indicate carrion and the presence of feeding bears.

3. Always use good judgment to avoid a potentially dangerous situation. If fresh bear signs are seen, such as tracks (Figure 32-22), droppings, tree scratchings (Figure 32-23), or a carcass (or even scavenger activity indicating that a carcass may be nearby), consider that a bear is in the vicinity and take an alternate route. If the bear is seen first, slowly and quietly retreat to safety; consider aborting the trip or taking an alternate route. Do not approach bears, or any wild animals, too closely for a better view or photograph.

Bears in bear-bear confrontations (Figure 32-24) demonstrate signs of aggression and annoyance. These include standing or turning in profile to appear larger and intimidating, vocal hissing and jaw popping, "yawning" (Figure 32-25), and head swinging (Figure 32-26).[18]

FIGURE 32-22 Bear prints. *(Courtesy Timothy Floyd.)*

FIGURE 32-23 Tree scratchings from bear claws. *(Courtesy Timothy Floyd.)*

FIGURE 32-21 One hopes not to find bear bells within or on bear scat. *(Courtesy Timothy Floyd.)*

FIGURE 32-24 Brown bears spar for a prime fishing spot. *(Courtesy Luanne Freer.)*

FIGURE 32-25 Yawning behavior may indicate agitation in a bear. *(Courtesy Timothy Floyd.)*

FIGURE 32-27 Curling into the fetal position to defend against a bear attack. *(Courtesy Marilynn G. French.)*

AVOID PROVOKING AN ATTACK

The best way to avoid bear-inflicted injuries is simply to avoid surprising a bear in a close-encounter situation. Although no set of responses is guaranteed to prevent injury in a close encounter, the following generalizations may be useful:

1. Allow the bear to know you are human and not a prey species. Step away from any visual obstruction to allow the bear to see you fully. Any attempt to hide at this point will only confuse the bear, which may approach closer to identify you, thus creating an encounter at an even closer distance. It is probably best to talk in a calm voice to allow the bear to identify you as a human.
2. Although remaining calm is difficult, do not make sudden movements or yell out, particularly with a grizzly bear. The bear may view this as an aggressive action and respond with aggression.
3. Do not stare directly at the bear. Look to the side or stand sideways to the bear. Standing your ground is important in determining the bear's response.[60] This posture tells the bear you are willing to defend yourself if necessary, and it may prevent further aggressive behavior.
4. Do not consider climbing a tree or running away. It is impossible to outrun a bear, and running may prevent the bear from correctly identifying a human and may initiate a charge. Once a bear charges, you cannot locate a climbable tree and achieve a safe height fast enough. Attempting to climb a tree may also prevent the bear from correctly identifying you as a human. Therefore, the best defense during a charge is to stand quietly and nonaggressively, and allow the bear to identify you as human and not a prey species.

In most cases, the bear aborts the charge after a close encounter without making contact or causing injury. At this point, you should leave the area, retreating in the direction opposite to that taken by the bear. If a bear continues to charge, however, resulting in physical contact, your actions depend on the species, and information from bear attack victims is useful.

REDUCING THE SEVERITY AND EXTENT OF INJURIES

If attacked by a bear, a victim can take several important steps to minimize injury. The actions taken immediately before, during, and after an attack will most likely influence the type and severity of the injuries.

Humans are rarely killed during an attack precipitated by a surprise close encounter, even though bears could do so easily and quickly. During these attacks, grizzlies are only trying to remove what they perceive as a threat, and their intent is to use only as much force as necessary. When interacting with others of their species, grizzly bears are head oriented, and they usually direct their aggression toward humans in the same manner—toward the head and neck. Therefore, the general rules to follow during a grizzly attack are to "help" the bear remove the perceived threat and to protect vital body parts, as follows:

1. Do not run, try to climb a tree, fight, or scream.
2. Drop to the ground and protect the head and neck by interlocking the hands behind the head (ear level) and flexing the head forward, either in the fetal position or flat on the ground facedown (Figures 32-27 and 32-28). Use elbows to cover the face if the bear turns you over.

FIGURE 32-26 Head-swinging behavior in a polar bear. *(Courtesy Timothy Floyd.)*

FIGURE 32-28 Prone position to defend against a bear attack. *(Courtesy Marilynn G. French.)*

3. Do not hold out a forearm or hand to ward off the attack. Bears can readily cause significant injuries to these structures.
4. Never try to look at the bear during an attack because it could expose you to serious facial injuries.
5. After the attack, stay down until you are sure the bear has completely left the area. This is extremely important. Victims who have gotten up before the bear has left after the first attack generally received more severe injuries during the second attack.
6. When you believe the bear has left the area, peek around while moving as little as possible, try to determine which way the bear went, evaluate options, and then leave the area.

In a close-encounter situation, attack victims who immediately protected themselves and did not try to resist typically received minor injuries. Victims who tried to run or fight the bear and those who left after the initial attack but before the bear had left the area typically received more severe injuries that required multiple surgical procedures, resulting in permanent cosmetic or functional disabilities.

If the attack is by a black bear, a different set of guidelines should be followed. Black bear aggression should be countered with aggression, such as shouting, yelling, throwing rocks or sticks, or whatever other means are available. The victim should never lie down in a protective, submissive position because black bears are more likely to prey on humans they encounter at close range than are grizzly bears.

The data on polar bears are less complete but suggest that attacks by females with offspring are behavioral responses similar to those of grizzly females with offspring. The attacks are defensive, brief, and result in nonlethal injuries. In addition, the bear typically leaves shortly after the incident. If a polar bear is alone, however, a person should assume it is a male, whose behavioral response is most likely to be predatory, and should use any aggressive response available.

PREVENTING PREDATORY BEHAVIOR

The most important way to reduce the chance of being preyed on by a bear is to avoid anything that may attract a bear to the campsite while the occupants are sleeping:

1. Avoid camping along bear travel corridors or at seasonal feeding sites.
2. Avoid campsites littered with human refuse.
3. Use proper food storage to render human food unavailable to bears. Bear-resistant food storage containers are often provided at designated campsites in bear country (Figure 32-29). Instructions for setting up a safe campsite and for hanging food at sites not equipped with bear-proof containers may be found at http://www.nps.gov/yell/planyourvisit/upload/bctrip-planner_2012.pdf.
4. Reduce food odors by cooking and eating at a site at least 90 m (100 yards) away from the sleeping area. Do not sleep in clothes worn when cooking and eating.
5. Do not leave garbage or food buried or poured into the ground at the campsite. This can cause problems for future campers at this site. This website lists different manufacturers of bear-proof storage and garbage cans: http://www.state.nj.us/dep/fgw/bearcont.htm.

There is little chance of a bear entering a campsite to prey on humans, but everyone in the camp should be familiar with a contingency plan. Everyone should know the area, even in the dark, and should be aware of potential escape options, such as climbable trees or rocky ledges. Everyone should sleep in a tent because it offers a boundary of protection and may deter an inquisitive bear from walking directly to the campers. Although no study has proved its effectiveness, some people build a brush barrier around the tent to prevent a bear from readily approaching it.

Sleeping bags should be kept at least partially unzipped to facilitate a quick exit. In several instances, a victim trapped inside a sleeping bag has been dragged away from a campsite by a bear.

Each tent should be equipped with a flashlight. Pepper spray is useful, as well as a firearm, unless prohibited in that area. Again, a bear that enters a tent or picks up a sleeping camper is trying to prey on that person, so all available defenses should be used.

The behavior of a predatory bear is different from that of a bear responding to a close encounter. During a close encounter, a bear's response is driven by a defensive reaction, which can be aggressive and injurious. In contrast, the behavior of a predatory bear is driven by the desire for food. The bear is not looking for a confrontation or fight but rather a victim to drag from camp, usually only a few hundred feet, and to consume. Predatory grizzly and black bears rarely kill their victims before consuming them. They concentrate on soft tissue or visceral consumption, and victims frequently remain alive for an hour or more. Therefore, a quick, aggressive, and unified response by companions may save the victim's life. Surprising, yelling, throwing rocks, or striking the bear with a stick has been effective in driving bears away from victims. Approaching a predatory bear in the dark while it is feeding on a human is risky, but it is probably the victim's only chance for survival.

In contrast, the victim of a predatory attack by a polar bear is typically killed instantaneously, so prevention of such attacks is the only chance for survival. In all predatory attacks by polar bears, all defensive measures must be considered, including guns where permitted.

FIGURE 32-29 Standard government-issued bear-resistant food container. *(Courtesy Marilynn G. French.)*

SPECIAL CONSIDERATIONS

Menstruation

In August 1967, two women were killed in separate events on the same night by different grizzly bears in Glacier National Park. The postmortem examination showed that one had been menstruating. The assumption that menstruation may be a precipitating factor in bear attacks has unfortunately become solidly ingrained into popular opinion. Hysterical coverage by the media enhanced this misconception, and the scientific question was left unanswered by both scientists and government officials.[7] This is the only serious attack on a menstruating woman that has been documented in North America, and even the official investigating team at that time concluded that menstruation did not appear to have played a major role.[30]

A study of polar bear response to menstrual odors was published in 1983.[14] Although it was not designed to test adequately the hypothesis that menstruating women were more likely to be either attacked or preyed on by bears, the press came to this conclusion.

Black bear researchers in North America report no evidence of black bears attacking or being attracted to menstruating women.[54] Furthermore, no evidence links menstruation to any of the 21 grizzly bear attacks in Yellowstone National Park from 1980 to 1994.[28,29]

Sexual Activity

A common concern among backcountry users is that sexual activity may attract bears and make them more aggressive toward

campers. As with menstruation, these fears are based on hysteria and folklore. No anecdotal or scientific evidence supports this hypothesis.

Pepper Spray

Over the past few decades, because of the desire for protection against aggressive bears, several chemical dispersants have been investigated for backcountry users. The most effective method was an aerosol spray containing capsicum oleoresin, a derivative of red pepper. Captive grizzly bears were sprayed in the face at close range when they charged the researchers (who were outside the cage). Under these controlled conditions, red pepper spray was found to be highly effective in deterring a charging grizzly bear.

Pepper spray (5% to 10% capsicum oleoresin) is commercially available as personal protection against aggressive animals.

By 1985, pepper spray was used in the field against aggressive black and grizzly bears in 66 documented cases.[32] In general, it appeared more effective in deterring bears that charged after a close encounter than against food-conditioned bears in search of food. During the 1990s, however, most professional outfitters and guides in the northern Rocky Mountains began carrying pepper spray to deter aggressive grizzly bears, preferring spray over firearms. A retrospective study of bear spray incidents in Alaska from 1985 to 2006 included data from 83 incidents involving brown, black, and polar bears. A defensive spray terminated a bear's undesirable behavior in 92% of brown bear conflicts, 90% of black bears events, and 100% of polar bear interactions. Of persons carrying spray, 98% were uninjured by bears during close-range encounters.[61]

However, carrying pepper spray does not substitute for knowledge of bear safety and good judgment to avoid aggressive encounters. If carried, spray must always be readily available, either in a belt-mounted holster or on a chest strap. It should be test-fired, and the user should practice drawing and firing it regularly (Figure 32-30). Despite a manufacturer's claim that pepper spray has an effective range of 9 m (30 feet), the effective range under field conditions is significantly less when there are headwinds or crosswinds. Care should be taken to purchase pepper spray tested for use on bears, because the volume, pressure, and range of spray is designed differently for a charging bear than for a canine or human attacker.

Unfortunately, people who failed to read instructions have used pepper spray in the same way they use mosquito spray. Despite its obnoxious and caustic smell, some sprayed it on themselves, as well as their tent, sleeping bags, and ground around their campsite. Once the aerosol has been released, the capsicum begins to lose its potency, and soon the active ingredient dissipates. At this point, bears may investigate the smell of pepper. Pepper spray thus used becomes a bear attractant rather than a deterrent. One manufacturer of pepper spray (UDAP Industries, http://www.udap.com) provides a detailed instructional pamphlet on its proper use.

FIGURE 32-30 Discharging a canister of pepper spray. *(Courtesy Marilynn G. French.)*

FIGURE 32-31 Cranial vault of a bear. *(Courtesy Timothy Floyd.)*

Pepper spray should be aimed toward a charging bear and discharged when the bear is within 6 to 9 m (20 to 30 feet). The person should continue spraying until the bear has stopped its charge, keeping the sprayer aimed at the bear in case the animal charges again. This continues until the bear has left the area. If the pepper spray is depleted, the best defense if the bear attacks is to lie down, cover the face, and offer little or no resistance. Again, there is no guarantee that pepper spray (or anything) will prevent injury by an aggressive bear.

If pepper spray is accidentally discharged into a person's face, it stimulates facial nociceptors and causes eyelid, ocular, and facial muscle spasms, which may result in temporary blindness. The victim should not rub the eyes (to avoid corneal abrasions) and should irrigate the eyes and skin vigorously with water for at least 15 minutes. Intraoral burning may be relieved by swishing and spitting milk or another casein-containing food product.[18]

Firearms

Many people consider carrying firearms for protection when they enter bear country. Guns can be useful in some situations. However, the anatomic target area to kill a grizzly with a shot to the head is only about 30 cm^2 (12 square inches). The cranial vault is narrow and sloped caudally (Figure 32-31). A bear initiating a charge from a distance of about 45 to 55 m (50 to 60 yards) will take only 4 to 5 seconds to reach its victim.

Unless a proficient marksman, a person is unlikely to access a weapon, release the safety, aim accurately, fire, and hit a small target in a very brief time under stress. Also, even if a shot could be fired, it probably would only wound the bear. Wounding a charging bear changes its behavior and may make its attack even more aggressive. Because of these factors, pepper spray should be considered as a nonlethal alternative to guns, especially when traveling in places where loaded guns are not permitted, such as national parks.

A recent study of 444 armed people and 367 black, grizzly, and polar bear incidents revealed no significant difference in rate of success between handguns or long guns in terminating an aggressive bear advance. In addition, persons equipped with firearms had the same injury rates in bear conflicts whether their firearms discharged or not.[62] The effective ranges of a pistol and pepper spray are about the same, but it is easier to hit a moving target with pepper spray because of its shotgun-like aerosol pattern.

Dogs

In most national parks, dogs are not permitted in backcountry settings. Unfortunately, rare and questionable accounts report a dog stirring up a grizzly bear, then running back to its owner with the bear in pursuit. However, most outfitters, guides, and hunters report positive experiences with dogs in grizzly bear country. Their dogs are generally well trained and have been raised in wilderness environments. Most of these dogs can effectively deter grizzly and black bears from coming into a camp. Although no study has been conducted on the use of untrained

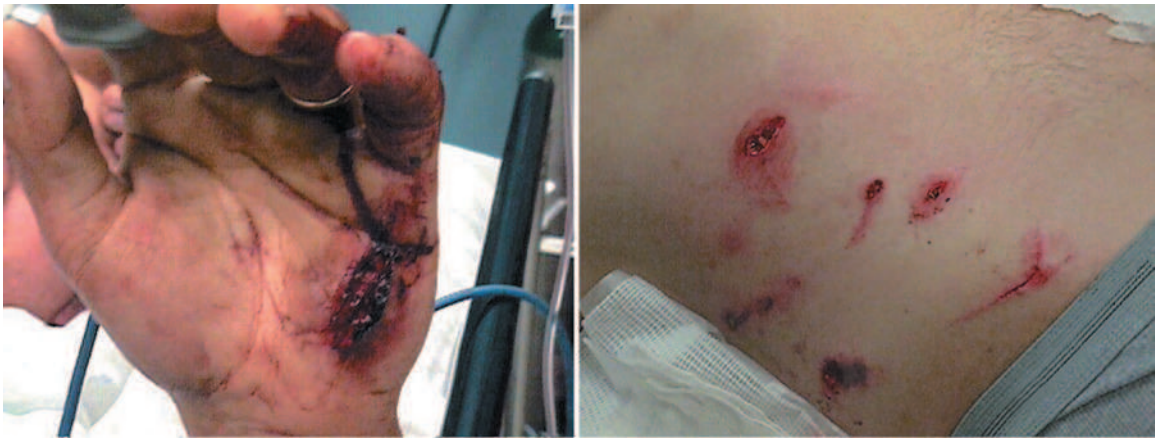

FIGURE 32-32 Bite wound injuries typical of a bear attack. *(Courtesy Luanne Freer.)*

dogs to deter aggressive bears, most people who spend considerable time in grizzly bear country use their dogs for this purpose.

Horses

For individuals concerned about an aggressive bear encounter, another option is using horses. No one has been injured by a grizzly or black bear while riding a horse. Horses that frequently travel in bear country are the best to use, because they generally do not react unpredictably and endanger the rider when they encounter bears. Although horses may protect against aggressive grizzly bear encounters, riders may still be injured by the horse. People are seriously injured or killed in horse accidents each year in the northern Rocky Mountains.

Hunter Safety

Many people participate in sport hunting in bear country each year. Some hunt for bears, but most hunt for other game species.

For bear hunters, the risks are obvious. Bear hunters intentionally break bear safety rules to close in on prey. The most dangerous situation, however, is after they shoot and injure a bear. They have an ethical obligation to track the wounded animal and kill it; this is when most bear hunters are injured. This confirms that guns are not completely effective in preventing bear injury. An injured bear may take refuge in heavy cover, then charge when the hunter is at close range. With so little time, a surprised hunter often cannot fire a lethal round, and even when shot, the bear can continue its attack and cause significant injury before it dies.

Hunters of other game species in bear country are at significant risk of close encounter and injury. Besides violating bear safety rules, they frequently become preoccupied with the stalk and forget they may encounter a bear. During the 1990s, more than one-half the people injured by grizzly bears in the Yellowstone ecosystem were elk hunters. Some injuries occurred during the stalk, but other factors contributed. Grizzly bears in this ecosystem have learned the association between gunfire and available food. After an elk or other game (moose, deer, bighorn sheep) has been killed, hunters field-dress their kills and leave edible remains (gut piles) on the ground. In several cases, bears approached the kill site before the hunters completed this process. In other cases, an elk or animal was field-dressed late in the evening and then hung in a nearby tree. When the hunters returned the next morning, they encountered a grizzly bear that had claimed the gut pile or the carcass. Hunters must assume that under these circumstances, at least one grizzly bear will be at the site, and they must approach cautiously, preferably on horseback.

Bow hunting represents another high-risk activity. In most states, bow hunters are not allowed to carry a firearm as a backup weapon. They also tend to violate bear safety rules to set up a shot. Elk hunters blow an artificial elk call (a bugle or a cow call) to lure in bull elk. This also alerts grizzly bears that prey on adult male elk (bulls) during the breeding season. For protection, bow hunters should (1) hunt from a tree stand, which provides some protection from grizzly bears, who are poor tree climbers, and (2) carry pepper spray and be prepared to use it.

BEAR-INDUCED INJURIES

Bear-inflicted injuries range from minor, treated on an outpatient basis, to complex, requiring hospitalization and surgery, typically resulting in significant cosmetic and functional disability. In this regard, bear attacks are similar to most other animal attacks, particularly those inflicted by large animals.

The character of such injuries is determined in part by the three main sources: teeth, claws, and paws. The teeth of bears, especially the canines, are large and sturdy. Although the teeth are not particularly sharp, the power of the jaw muscles allows the teeth to penetrate deeply into soft tissues and fracture with ease facial bones and bones of the hand and forearm. The trauma characteristically results from punctures, with shearing, tearing, and crushing forces (Figure 32-32).

The claws are another important source of trauma (Figure 32-33). Although the claws on the front pads can be as long as human fingers, they are not particularly sharp on grizzly and polar bears. The bear's shoulders, however, provide the force and speed that allow claws in a scraping maneuver to cause significant soft tissue damage resulting in deep, parallel gashes. Because black bear claws are sharper and more curved, the cuts tend to have sharper, less ragged edges.

The bear paw is capable of delivering a powerful force, resulting in significant blunt trauma, particularly to the head and neck, rib cage, and abdominal cavity, the latter site particularly with solid-organ rupture. Therefore, victims of bear attacks should be evaluated for occult blunt trauma.

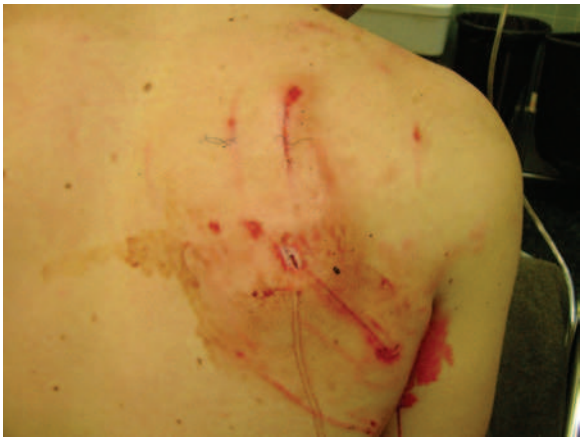

FIGURE 32-33 Claw markings from a bear attack. *(Courtesy Luanne Freer.)*

Several victims of a bear attack were further injured when a companion accidentally shot them while trying to kill the attacking bear.[27] Others were injured when they fell out of a tree while escaping a bear; some sustained long-bone fractures. At least two persons in North America have been killed by such falls; in both incidents the bear did not attack the victims once they fell to the ground.

WOUND MANAGEMENT

The specifics of initial wound treatment are determined in part by available medical equipment and the location where the patient is first received. Stabilization of the patient remains the primary objective. All victims of bear attacks should be considered to have major trauma and transported to the most appropriate facility after stabilization.

By the time most bear attack victims reach medical care, their injuries are relatively old. Bear-inflicted injuries are often occult, producing greater deep structure involvement and tissue necrosis than initially expected. Internal injuries from either direct penetration (claws, teeth) or blunt trauma are common. Neurovascular injuries must be considered with trauma to the extremities, and neurosensory and cosmetic injuries are common with facial trauma.

ANTIBIOTIC THERAPY

Only a few published studies address the oral flora of black or grizzly bears.[19,26,50] The bacterial spectrum of black bear– and grizzly bear–caused infection appears similar to that of dogs, although anaerobes (common in human, dog, and cat bites) are only rarely reported in survivors of bear attack.[41,42,55] Liu and Hsu[43] reported a 4-year-old who developed chronic osteomyelitis after being bitten by a bear in captivity. The wound grew *Prevotella oralis, Streptococcus viridans,* and *Propionibacterium acnes*. There is no evidence that bear attack victims develop rare or unusual septic complications from unknown pathogens, with the exception of a single reported case of an atypical mycobacterial infection after a brown bear bite in Finland.[42]

The use of antibiotics shortly after the injury but before clinical evidence of infection is guided by risk assessment. The usual risk factors should be assessed (Box 32-2).[8] However, the blunt trauma, deep punctures, and shearing-tearing forces typical of bear attacks create significant tissue ischemia and necrosis that may not be apparent on initial examination. In one study, almost 50% of bear attack victims (four of nine) developed clinical infections.[55] Victims of bear attacks deemed to be in a moderate- to high-risk category should be treated with broad-spectrum agents to cover *Staphylococcus aureus* and gram-negative rods in addition to anaerobes. However, adequate wound debridement and cleansing are instrumental in reducing the infection rate. For prophylactic antibiotic recommendations, see Chapter 30, Table 30-3. Treatment of established wound infection should follow guidelines for empirical antibiotic use (see Chapter 30, Box 30-5).

RABIES

Although rare, rabies has been documented in black bears in the Canadian provinces of Alberta, Ontario, Quebec, and Northwest Territories,[67] and cases have been reported in the U.S. states of Maryland, Pennsylvania, Arizona, New Jersey, and Virginia.[9,36,46,63]

Scientists suggest a possible link between the timing of rabies infection (early in the season) and hibernation, proposing that the bears may have been bitten by rabid animals while they hibernated, or that the stress of coming out of hibernation could have induced latent virus from an exposure before hibernation. A rabid polar bear in Canada remains the only documented case reported in polar bears.[65] A rabid brown bear killed two men and injured six others in Brasov, central Romania, in 2004.[4] There are no reports of clinical rabies in North American brown bears, but rabies-neutralizing antibody was documented in one brown bear;[48] the positive titer is thought to have resulted from ingestion of an oral wildlife rabies vaccine and not from infection with rabies virus.

Although rabies in bears is exceedingly rare, the U.S. Centers for Disease Control and Prevention (CDC) recommends rabies immunization for victims attacked by wild carnivores. Therefore, all victims of bear attacks should receive the standard informed-consent discussion of the risks and benefits of rabies immunization.

BOX 32-2 Risk Factors for Infection from Bear (Animal) Bites

High Risk

Location

Hand, wrist, or foot
Scalp or face in infants
Through-and-through bite of cheek
Bites over vital structures (e.g., artery, nerve)
Bites over a major joint

Type of Wound

Puncture
Tissue crushing that cannot be debrided

Victim Characteristics

Older than 50 years
Asplenic
Chronic alcoholic
Altered immune status
Diabetic
Peripheral vascular insufficiency
Chronic corticosteroid therapy
Prosthetic or diseased cardiac valve
Prosthetic or seriously diseased joint

Low Risk

Location

Face, scalp, ears, or mouth
Self-bite of buccal mucosa

Type of Wound

Large, clean lacerations that can be cleansed
Partial-thickness lacerations and abrasions

Victim Characteristics

Younger than 50 years
Good medical health

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CHAPTER 33

Alligator and Crocodile Attacks

BENJAMIN B. CONSTANCE AND MARK A. READ

People have a deep-seated fear of wild animals that have the capacity to injure or kill prey. These fears are compounded by a poor understanding of the true risks of attack and saturation exposure by the media. Attacks by alligators and crocodiles fall into this category. In addition to their fearful appearance, they are among the few animal species that will attack and kill humans unprovoked.[25] Evidence can be found in paleontologic references that crocodilians preyed on human ancestors.[10] Crocodilians have been feared and worshiped in ancient societies, such as the Australian Aborigines, Iban people of northern Borneo, Cambodian villagers, ancient Egyptians, and Native Americans.[3] After World War II, alligators were increasingly hunted, and because of a decline in numbers, they were listed in 1967 on the endangered species list. Following federal protection, they were removed from the list in 1987; alligator populations in the southern United States have since increased.[18] Many populations of crocodilians, however, are in decline worldwide, particularly in undeveloped countries where the human population is increasing. With rising human habitation in mainland Africa, around the coastal zones of the Indo-Pacific, and in the southern United States, human-crocodilian interactions are likely to increase.[7]

Crocodiles, alligators, and caimans all belong within the reptilian order Crocodylia, comprising a total of 23 species separated into three families: Alligatoridae (with eight species, including alligators and caimans), Crocodylidae (14 species, including the true crocodiles), and Gavialidae (the Indian gharial) (Figure 33-1).[3] The crocodilians are classified as *archosaurs,* whose living representatives consist of birds and crocodilians, and included all extinct dinosaurs, extinct crocodilian relatives, and pterosaurs. There are morphological and anatomical differences between crocodiles and alligators. True crocodiles possess functional salt glands in the tongue (for osmoregulation) and have the fourth tooth on the lower jaw exposed, whereas alligators do not have functional salt glands, and the fourth tooth on the lower jaw fits into a socket in the top jaw. Three species of crocodilians exist in the United States, two native and one foreign.[40] The American alligator (*Alligator mississippiensis* [Figure 33-2, *A*]) is the most common species and found in most southern states, including Florida, Georgia, South Carolina, North Carolina, Louisiana, Alabama, Arkansas, Mississippi, Texas, Oklahoma, and likely Tennessee (Figure 33-3). The American crocodile (*Crocodylus acutus* [Figure 33-2, *B*]) is found only in south Florida. The nonnative caiman (*Caiman crocodilus* [Figure 33-2, *C*]) is becoming increasingly established in south Florida.[19]

Worldwide, crocodilian habitats include the southern United States, Central and South America, sub-Saharan Africa, India, Sri Lanka, southern China, the Malay Archipelago, Palau, the Solomon Islands, and northern Australia (Figure 33-4). Larger species of crocodiles include the estuarine (or saltwater) and Nile crocodiles. These two species are recognized as the most dangerous and are responsible for hundreds of human fatalities and injuries every year in Africa and Southeast Asia.[7,33]

CHARACTERISTICS, LIFESTYLE, AND HABITS

The order Crocodylia dates back 225 million years to the Mesozoic Era. Crocodilians evolved, along with dinosaurs and modern birds, from a group of animals known as *thecodonts*.[39] Crocodilians can live in captivity up to 66 years of age, with one study demonstrating that freshwater crocodiles (*Crocodylus johnstoni*) can attain age 60 years in the wild.[11,36] Crocodilians vary in size and exhibit sexual dimorphism. Adult males are much larger than adult females, with the most growth occurring during the first 5 years of life.[39] For example, the common caiman reaches only 2.8 m (9.3 feet); the American alligator reaches a maximum adult size of 4.5 m (14.8 feet) and the American crocodile, 6 m (19.7 feet). The Nile crocodile reaches 5.5 m (18 feet) and the estuarine or saltwater crocodile, 6.1 m (20 feet) (Table 33-1).[11] Breeding season varies between species, with females laying clutches of 8 to 70 eggs. Their diet is predominantly carnivorous and includes crustaceans, insects and spiders, snails, fish, frogs, birds, and mammals.

Crocodilians, as with all reptiles, are poikilothermic and rely on their environment to determine their body temperature. As a result, their activity level depends greatly on the ambient temperature and therefore time of day. To regulate body temperature, crocodilians shuttle between basking in the sun to increase their temperature and retreating to the water or shade to cool down.[32] They may remain submerged for more than 1 hour,[31] and some species maintain burrows close to the water's edge as a retreat from the water during colder months.[6,34,36,37]

Crocodilians have a range of morphological adaptations that make them successful predators in the aquatic environment. They can maintain a "minimum exposure" posture in the water, where only their eyes, cranial platform, ears and nostrils remain out of the water. This is a key strategy for approaching potential prey unseen. They have binocular vision, can see color, and have excellent night vision, relying on their characteristic slit-like pupils to make use of more light than does a round pupil.[11] A third eyelid helps protect their eyes while they swim underwater, making them more effective hunters in murky water. They have the most highly developed hearing of any of the reptiles and also have densely innervated, integumentary sense glands located around their jaws (and the remainder of the body for true crocodiles), which act as a "vibration detection" system.[20] Crocodilians have about 28 to 32 conical teeth in the lower jaw and 30 to 40 teeth in the upper jaw. These teeth are excellent for grabbing and tearing but cannot be used for chewing. Thus, crocodilians must either swallow prey whole or tear it into pieces before swallowing. Crocodilians exhibit continuous tooth replacement, with broken teeth replaced by new teeth growing under exiting teeth.[11] The jaws of the American alligator were noted in one study to produce a biting force of 1000 kg (1.1 tons).[3] This is enough force to crush large bones and shells. The muscles used to open these massive jaws, however, are quite weak and can be held closed by a two-handed grip, as depicted by popular television and alligator tourist shows.

FEEDING AND PREDATION HABITS

All species of crocodilians are more active at night and during the summer months but are opportunistic feeders and will pursue a meal when one becomes available. Larger crocodilians have been known to attack larger prey such as pigs, cattle, buffalo, horses, and humans. In addition to within shallow and deep water, attacks have been recorded on land, beaches, and riverbanks.

Crocodilians have peg-like teeth well adapted for catching and holding onto prey. Once captured, prey is often completely neutralized by being crushed by the attacker's powerful jaws. Larger prey animals are often attacked at the lower extremities, throwing them off balance before they are dragged into the water

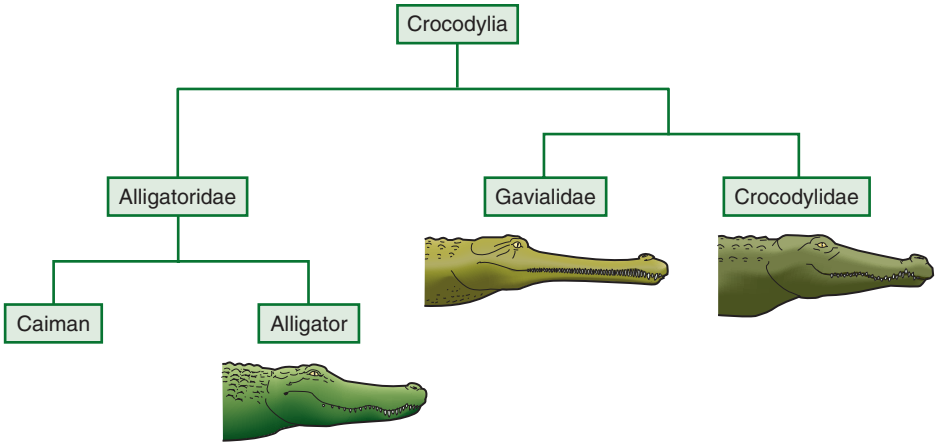

FIGURE 33-1 The order Crocodylia is broken into three families: Alligatoridae, including alligators and caimans; Crocodylidae; and Gavialidae, which includes the gharial.

FIGURE 33-2 Three species of Crocodylia live in the Americas: **A,** the American alligator (*Alligator mississippiensis*); **B,** the American crocodile (*Crocodylus acutus*); and **C,** the common caiman (*Caiman crocodilus*). (***A** Courtesy Brad Weinert; **B** courtesy Gerard Caddick and Terra Incognita; **C** courtesy George Hertner.)*

and drowned. Once overtaken, smaller animals are swallowed whole. Their teeth are not well suited for chewing, so crocodiles hold the prey in their jaws and swing the head rapidly in a "whiplash" motion, dismembering larger prey. Further attempts of separating smaller pieces may be accomplished by the animal taking a bite and then rolling their body rapidly, usually tearing off a piece of the prey during the "death roll."[40] As a result, victims of crocodilian attacks are generally severely disfigured with significant crush injuries.[25]

OVERVIEW OF ATTACKS

Most crocodilian attacks occur "out of the blue" as the attacking animal utilizes a sudden burst of speed and the advantage of surprise.[8] Crocodiles can only consume about 10% of their live body weight in a feeding event,[9] but a male adult estuarine or Nile crocodile weighing more than 900 kg (1 ton) can devour prey much larger in size than a human. According to one report, the stomach of an Australian estuarine crocodile contained the remains of an aborigine and a 4-gallon drum containing two blankets. The crocodile can travel in water at a speed of 32 km/hr (20 miles/hr) and can charge a short distance over land at a maximum recorded speed of 17 km/hr (9.5 miles/hr).[39] The enormous jaws and sharp teeth can bite with sufficient force to puncture an aluminum boat. Feeding in waterways adjacent to rural and urban areas has introduced crocodilians to cows, horses, and humans, who are attacked when they cross rivers, catch fish, draw water, wash, swim, or work in the fields.[38] Alligators residing in lakes and ponds associated with golf courses, parks, and tourist attractions have attacked humans in the United States.[30]

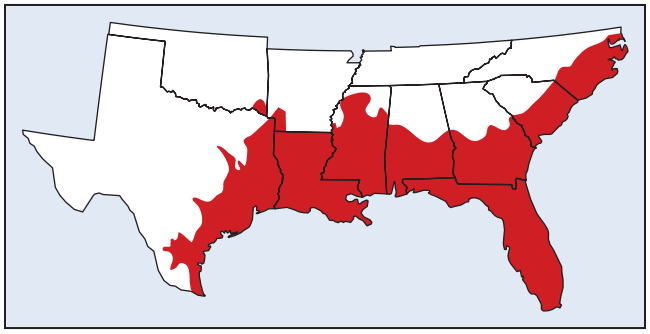

FIGURE 33-3 Map of crocodile- and alligator-inhabited regions of the United States.

TABLE 33-1 Crocodilian Lengths by Species

Species and Latin Name	Maximum Adult Male Size
American alligator (*Alligator mississippiensis*)	4.5 m (14.8 feet)
American crocodile (*Crocodylus acutus*)	6 m (19.7 feet)
Australian freshwater crocodile (*Crocodylus johnstoni*)	3 m (10 feet)
Black caiman (*Melanosuchus niger*)	4.6-6 m (15-19.7 feet)
Common caiman (*Caiman crocodilus*)	2.8 m (9.3 feet)
Nile crocodile (*Crocodylus niloticus*)	5.5 m (18 feet)
Saltwater crocodile (*Crocodylus porosus*)	6.1 m (20 feet)

Data from Dudley K: *Alligators and crocodiles*, Calgary, 1998, Weigl Educational Publishers.

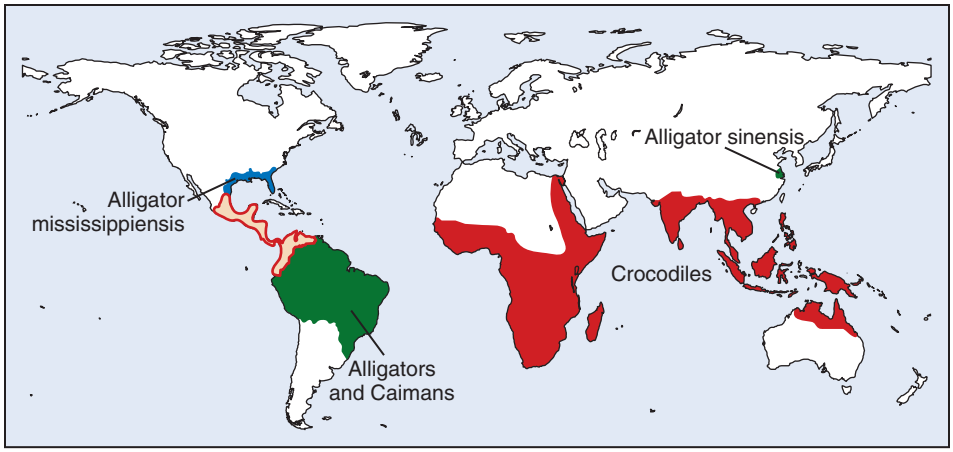

FIGURE 33-4 Map of crocodile- and alligator-inhabited regions of the world.

The number of attacks by crocodilians is significant, particularly for developing countries. Between January 2008 and July 2013, there were 1237 attacks worldwide, resulting in 674 fatalities.[33] Fifteen species of crocodilian were responsible for the attacks, with seven species causing fatalities (Figure 33-5). A total of 88.1% of all the fatalities were caused by the Nile crocodile (45.8%) and estuarine crocodile (42.3%).[33]

A U.S. study of crocodilian attacks between 1928 and 2009 identified reports of 567 adverse encounters and 24 deaths. These events are thought to be largely underreported and may not be representative of notably higher incidence in other countries. Most fatalities are reported in Florida, followed by Texas, Georgia, and South Carolina.[19] Severe injuries described as life or limb threatening represented only 11.8% of cases. Attacks in most instances were a single bite (81%). Victims were more likely to be males (85.4%) and adults 18 years of age or older (78.6%).[19] Most injuries were classified as lacerations and punctures to the arms, forearms, hands, fingers, legs, and thighs (Figure 33-6). Most injuries occurred while handling alligators, followed by wading or swimming, typically occurring in deep water (>1 m [3.3 feet]), followed by shallow water, and within 1 m from shore.[19] Most attacks occurred between the months of May and August and during the afternoon hours to twilight (Figure 33-7). Of the attacks in this study, 33% were believed to be provoked, with most caused by the victim trying to handle the alligator or trying to rescue another human or animal victim. The majority (54.8%) of cases were thought to be unprovoked.

In a comprehensive analysis of the crocodile attacks recorded in Australia between 1971 and June 2013, the reasons for the attack were attributed to nest defense, mistaken identity/self-defense, food capture, or territorial threat.[22] Most of the attacks were on males (74.5%), with a mean age of slightly under 34 years. Alcohol and complacency were considered contributing factors, with alcohol consumption implicated in 45.5% of the fatal attacks on adults. Locals in the Northern Territory and Queensland (those who should be most aware of the risks posed by crocodiles) were much more likely to be attacked (92.1% and 87%, respectively) than tourists or visitors. Other characteristics of the

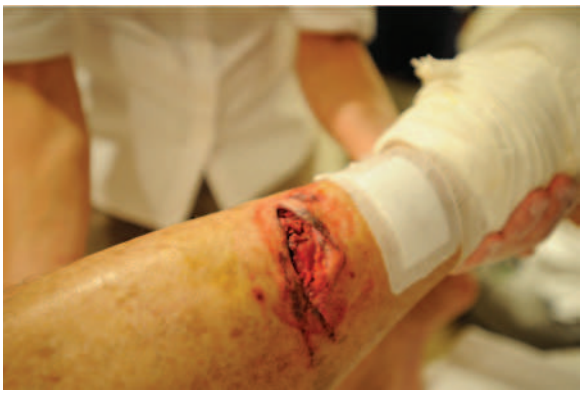

FIGURE 33-6 Forearm laceration with significant soft tissue injury after an attack. *(Courtesy Jennifer Hayes.)*

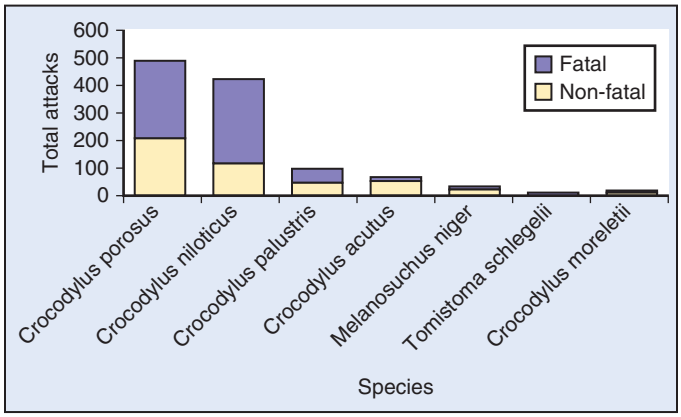

FIGURE 33-5 Attack statistics for the crocodilian species responsible for fatal attacks on people between January 2008 and July 2013.

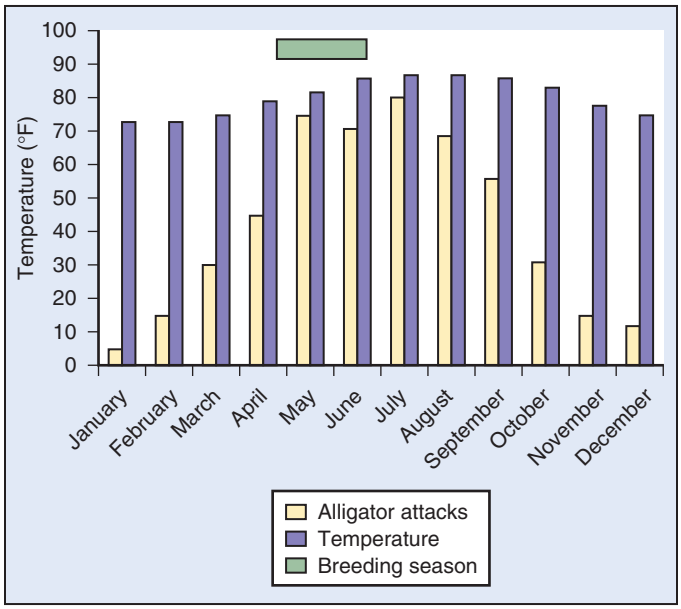

FIGURE 33-7 Distribution of alligator attacks and temperature by month.

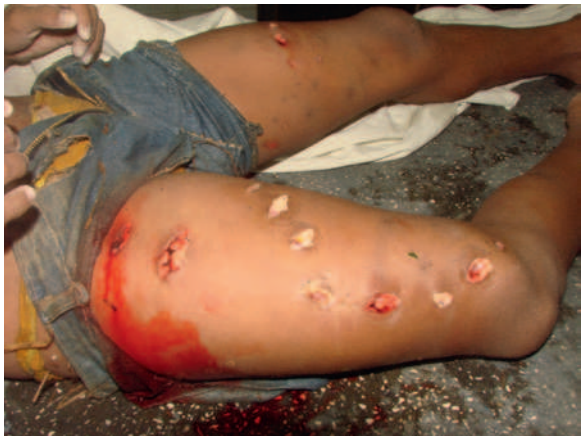

FIGURE 33-8 Superficial lacerations and bruises were the only injuries noted on this victim of a black caiman (*Melanosuchus niger*) attack in the Amazon region of Brazil. An underlying, severe femoral fracture was noted on autopsy. *(Courtesy Vidal Haddad Jr.)*

attacks were that the majority (78% of all attacks; 81.4% for fatalities) occurred during daylight hours, during the warmer months between August and April (85.3% of attacks), involved victims engaged in some form of recreational activity (90.2% of attacks), and not surprisingly, with the victim in the water (86% of attacks). The average size of the crocodile responsible for fatal attacks was 4.2 m (14 feet), whereas for non-fatal attacks it was 2.8 m (9.2 feet).[22]

In riverine areas of Tanzania, crocodiles are a considerable health hazard. In the Korogwe District from 1990 to 1994, 51 human and 49 crocodile deaths were reported. The attacks are attributed to increased waste products in the water, which reduces the crocodiles' primary food supply. In addition, "tamed" crocodiles are not hunted because of local superstitions and fear of reprisal by witchcraft.[30] A study of crocodile attacks in Malawi noted that 60 persons were injured during a 4-month period; 24 (40%) had significant bite injuries, including permanent deformity and one death from sepsis.[38]

Smaller crocodilians generally bite only once, but one-third of attacks may involve repeated bites.[18] Crocodilians greater than 2.5 m (8.2 feet) in length more often cause serious and repeated attacks, likely attributed to chasing or feeding behavior.[18] Even though external injuries may appear to be only minor lacerations, underlying significant crush injuries often exist[17] (Figures 33-8 to 33-10).

TREATMENT OF CROCODILIAN BITES

FIRST AID

Crocodilian bites can produce large crush injuries, punctures, and lacerations. Polymicrobial infections have been found frequently to cause serious deformity, sepsis, and even death.[15]

Evaluation of every crocodilian attack victim should begin with evaluation of airway, breathing, and circulation. Although it is tempting to direct one's attention to obvious bite wounds, more severe and life-threatening injuries, such as solid-organ laceration, may exist that are less apparent. Once the airway has been secured, breathing assessed, and bleeding controlled, the patient should be completely examined from head to toe for other injuries. Basics of wound management include hemostasis, fracture stabilization, analgesia, thorough decontamination, and debridement[1,16] (Box 33-1). Wounds should be copiously irrigated with clean water or sterile normal saline. Early analgesia will help facilitate patient comfort and debridement. If a patient is unlikely to receive hospital care shortly after injury, empirical antibiotic therapy with a fluoroquinolone or third-generation cephalosporin should be initiated. Culturing fresh wounds immediately after injury has not been shown to be useful for antibiotic selection.[13]

FIGURE 33-9 This black caiman (*Melanosuchus niger*), measuring 4 m (13 feet), was pulled from an Amazonian stream by a local police group after an attack. *(Courtesy Vidal Haddad Jr.)*

FIGURE 33-10 The caiman has large, powerful teeth for gripping more than chewing. *(Courtesy Vidal Haddad Jr.)*

BOX 33-1 Summary of Recommendations for Empirical Treatment of Crocodilian Attack Victims

- Analgesia and/or regional anesthesia
- Hemostasis
- Aggressive debridement and irrigation
- Empirical antibiotic coverage with a fluoroquinolone or third-generation cephalosporin
- If patient is allergic to cephalosporin, also consider trimethoprim-sulfamethoxazole or carbapenem.
- In wounds presenting with hemorrhagic bullae or necrosis, *Vibrio* species should be considered and the wound treated with surgical drainage and doxycycline, fluoroquinolone, carbapenem, or other appropriate antibiotic.
- Patients who develop cellulitis or signs of sepsis should be admitted to the hospital and treated aggressively.

Bony injuries or significant bleeding should prompt application of splints to prevent further neurovascular injury and blood loss, improve pain control, and aid in transportation of the patient. Clean dressings should be applied to all open wounds.

HOSPITAL MANAGEMENT

Patients presenting to a hospital following a crocodilian attack should receive a complete trauma evaluation, starting with assessment of the airway, breathing, and circulation. Patients with severe injuries or unstable vital signs should be placed on a cardiac monitor and given supplemental oxygen, and intravenous (IV) access should be obtained. Nontrauma receiving facilities might consider early consultation with a trauma center, with local goals of care directed toward stabilization, analgesia, antibiotic administration, and wound irrigation before transfer to a higher level of care.

Early analgesia should be initiated, preferably with parenteral narcotics. In patients with severe deformity and pain not relieved by opiate analgesics, brachial plexus nerve blocks have been successfully used for wounds to the upper extremity.[5] Small wounds may be anesthetized with local infiltration and nerve blocks. Severely injured patients with deep tissue destruction or multiple sites of injury may require general anesthesia to facilitate intraoperative cleansing and debridement.

Initial evaluation of crocodilian attack wounds should include radiographs to assess for underlying fractures or tooth fragments. Computed tomography (CT) may be warranted for further evaluation or operative planning. Patients with injuries to the head and neck, loss of consciousness, or severe scalp injuries should receive a CT scan to assess for intracranial or skull injury. Injuries close to a joint should be considered open until proved otherwise, with orthopedic consultation for possible exploration and cleansing. Areas of concern for compartment syndrome, with associated symptoms and signs of increased pain, tense compartments, and decreased circulation or temperature, should be evaluated with tissue manometry. Compartments with measured pressures greater than 30 mm Hg should be considered for fasciotomy.[23] Tetanus prophylaxis and an appropriate broad-spectrum antibiotic (e.g., fluoroquinolone, third-generation cephalosporin) should be given.

After exploration, irrigation, and debridement, bite wounds should preferably be left open because they are typically crush wounds or deep lacerations with significant bacterial contamination and surrounding soft tissue trauma. Cosmetically sensitive areas should be copiously irrigated and referred for delayed closure after 5 days of antibiotic therapy.[35]

Patients with severe trauma or infection should be admitted for further evaluation and management. Only minor wounds and patients with comprehensive plans for follow-up should be managed on an outpatient basis. Injuries causing significant trauma to the hands, face, and genitalia may require specialty surgical consultation.

Crocodilian attacks should be reported to local authorities or land management bureau agents to facilitate nuisance animal tracking and relocation, as well as compilation of accurate statistics for prevention programs.

MICROBIOLOGY AND ANTIMICROBIALS

In a study of the oral flora of *Alligator mississippiensis*, more than 38 species of bacteria and 20 species of fungi were identified by culture techniques (Box 33-2).[12] Another study of both cloacal and oral swabs from 43 American crocodiles (*Crocodylus acutus*) and 28 Morelet's crocodiles (*C. moreletii*) in Quintana Roo State, Mexico, identified 47 bacterial species, 51.1% belonging to the family Enterobacteriaceae. The most commonly isolated bacteria from oral samples were *Aeromonas hydrophila* and *Arcanobacterium pyogenes*. *Salmonella arizonae* and *S. typhi* were also detected.[4] Prophylactic antibiotic therapy should be initiated to accomplish broad-spectrum coverage against gram-negative species, especially *Aeromonas,* anaerobes, and normal skin flora.[12] The current recommendation is to give a fluoroquinolone such as ciprofloxacin, 400 mg intravenously (IV) every 12 hours or 500 mg orally (PO) every 12 hours, or a third-generation cephalosporin such as ceftriaxone, 1 g IV or intramuscularly every 24 hours.[21] Adults with cephalosporin allergies can be treated with trimethoprim-sulfamethoxazole, 8 to 10 mg/kg/day of trimethoprim IV divided every 6 to 12 hours, or 160/800 mg PO twice daily, or a carbapenem such as imipenem-cilastatin, 500 mg IV every 6 to 8 hours, for a maximal dose of 50 mg/kg/day.[29] No good study has evaluated duration of antibiotic treatment. Soft tissue infections should generally be treated for 7 to 10 days, although a longer duration of antibiotic therapy may be required for bone or connective tissue involvement.

Special attention is given to treating *Aeromonas* infection, because this can become fulminant and rapidly progress within 24 to 48 hours to cellulitis, bullae formation, local necrosis, and sepsis. There have been case reports of *Vibrio vulnificus* infections after alligator attacks. *V. vulnificus* exists in marine and estuarine environments and causes lesions presenting with hemorrhagic bullae or vesicles, followed by necrotic ulcers.[2,19] These wounds should be surgically drained and treated, at a minimum, with doxycycline in addition to empirical therapy.[21] Suspected or established *Vibrio* or *Aeromonas* infection should be treated as discussed in Chapter 73.

BOX 33-2 Bacterial Species Isolated from Crocodilian Species

Aerobic
Aeromonas hydrophilia
Citrobacter freundii
Citrobacter diversus
Bacteroides oralis
Proteus vulgaris
Pseudomonas spp.
Enterobacter agglomerans
Burkholderia pseudomallei

Anaerobic
Clostridium bifermentans
Bacteroides bivius
Fusobacterium varium
Peptococcus prevotii
Clostridium tetani

From references 13, 17, 24, and 26-28.

PREVENTION OF CROCODILIAN ATTACKS

The alligator population is increasing in the United States, with nuisance complaints now registered yearly in the thousands (Box 33-3). In Florida, the number of nuisance complaints related to alligators increased from 4914 in 1987 to 18,307 in 2006.[19] In 2013 the Florida Statewide Nuisance Alligator Program (SNAP) received 15,036 nuisance alligator complaints, resulting in removal of 6605 nuisance alligators. These alligators are often moved to other areas or harvested. For example, the Florida Fish and Wildlife

BOX 33-3 Summary of Recommendations for Prevention of Crocodilian Attacks

- Be cautious around habitats that support crocodilians, including their nesting habitats.
- Be particularly vigilant of small children and pets.
- Avoid swimming at night, and swim only in designated areas.
- Carefully dispose of food scraps away from camping areas and public facilities like boatramps.
- Do not feed crocodiles or alligators, and do not take them as pets.
- Observe or photograph crocodiles or alligators only at a safe distance, with the ability rapidly to enter a protected shelter or vehicle.

Conservation Commission permits the killing of approximately 7000 nuisance alligators each year.[14]

Persons in the United States traveling to regions inhabited by crocodilian species should exercise extreme caution, especially during the breeding season, as about 34% of attacks are thought to be defensive in nature.[19] Most attacks occur in the deep or shallow regions of slow-moving water or in muddy areas within 1 m (3.3 feet) of shore. Crocodilians are more active during temperatures between 28° and 33° C (82.4° and 91.4° F) and become more dormant below 12.8° C (55° F).[40] Crocodilians may quickly become habituated to humans, and travelers should avoid areas where these animals are fed. Caution should be used when traveling with pets because small cats and dogs are natural prey. People should be aware of the locations and activities of small children and should not allow them to approach bodies of water outside of posted swimming areas. Avoid outdoor swimming at dawn or dusk or during nighttime. Do not throw fish or scraps of food into the water. Do not remove crocodilians from their natural environment or keep one as a pet.

IF AN ATTACK OCCURS

The best way to deal with a crocodilian attack is to prevent it by being "crocodile wise" and taking steps to avoid an encounter. If an attack does occur, it is important (but perhaps difficult) to remain calm and think clearly. The majority of crocodilian attacks are single bites to an extremity and are nonfatal. Although there is little to no medical literature on surviving crocodilian attacks, anecdotal suggestions abound from communities inhabited by crocodilians. The following suggestions are presented based on their relevance to the limited case series of crocodilian attack patterns on humans and general predation habits.

In the event of an encounter with an aggressive crocodilian, it is best to run away in a straight line, covering the greatest distance possible away from areas of water. Most fatalities occur in the water, reflecting the opportunistic predatory behavior of crocodilians at the land-water interface. Loud noises and whistles may be helpful in fending off an attack, because these may distract the animal.

If a bite occurs, most crocodilians will release their prey to gain better purchase or further crush and dismember. This may provide an opportunity to escape. Therefore, the victim of an attack should be prepared to run away at any time. If attacked, avoid the water by any means possible to avoid drowning. In the event of a water attack or being pulled into the water, roll in the same direction as the crocodilian, if possible, to prevent further injury to an entrapped limb. Crocodilians have a palatal valve in their posterior pharynx that prevents water from pouring into their lungs (Figure 33-11). This may be disrupted with a foot or hand and may cause the crocodilian to release its grip.

It is advised to be aggressive and fight back if an attack is inescapable. Crocodilians have few sensitive areas, but present with their eyes and nostrils on the top of their head. Gouging the eyes or nostrils may result in a release of grip. Attacks by crocodilians on wild prey are generally persistent until escape or death. Therefore, one should only "play dead" if all attempts at escape have been made and further efforts at fighting back are futile. In addition, try and recruit someone to assist in escaping or to attack the crocodile by jumping on it. As counterintuitive as that sounds, in all cases of which we are aware, when the victim was assisted by someone attacking the crocodile, the animal released the victim.

FIGURE 33-11 Close-up of the mouth of a juvenile freshwater crocodile (*Crocodylus johnstoni*) showing the upper and lower flaps of the palatal valve, which when closed, stops water from entering the throat when the crocodile opens its mouth underwater. *(Courtesy Mark Read.)*

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CHAPTER 34
Wilderness-Acquired Zoonoses

JAMIE R. SHANDRO AND JOSHUA M. JAUREGUI

A *zoonosis* is an infectious disease that may be transmitted from animals to humans under natural conditions. There are more than 200 zoonotic pathogens, and potential infections vary by animal species (Table 34-1). The risk of acquiring zoonoses increases proportionately with the frequency and intensity of contact with animals. For example, hunters and trappers who handle and are exposed to the blood, viscera, secretions, and excretions of wild animals are at much greater risk than are recreational campers. Similarly, international travelers who frequent locations with a much higher density of infected animals are at greater risk for infection. The trekker in Nepal is more likely to confront rabies than is the hiker in California. With the current ease of

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TABLE 34-1 Animals and Some Associated Zoonoses

Animals	Associated Zoonoses
Dogs	Rabies, echinococcal diseases, ehrlichiosis (via ticks), *Pasteurella*, *Campylobacter*, *Toxocara*, leptospirosis
Sheep	Anthrax, brucellosis, echinococcal disease, melioidosis
Cattle	Anthrax, brucellosis, *Salmonella*, *Taenia* tapeworms, variant Creutzfeldt-Jakob disease
Goats	Anthrax, brucellosis, melioidosis
Horses	Anthrax, glanders, Hendra virus, *Coxiella* (Q fever)
Cats	*Bartonella* infections (cat-scratch disease, bacillary angiomatosis), *Pasteurella*, *Capnocytophaga*, *Toxoplasma*, tularemia, cowpox
Swine	Brucellosis, influenza, melioidosis, Nipah virus, cysticercosis, trichinellosis
Rodents	Hantavirus, leptospirosis, rat-bite fever, plague, tularemia, monkeypox, cowpox, *Salmonella typhimurium*, rickettsial diseases
Wild mammals (raccoon, skunk, etc.)	Leptospirosis, rabies, *Giardia*
Rabbits	Tularemia, babesiosis
Birds	Avian influenza, psittacosis, *Salmonella*, West Nile virus
Monkeys	Rabies, herpesvirus B, filoviruses, hepatitis, tuberculosis, parasitic infections, flaviviruses (yellow fever), chikungunya

international travel, travelers are increasingly exposed to a wider range of animals and potential zoonoses.

This chapter emphasizes diseases in which wildlife plays a significant role in transmission to humans. Rabies is discussed in Chapter 31, and the majority of arthropod and mosquito-borne diseases in Chapters 39 to 41. Zoonoses acquired primarily from domestic animals that also have a minor reservoir in wildlife are mentioned briefly; standard texts of veterinary public health[167,308,333] and infectious disease[144,216] provide further discussion of zoonoses acquired from laboratory or exotic animals.

ANTHRAX

Anthrax is a traditionally zoonotic disease that has come to the forefront most recently as a result of bioterrorism. It still deserves attention as a disease acquired through exposure to animals. Anthrax has afflicted men and beasts for centuries.[336] The word *anthrax* comes from the Greek word *anthrakites* for coal, referring to the black eschar seen in cutaneous anthrax. Anthrax is believed to have been one of the ancient Egyptian plagues that affected cattle.[106] Virgil[365] described clinical anthrax as the "murrain of Noricum" in his works on agriculture, *The Georgics:* "The pelts of diseased animals were useless, and neither water or fire could cleanse the taint from their flesh. The sheepmen could not shear the fleece, which was riddled with disease and corruption, nor did they dare even to touch the rotting strands. If anyone wore garments made from tainted wool, his limbs were soon attacked by inflamed papules and a foul exudate."[5]

The anthrax bacillus was the model first used by Robert Koch in the 1870s in the development of his postulates on the germ theory of disease. In the mid-19th century, anthrax was called woolsorters' and ragpickers' disease in England and Germany, because workers contracted the disease from working with hides and fibers contaminated with anthrax spores. In the United States in the early 1900s, cutaneous anthrax cases were reported among textile and tannery workers. The decrease in the incidence of disease by the late 20th century is attributed to improved animal hygiene as well as the animal anthrax vaccine, developed by Louis Pasteur in 1881.

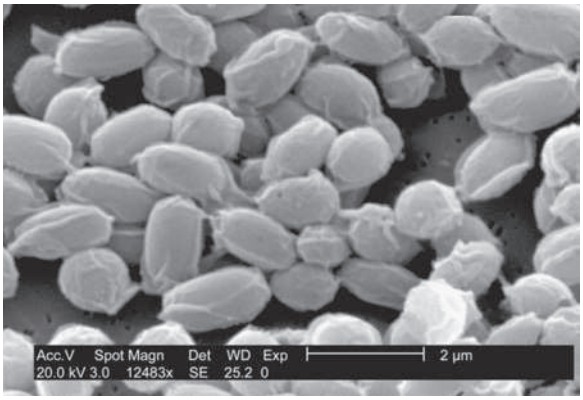

FIGURE 34-1 Anthrax spores. *(From* http://bepast.org/docs/photos/Anthrax/anthrax%20spores.jpg.*)*

Because anthrax spores resist heat and drying and may remain dormant for decades, they have long been considered a potential biologic weapon (Figure 34-1). Germ warfare programs in the Soviet Union during the 1920s and 1930s included development and stockpiling of anthrax spores. The first report of anthrax spores used as a weapon of war was in the 1940s, when the Japanese army used them in Manchuria during the Chinese-Japanese war.[155] Japan killed thousands of Chinese in widespread attacks with anthrax, typhoid, and plague in its assault on Manchurian towns and cities. *Bacillus anthracis* spores were accidentally released at a military facility in Sverdlovsk in 1979, resulting in 66 deaths.[235] In 2001, the intentional contamination of U.S. mail with *B. anthracis* spores turned attention once again to anthrax as an agent of bioterrorism.

BACTERIOLOGY

Anthrax is caused by *Bacillus anthracis* bacteria, which are encapsulated nonhemolytic, nonmotile, spore-forming, gram-positive rods that grow well on blood agar (Figure 34-2). *B. anthracis* has a polysaccharide cell wall antigen and an anthrax toxin. Anthrax spores resist heat, drying, ultraviolet light, and disinfectants, and may survive up to decades in soil.[373] They are alleged to be destroyed by high heat (140°C [284°F] for 3 hours, or 10 minutes of boiling) but may survive for up to 70 hours in mercuric chloride.[142] Infections are initiated by skin, pulmonary, or gastrointestinal (GI) contact with endospores, which are phagocytosed by macrophages and carried to regional lymph

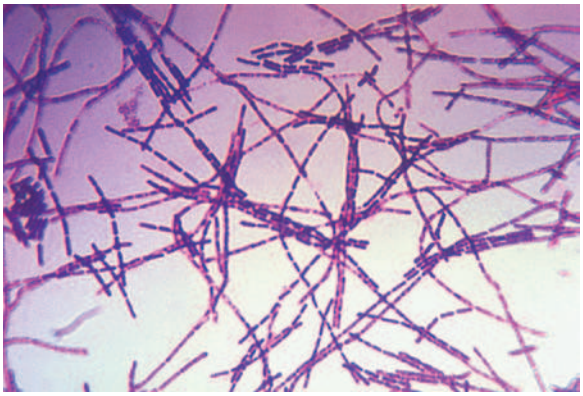

FIGURE 34-2 Photomicrograph of *Bacillus anthracis* bacteria using Gram stain. Anthrax is diagnosed by isolating *B. anthracis* from blood, skin lesions, or respiratory secretions, or by measuring specific antibodies in the blood of persons with suspected cases. *(From Centers for Disease Control and Prevention Public Health Image Library.* http://phil.cdc.gov/Phil/home.asp.*)*

nodes.[108] Inside macrophages, the spores germinate into vegetative bacteria, which can then rapidly divide and initiate further spread of infection. *B. anthracis* produces a toxin that is a tripartite polypeptide consisting of a lethal factor, edema factor, and protective antigen. This tripartite toxin stimulates release of tumor necrosis factor (TNF)–α, interleukin-1β, and other factors that lead to disruption of water balance and neutrophil function in the body, inhibiting the innate and adaptive immune responses to bacteria. In essence, this allows the bacteria to proliferate in the body, potentially leading to sepsis and death.[142]

EPIDEMIOLOGY

Most animals are susceptible to anthrax to some degree, but clinical anthrax is primarily a disease of herbivores, such as sheep, cattle, horses, and goats. Most birds are immune to anthrax, although they may carry it on their talons or beaks. The disease is rarely seen in countries where vaccination of herbivore stock is practiced. Outbreaks among herbivores are thought to occur under environmental conditions that are favorable for bacterial multiplication, such as where the pH is higher than 6.0 and the soil is rich in organic matter.[318] Such an outbreak occurred in North Dakota in 2005.[10]

Anthrax is rare in developed nations with aggressive vaccination of livestock, but it is still problematic in areas of Asia and Africa with sporadic vaccination and significant wildlife reservoirs. Most cases in industrialized nations are seen after exposure to contaminated animal products, such as goat hair imported from Turkey and Pakistan.[405] Shepherds, farmers, and workers in industrial plants with potentially contaminated animal products are at highest risk. Recurrent outbreaks of cutaneous anthrax occurred in Bangladesh in 2009 and 2010, resulting largely from contact with contaminated cattle meat.[322] Inhalation anthrax cases in the United States include a 2006 case in New York of a man exposed to contaminated dust while skinning a hide for a drum and a 2011 case report of a man exposed to animal products and dust while traveling through the Midwest.[142,199] Injection anthrax has been reported among intravenous (IV) drug users, including an outbreak in Europe and the United Kingdom (UK) in 2009-2010 affecting 54 patients, including 18 fatalities.[342]

Even more concerning are anthrax-related bioterrorism events, such as the 2001 U.S. mail contamination outbreak, when 22 people were affected, with 11 cases of inhalation and 11 of cutaneous anthrax. The majority of the people affected were mail workers. The survival rate for inhalation anthrax was 55%.

TRANSMISSION

Transmission of *B. anthracis* occurs through direct contact with, ingestion of, or inhalation of spores. Humans are infected by anthrax through contact with infected animals or animal products, or through a preparation of spores in the case of bioterrorism attacks. Notably, there has been no documented human-to-human transmission of anthrax.[108]

PRESENTATION AND SYMPTOMS

The multiple forms of anthrax infection include cutaneous, inhalation, GI, and injection. The forms are defined by the route of entry of *B. anthracis* spores into the human body, as well as by the constellation of manifesting symptoms.

Cutaneous anthrax is the most common form, accounting for 90% to 95% of cases, and is most often acquired by close contact with infected animals or their products. The primary skin lesion typically begins 3 to 5 days after exposure as a nondescript, painless, and pruritic papule at an area of the skin with a previous abrasion or wound. This progresses within 1 to 2 days to a vesicle that undergoes necrosis and drying to leave the characteristic black eschar surrounded by edema (Figure 34-3).[108] Untreated, the disease can lead to tender regional lymph nodes with eventual spread to the bloodstream. Once in the bloodstream, anthrax can rapidly become systemic. Without treatment, cutaneous anthrax has a mortality rate of up to 20%.[373] With treatment, death is rare (<1%).

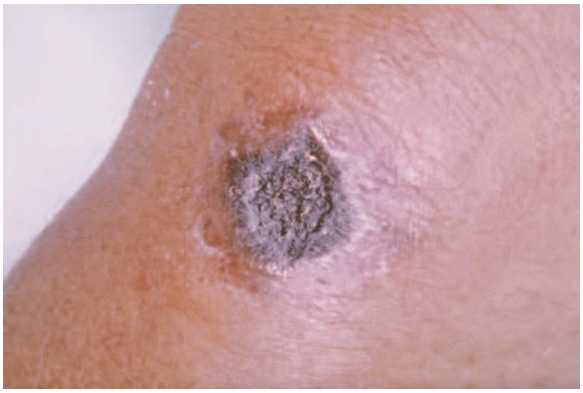

FIGURE 34-3 Cutaneous anthrax lesion on the skin of the forearm caused by the bacterium *Bacillus anthracis. (From Centers for Disease Control and Prevention Public Health Image Library.* http://phil.cdc.gov/Phil/home.asp.*)*

Gastrointestinal anthrax, which is more common outside the United States, is caused by ingesting *B. anthracis* spores. These usually are found in putrid meat from infected animals.[24] The two forms of GI anthrax are oropharyngeal and intestinal, each with an incubation period of 1 to 6 days.

Symptoms of *oropharyngeal* anthrax include fever greater than 39°C (102.2°F), severe sore throat, dysphagia, posterior oropharyngeal ulcers, and regional lymphadenopathy. Oropharyngeal lesions begin as edematous ulcerations that variably progress to ulcerations with central necrosis and then a pseudomembranous covering. The oropharyngeal form of GI anthrax is also associated with significant soft tissue neck swelling, which may progress to the point of upper airway obstruction.

The *intestinal* form of GI anthrax is characterized by anthrax spore infection of the stomach or bowel wall. Initial symptoms include nausea, vomiting, anorexia, and fever greater than 39°C (102.2°F). Symptoms progress to include severe abdominal pain, hematemesis, and watery, melanotic, or bloody diarrhea. Patients can present with symptoms of an acute abdomen or new-onset ascites. Mortality can result from bowel perforation or *B. anthracis* septicemia.

Inhalation anthrax is rare worldwide and is associated most prominently with bioterrorism. Inhalation anthrax has an incubation period of 8 to 10 days after inhalation of spores into the airways.[44] Symptoms include insidious flulike onset of malaise, fatigue, fever, nonproductive cough, and myalgia.[318] The rapid deterioration that follows includes dyspnea, cyanosis, respiratory failure, meningismus, mediastinal hemorrhage, hypotension secondary to septic shock, and possibly death.

Injection anthrax was most recently described in an outbreak among IV drug users in Europe and the UK.[342] It presents similar to cutaneous anthrax, with the addition of deeper involvement, increased difficulty in diagnosis, and higher risk of systemic involvement. Mortality rates of 25% to 37% have been cited.[29]

Of the forms of disease, inhalation anthrax has the highest mortality rate (45% with antibiotic treatment and 97% without), followed by GI anthrax (40% with antibiotics, injection anthrax (25 to 37% with antibiotic therapy), and cutaneous anthrax (1% with antibiotics and 10% to 20% without).[171,318]

DIAGNOSIS

Cutaneous and injection anthrax can be diagnosed by culture of cutaneous lesions. GI anthrax can be diagnosed by cultures from oropharyngeal lesions, blood, and ascites. Computed tomography (CT) of the abdomen is likely to show mesenteric adenopathy. Abdominal radiographs may show nonspecific bowel gas patterns and do not aid in diagnosis of the disease. Stool culture has also not been shown to be useful in aiding the diagnosis of anthrax. Autopsies of patients dying of GI anthrax show hemorrhagic inflammation of the small intestine with lymphadenopathy.[373] On entrance to the GI tract, anthrax is known to cause

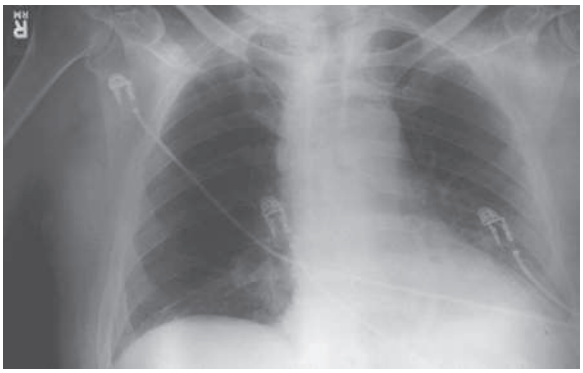

FIGURE 34-4 Anthrax-widened mediastinum. *(From Jernigan JA, Stephens DS, Ashford DA, et al: Bioterrorism-related inhalational anthrax: The first 10 cases reported in the United States,* Emerg Infect Dis *7:933, 2001.)*

ulcerations that can be seen on autopsy to extend the length of the GI tract, but most frequently are found in the mouth, stomach, and duodenum.[24]

Patients with inhalation anthrax typically present with a normal to elevated white blood cell (WBC) count. Chest radiographs demonstrate mediastinal widening secondary to hilar adenopathy and may demonstrate pleural effusions (Figure 34-4).[171] A chest CT scan, which can be the earliest diagnostic clue and is often pathognomonic for inhalation anthrax, is recommended in any suspected case.[130] The Centers for Disease Control and Prevention (CDC) recommends that cultures of blood, sputum, pleural and cerebrospinal fluid (CSF) be obtained for culture and antibody/toxin analysis in suspected cases of systemic anthrax.

TREATMENT

Effective treatment of all forms of anthrax requires a high index of suspicion and prompt antibiotic therapy. In the 2001 outbreak of bioterrorism-related anthrax, all isolates were susceptible to ciprofloxacin and doxycycline, as well as to other agents.[66] Because *B. anthracis* has the potential for penicillinase and cephalosporinase activity, ciprofloxacin and doxycycline, rather than penicillin-based antibiotics, are the first line of therapy.

Treatment for cutaneous anthrax without systemic involvement is oral ciprofloxacin or doxycycline, twice daily for 60 days.[160] In children, the dose of ciprofloxacin is 10 to 15 mg/kg/day divided every 12 hours (not to exceed the adult dose of 500 mg every 12 hours), or doxycycline, 4.4 mg/kg/day divided every 12 hours (not to exceed the adult dose of 100 mg every 12 hours). If patients are clinically improved, therapy may be changed to amoxicillin, 500 mg three times daily for adults, or 80 mg/kg/day divided three times daily for children.

For systemic anthrax (GI, inhalation, meningitis, injection), treatment should begin with a three-drug regimen, to include two bacteriocidal agents with good central nervous system (CNS) penetration and one protein synthesis inhibitor; preferred agents are ciprofloxacin and meropenem plus linezolid or clindamycin. If meningitis is ruled out, CDC recommendations include 2 weeks of IV ciprofloxacin as well as one additional agent e.g., clindamycin, linezolid, or doxycycline). If symptoms improve, treatment switches to an oral regimen of ciprofloxacin or doxycycline for a total course of 60 days. Treatment is the same during pregnancy; the risk of doxycycline or ciprofloxacin during pregnancy is outweighed by the potential mortality resulting from undertreated anthrax infection.

In the event of potential exposure to inhaled anthrax spores, the CDC recommends 60 days of ciprofloxacin or doxycycline in combination with a three-dose regimen (0, 2, 4 weeks) of anthrax vaccine (BioThrax, formerly known as AVA) as an emergency public health intervention. Postexposure prophylaxis is not recommended for exposure to cutaneous anthrax alone.

PREVENTION

The first anthrax vaccine was created in 1881 by Louis Pasteur in an effort to prove the germ theory of disease.[336] In the 1950s, a human anthrax vaccine was created by the U.S. Army Chemical Corps. This was replaced by a licensed vaccine in 1970. At first, this vaccination was mandatory for all U.S. military personal, but after concerns for vaccine safety arose, refusal followed. Safety was subsequently proved, so mandatory vaccination was reinstituted for the military. Vaccinations for the public are still debated. Opponents of routine vaccination argue that most anthrax in the United States is cutaneous and easily treatable with oral antibiotics. The vaccine is given in five injections, and immunity is thought to last 2 years; therefore the vaccine has been judged not suitable for public dispersal.[376] According to a study done by Fowler and colleagues, given a 1% risk of anthrax attack each year, it would be more cost effective and safer to give postexposure antibiotics and vaccines than to prevaccinate the entire population.[10] People who are at risk for acquiring the disease, including wool handlers, mail workers, and military personnel, can be inoculated. Prevention of zoonotic anthrax infection largely relies on vaccination of animals and people at risk. Travelers should avoid contact with infected animals and undercooked meat.

BARTONELLA INFECTIONS

In the early 1990s, it was determined that organisms of the genus *Rochalimaea* caused a diverse array of clinical syndromes, including cutaneous bacillary angiomatosis, bacillary peliosis hepatitis, fever with bacteremia (formerly known as *Rochalimaea* bacteremic syndrome), and cat-scratch disease (CSD). Whether the different clinical syndromes result from subtle differences in the infecting organisms or in the response of the immune system remains unclear. Each of these conditions is caused by the bacteria now known to be *Bartonella* (formerly *Rochalimaea*) *henselae* and *Bartonella quintana*, also the agent of trench fever.

BACILLARY ANGIOMATOSIS

Bacillary angiomatosis, first described in 1983 during the early years of the acquired immunodeficiency syndrome (AIDS) epidemic, forced reconsideration of CSD, bartonellosis, and trench fever.[338]

Epidemiology

Although clinically different from CSD, bacillary angiomatosis is also closely associated with a recent cat scratch or bite. One study showed that two-thirds of patients with bacillary angiomatosis had cats with the same genotype of *B. henselae.*[75] *Bartonella quintana* may also be causative and is thought to be transmitted through lice; a study of homeless patients screened for lice in San Francisco revealed that 16% of head lice samples and 37% of body lice samples carried *B. quintana.*[33] The vast majority of patients are human immunodeficiency virus (HIV) positive, usually with CD4 count less than 200 cells/mm^3.[238,347] In 34% of cases, this infection was the first one to establish the diagnosis of AIDS in a given patient. AIDS patients with bacillary angiomatosis can die if untreated, but erythromycin is usually effective.[30]

Symptoms

Most cases of bacillary angiomatosis involve cutaneous or subcutaneous lesions. The lesions typically consist of elevated, friable, red granulation tissue that is papular, verrucous, or pedunculated and resembles pyogenic granulomas, numbering a few to thousands (Figure 34-5). The lesions tend to enlarge if left untreated. Deeper subcutaneous nodules with or without overlying tenderness and erythema are seen in about half the patients. These lesions can be almost indistinguishable from those of Kaposi's sarcoma and can also coexist in the same patient.[30] Similar lesions can occur in other body tissues, with almost all visceral organs, including the brain, heart, larynx, cervix, and vulva, being vulnerable.[30] Visceral lesions may be the first sign of infection; patients often have fever, weight loss, and

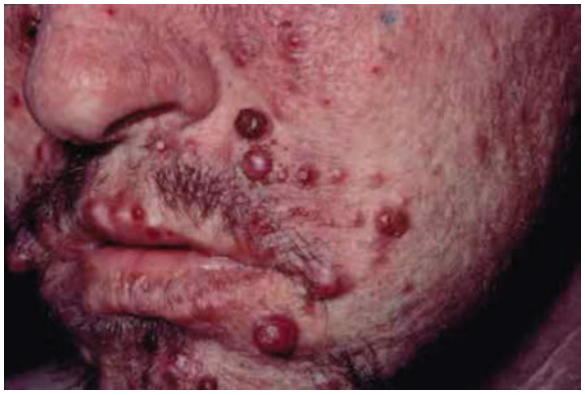

FIGURE 34-5 Bacillary angiomatosis. (*From* http://prn.org/index.php/complications/article/common_skin_problems_of_HIV_disease.)

malaise.[99] Hepatic involvement (bacillary peliosis hepatitis) can lead to hepatic failure or even rupture. This usually manifests with GI symptoms (nausea, vomiting, diarrhea, or abdominal distention), fever, chills, and hepatosplenomegaly. Histopathologic examination of liver biopsy specimens reveals dilated capillaries or multiple blood-filled cavernous spaces, some of which can be seen on endoscopy or bronchoscopy.[238]

Bacillary angiomatosis may cause osteomyelitis, manifesting as an extremely painful focal area of a bone that appears as a lytic lesion on radiographic analysis. This usually occurs on the tibia, radius, or fibula and occasionally has a cellulitic tender erythematous plaque overlying the area of concern.[18] The organism can also cause bacteremia, even in immunocompetent patients. *Bartonella* bacteremia is characterized by a prolonged symptom complex of malaise, fatigue, anorexia, weight loss, and recurring fevers with ever-increasing temperature.[27,28] Often, no site of focal infection is apparent. The symptoms are usually present for weeks to months before the diagnosis is finally made by isolation of the organism in blood cultures.[326]

Diagnosis

Bartonella henselae and *B. quintana* can be isolated from blood using lysis-centrifugation blood cultures,[19] but both species have also been isolated with traditional blood culture systems. Serologic diagnosis can also be made using techniques of indirect fluorescent antibody (IFA) testing. Serum samples can be sent (for both *B. henselae* and *B. quintana*) to the CDC. A commercially available enzyme immunoassay for detection of IgG antibodies to *B. henselae* is reportedly 5 to 10 times more sensitive than is the IFA test.[100] Positive results should be interpreted cautiously, taking into account the clinical context, because the meaning of positive serologic results awaits further evaluation with stricter epidemiologic methods.

Diagnosis of bacillary angiomatosis is usually made from clinical features and biopsies of lesions, with characteristic histopathologic findings in tissue sections. Blood cultures should be obtained and incubated for a prolonged period. As more is learned about their growth requirements, the causative organisms may become easier to culture directly from skin lesions and lymph nodes. Serologic analysis will become an important means of diagnosis.[1]

Treatment

Recommended treatment of *Bartonella* infection is with doxycycline, 100 mg orally (PO) twice daily, or erythromycin, 500 mg PO four times daily. Azithromycin and clarithromycin are alternative treatments.[283,309] Penicillin and first-generation cephalosporins are not beneficial. For CNS disease, rifampin, 300 mg intravenously (IV) twice daily, may be added, and for bacteremia, gentamicin, 1 mg/kg IV three times daily, may be added to doxycycline or erythromycin. Therapy is for a minimum of 4 weeks and may have to continue indefinitely in an immunosuppressed patient. Immunocompromised patients may develop a Jarisch-Herxheimer reaction after the first several doses of antibiotics.[347]

Prevention

There is ongoing discussion regarding prevention of bacillary angiomatosis in HIV/AIDS patients. Many HIV/AIDS patients possess cats for companions and in doing so, risk contracting *B. henselae*. The current recommendation is for these patients to decrease rough play with the animals and make medical caregivers aware that they own a cat.[347] With current antiretroviral therapies, prophylactic antibiotics are infrequently used, given that these infections typically occur with low (<200 cells/mm^3) CD4 counts. There is no vaccine for animals or patients at risk.

CAT-SCRATCH DISEASE

Cat-scratch disease is typically transmitted from a cat through a break in the skin (bite, scratch, lick, or other injury). It is usually self-limited and lasts 6 to 12 weeks. The first reference to the disease was in 1889 in the French literature by Henri Parinaud. The first to recognize the cat as the vector for the disease was Robert Debré at the University of Paris in 1931; however, the disease was not officially reported until 1951. CSD is probably the most common cause of unilateral lymphadenopathy in children.[331] The current cause of CSD is thought to be the gram-negative bacterium *Bartonella henselae*, previously known as *Rochalimaea henselae*.[38]

Epidemiology

Cat-scratch disease has been reported from all countries and in all races. An estimated 24,000 cases are recognized each year in the United States.[221] Most cases are found in the fall and winter months, a seasonality thought to be caused by the increase in kitten births in the summer and subsequent rise in flea infestation.[276] Compared with healthy cat-owning controls, patients with CSD are more likely to have at least one kitten age 12 months or younger, to have been scratched or bitten by a kitten, and to have at least one kitten with fleas.[404] It has been postulated that the domesticated cat *Felis domesticus* is the reservoir for the disease and that, as with other *Bartonella* species, the organisms may be transmitted between cats by fleas and ticks.[276]

Transmission

About 90% of cases are caused by scratches from cats, but dog and monkey bites, as well as thorns and splinters, have been implicated in transmission.[92] The organisms may be on the claws or in the oral cavity of the offending cat. Most cases occur in children, particularly boys, who tend to play more aggressively with domestic animals.

Symptoms

The average incubation period is 3 to 10 days. The characteristic feature of CSD is regional lymphadenitis, usually involving lymph nodes of the arm or leg. In one series, 54% of lymphadenopathy occurred in the axilla, with the remainder in the neck.[331] Often, only one node is involved. The nodes are often painful and tender, and about 25% suppurate.[372] Adenopathy may spread proximally; occasionally, cervical adenopathy is mistaken for Hodgkin's disease. Inguinal lymphadenopathy misdiagnosed as lymphogranuloma venereum (LGV) has later found to be caused by *B. henselae* from CSD.[311] In most cases, a characteristic raised, erythematous, slightly tender, and nonpruritic papule with a small central vesicle or eschar that resembles an insect bite is seen at the site of primary inoculation. Constitutional symptoms are mild, with approximately two-thirds of patients presenting with fever, which is rarely greater than 38.8°C (102°F). Chills, malaise, anorexia, and nausea are common. Infrequent evanescent morbilliform and pleomorphic skin rashes lasting for 48 hours or less have been reported in fewer than 5% of patients.[311] This typical clinical course occurs in 88% of patients; the remainder seek medical treatment for complications such as encephalopathy, atypical pneumonia, and severe systemic disease. The most common of the atypical forms of presentation is Parinaud's oculoglandular syndrome, which occurs in 2% to 8% of patients

and consists of granulomatous conjunctivitis and an ipsilateral, enlarged, tender preauricular lymph node.[222]

Serious complications are rare and include encephalitis, seizures, transverse myelitis, osteolytic bone lesions, arthritis, splenic and hepatic abscesses, mediastinal adenopathy, optic neuritis, and thrombocytopenic purpura.[37,222,244,267] Although encephalopathy is rare, CSD is becoming a more common cause of encephalopathy as other viral infectious diseases disappear; the incidence of CSD-associated neurologic complications now ranks with those of varicella and herpes simplex infections, Lyme disease, Rocky Mountain spotted fever, and Kawasaki disease.[49] CSD encephalopathy should enter the differential diagnosis of patients (especially young ones) with unexplained coma, seizure (half of whom may be afebrile), or fever of unknown origin. The prognosis for encephalopathy generally is good, and to date, documented neurologic sequelae in immunocompetent patients have been rare.

Diagnosis

Results of routine laboratory studies, including urinalysis and complete blood cell (CBC) count, are usually normal, although mild leukocytosis and elevation of erythrocyte sedimentation rate (ESR) may be seen as well. An enzyme assay and IFA assay for *B. henselae* are available, and polymerase chain reaction (PCR) testing is available in some reference laboratories.

Immunity is thought to be largely cell mediated.[139] An intradermal skin test of 0.1 mL of CSD antigen used to be a criteria for diagnosis of CSD and is positive in approximately 95% of patients, but with the advent of newer testing modalities, and because 10% of the population have a false-positive reaction, skin testing is no longer recommended as optimal testing. In confusing cases, biopsy of lymph nodes can yield characteristic findings of areas of granulomatous change and necrosis with central neutrophilic infiltration, a peripheral zone of histiocytic cells, and an outermost zone infiltrated by small lymphocytes and plasma cells.[219] This picture is not diagnostic, however, and is also seen in LGV, histoplasmosis, tularemia, brucellosis, sarcoidosis, and tuberculosis (TB). Thus, lymph node biopsy is most useful to rule out malignancy. Warthin-Starry or Brown-Hopps staining of the nodes or the primary skin lesion usually demonstrates small, pleomorphic bacilli.[222]

In most patients with CSD, clinical diagnosis is based on the constellation of clinical criteria, such as single or regional lymphadenopathy without obvious signs of cutaneous or throat infection, historical criteria of contact with a cat (usually an immature one), detection of an inoculation site, and positive serology or cultures.[52,330]

The workup should exclude other causes of regional lymphadenopathy, such as TB, tularemia, LGV, lymphoma, brucellosis, and sporotrichosis.[304] In general, only sporotrichosis and LGV demonstrate localized unilateral lymphadenopathy; LGV usually occurs in the groin. Cat scratches are normally found on the upper extremities. Skin tests, cultures, serologic tests, and biopsies are available for differentiation of these other diseases.

The tendency for dissemination is greater in immunocompromised patients, who may develop bacillary angiomatosis, as previously discussed.

Treatment

Cat-scratch disease usually resolves spontaneously in weeks to months, although in 2% to 14% of patients (usually adults) the course is prolonged and involves systemic complications.[220,222] Systemic CSD in an adult has been successfully treated with gentamicin,[201] and in a child with cefuroxime.[140]

Clear guidelines for treatment of CSD do not exist, mainly because few randomized controlled trials (RCTs) have been done. An RCT with azithromycin for CSD showed a significant decrease in volume of lymphadenopathy with treatment.[21] In a retrospective series of 71 patients, trimethoprim-sulfamethoxazole (TMP-SMX) was seen to have had good results; this was not the case with other antibiotics.[89] The largest study, of 268 patients, was also retrospective and found a response rate of 87% with rifampin, 84% with ciprofloxacin, 73% with intramuscular gentamicin, and 58% with TMP-SMX.[220] Antibiotics that were of no benefit included amoxicillin-clavulanate, erythromycin, dicloxacillin, cephalexin, tetracycline, cefaclor, ceftriaxone, and cefotaxime. No sequelae of CSD other than the rare complications previously mentioned are known. One recent article showed that one bout of CSD seems to offer lifelong immunity, with recurrences of lymphadenopathy shown only rarely.[330]

For the majority of immunocompetent patients, some experts recommend withholding antibiotic therapy and reassuring patients that the prognosis is excellent. Other experts recommend antibiotic treatment for all patients with CSD. For isolated lymph node involvement, a 5-day course of azithromycin (10 mg/kg on day 1 [maximum 500 mg], followed by 5 mg/kg/day for 4 days [up to 250 mg/day]) may shorten the duration of disease and possibly prevent complications. For patients intolerant of azithromycin, treat with clarithromycin, rifampin, TMP-SMX, or ciprofloxacin. For patients with severe or prolonged disease, or for immunocompromised patients, antibiotic treatment is indicated.

BRUCELLOSIS

Brucellosis is one of the most common zoonotic disease worldwide.[261] It is a chronic, granulomatous infection caused by gram-negative intracellular bacteria, presents with a broad clinical spectrum, and requires combined, lengthy antibiotic treatment (Figure 34-6). Brucellosis fits into the differential diagnosis of fever of unknown origin. Brucellosis usually results from ingestion of contaminated milk or milk products or by direct skin contact. *Brucella* organisms are carried chiefly by swine, cattle, goats, and sheep and may be recovered from almost all tissues in a sick patient. Most animals used as livestock are susceptible to brucellosis, whereas the occurrence in wild animals is rather small.[226] *Brucella* is also recognized as a potential biologic weapon.[259]

BACTERIOLOGY

Brucella organisms are small, gram-negative, unencapsulated, aerobic, and intracellular coccobacilli. The species causing disease in humans include *Brucella abortus*, *B. suis*, *B. melitensis*, and less commonly, *B. canis*. The bacterium can survive in soil for up to 10 weeks, in goat cheese for up to 180 days (at 4° to 8° C [39.2° to 46.4° F]), and in tap water for up to 60 days. It is, however, very sensitive to heat and most disinfectants and is entirely killed by pasteurization.

EPIDEMIOLOGY

Brucella in domesticated animals tends to be species specific, with *B. abortus* infecting cattle, *B. melitensis* goats, *B. suis* swine, *B. canis* dogs, and *B. ovis* sheep. Brucellosis is found worldwide

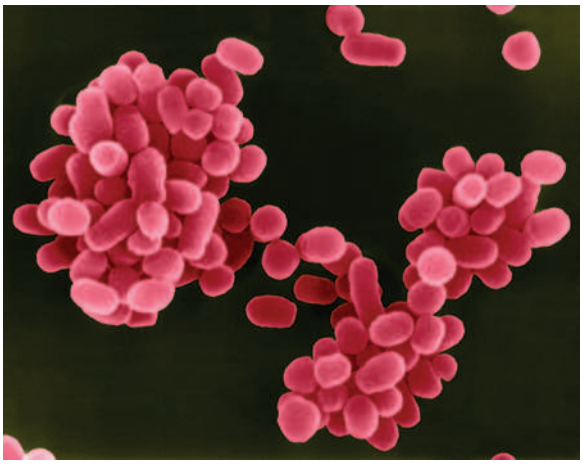

FIGURE 34-6 Electron micrograph of *Brucella abortus*. *(Courtesy Dennis Kunkel Microscopy.)*

and has an annual attack rate of about 500,000 persons; U.S. cases number less than 200. Significant endemic areas include Mexico, Central and South America, Mediterranean countries, the Arabian Gulf, and India. Most U.S. cases of brucellosis are found in Texas and California. The disease is imported across the border by means of infected dairy products. Risk factors for brucellosis include Hispanic ethnicity, travel to Mexico, and ingestion of unpasteurized dairy products.[351,261]

Humans are most often infected with *Brucella* through direct or indirect exposure to animals by ingestion of contaminated, unpasteurized animal milk products, direct inoculation through cuts and skin abrasions, and inhalation of infected aerosols.[401] Brucellosis is an occupational hazard for shepherds, farmers, veterinarians, abattoir workers, dairy industry professionals, and microbiologic laboratory workers. Rare cases of sexual transmission between humans have been reported.[232] A proven case of transmission by dog bite has been reported, and dogs carry their own pathogenic species, *B. canis*.[279] Most human cases are caused by infection with *B. melitensis*. A recent study found no clinical differences between cases of brucellosis caused by *B. melitensis* and those caused by *B. abortus*, which is typically acquired from cattle.[109]

Symptoms

Brucellosis may affect many organ systems, with a wide range of disease severity and acuity.[91] Because of this, it can cause fever with vague and varied symptoms and should be considered as a cause of chronic unexplained fever. Fever and tachycardia are present in more than 90% of patients, constitutional symptoms are generally present in 26%, and malodorous perspiration is almost pathognomonic. Physical examination is generally nonspecific, with hepatomegaly, splenomegaly, and lymphadenopathy most often found.[259]

The disease can be classified into three forms: acute, subacute, and chronic. In acute brucellosis, patients complain of headache, weakness, diaphoresis, myalgias, and arthralgias; this is the most common presentation. Anorexia, constipation, and weight loss are often seen in the first 3 to 4 weeks. Physical examination may reveal lymphadenopathy, hepatomegaly, or splenomegaly. Bacteremia in the early stages typically induces lesions of the viscera, bones, and joints; osteomyelitis, particularly spondylitis, is a common complication. Rare but serious complications include neurobrucellosis with meningitis, hepatic abscess, and endocarditis, which remains the main cause of mortality.[188]

In subacute, or undulant, brucellosis, symptoms are milder but with more frequent arthritis and orchitis. The clinical picture is more varied, and the diagnosis is considered in any fever of undetermined or unknown origin. Before the antibiotic era, most patients spontaneously cleared their disease in 6 to 12 months.

In chronic brucellosis, symptoms have persisted for more than 1 year. It is rare in children but increasingly common as patients age. Many describe chronic arthralgias and extraarticular rheumatism. Chronic brucellosis can mimic chronic fatigue syndrome.

DIAGNOSIS

Brucellosis is most often diagnosed by serologic testing, including serum agglutination, rose bengal dye, complement fixation (CF), and enzyme-linked immunosorbent assay (ELISA).[207] *Brucella* IgG antibodies or the presence of IgM antibody to *Brucella* can be used to make a presumptive diagnosis.[131] PCR testing is an effective method for detecting brucellosis.[225] After acute infection, high titers may persist for 18 months. False-positive results may be caused by *Francisella tularensis* or *Yersinia enterocolitica* infection. Definitive diagnosis of brucellosis requires isolating the organism from body fluids or tissue. Isolation of *Brucella* organisms by blood culture may be used for definitive diagnosis, although the cultures are not always positive. Blood cultures have a sensitivity of 50% to 80%. Bone marrow biopsy with culture is reportedly more sensitive than blood cultures and is still considered the gold standard for diagnosing brucellosis. It can be used in patients with clinically suspected brucellosis but negative serologic tests and blood cultures.[259]

TREATMENT

Brucellosis requires combined, protracted antibiotic treatment, most often with a tetracycline supplemented with a second antibiotic.[259] Typical treatment is with doxycycline, 100 mg PO twice daily for 6 weeks, plus either streptomycin, 1 g intramuscularly (IM) daily for the first 14 to 21 days; gentamicin, 5 mg/kg/day IM for 7 days; or rifampin, 600 to 900 mg PO once daily for 6 weeks.[90,157] Doxycycline plus streptomycin is considered the gold standard of therapy and has been shown to be superior to doxycycline plus rifampin.[325] No significant differences have been found between streptomycin and gentamicin as the second agent. The role of quinolones has been investigated, particularly in combination with rifampin.[4] Treatment with rifampin in combination with a quinolone is similar to the combination of rifampin with doxycycline.[328] Pregnant patients are treated with rifampin, 900 mg daily for 6 weeks, with the addition of TMP-SMX during the second trimester.[327] The American Academy of Pediatrics recommends children younger than 8 years take oral TMP-SMX, 10 mg/kg/day TMP (maximum 480 mg/day) and 50 mg/kg/day SMX (maximum 2.4 g/day) divided in two doses, plus oral rifampin, 15 to 20 mg/kg/day (maximum 900 mg/day) divided in one or two doses for 4 to 6 weeks, with gentamicin, 5 mg/kg/day parenterally divided in one to three doses, added for the first 14 days if osteoarticular, neural, or endocarditis manifestations are present. For children 8 years and older, antibiotic choices are the same as for adults. Focal disease is generally more difficult to eradicate than mild diffuse disease. Mortality is low, with only two deaths reported in several thousand cases.[128]

GLANDERS

Although little known in the Western world today, glanders is a classic infectious disease. Its greatest historical impact has been through its effect on cavalry horses during military campaigns, influencing battles from biblical times through World War I. There have been no reported cases in the United States since the 1940s.

Theories and disputes about the origin, nature, transmission, and treatment of glanders figured prominently in the development of veterinary science in Europe in the latter half of the 18th century. In 1795, Erik Viborg published an account that is remarkably close to our current understanding of the disease. He demonstrated that equine "farcy," characterized by cutaneous lymphangitis, and the respiratory form of the disease in horses, classically referred to as glanders, were different manifestations of the same infection. He demonstrated that the disease was transmissible from one horse to another by infectious exudates, and that the causative organism could be carried by fomites and killed by heat.

Transmission of glanders from horses to humans was documented in France and Germany during the first three decades of the 19th century. The causative organism was isolated by Loeffler and Schütz, as well as by Bouchard, Capiton, and Charrin in 1882. In 1891, Kalning and Helmann independently discovered *mallein,* derived from the glanders bacillus. As with tuberculin, mallein was thought to have therapeutic or prophylactic value. This turned out to be erroneous, but mallein provided a means of diagnosing the infection in clinically ill and carrier animals and provided a basis for test and slaughter techniques, which have largely eliminated glanders from most parts of the world.

BACTERIOLOGY

The causative organism in glanders is *Burkholderia mallei*, a member of the newly renamed *Burkholderia* genus, which includes *B. pseudomallei*, the cause of melioidosis, and *B. cepacia*. *B. mallei* is a gram-negative, nonsporulating, obligately aerobic, and nonmotile bacillus that requires glycerol for optimum growth in vitro.[274,332] In 1992, Yabuuchi and co-workers[399] proposed that seven species, formerly of the *Pseudomonas* RNA group II, should be transferred to a new genus, *Burkholderia*, with *B. cepacia* as the type species. The genus included *B. caryophylli*, *B. gladioli*, *B. mallei*, *B. pseudomallei*, *Ralstonia*

pickettii, and *R. solanacearum*; the latter two species were transferred to the genus *Ralstonia*.

EPIDEMIOLOGY

Glanders occurs in a few Asian and African countries, such as India, China, Mongolia, Egypt, and Mauritania. It is primarily a disease of horses and spreads most rapidly when large numbers of horses, mules, or donkeys are kept in proximity. Many carnivorous mammals are also susceptible to infection, and outbreaks have occurred when infected horsemeat was fed to lions, tigers, and other wild animals in zoos. Occasionally, infections occur in dogs, cats, sheep, and goats. Although glanders is limited to a few countries, there has been some concern that *B. mallei* could be used as a bioterrorism agent.[118]

TRANSMISSION

Humans are usually infected by exposure to sick horses. *B. mallei* infection can occur by inhalation of respiratory droplets or by contact with infected discharges. Human infections have occurred from direct contact in the laboratory and from patients.

SYMPTOMS

Equids

Horses may have unilateral or bilateral mucopurulent nasal discharge. There may be enlargement and induration of lymphatics, with ulceration and discharge, especially involving the legs. Nodules, pustules, and ulcers may be seen on the horse's skin. The cutaneous form of glanders is often referred to as farcy; the thickened, inflamed lymphatics as farcy pipes; and the enlarged lymph nodes as farcy buds. Horses also have pneumonia, with mild respiratory embarrassment in early stages and more severe respiratory difficulties and cachexia in later stages. Septicemia with lesions in multiple internal organs can occur.

Glanders can run an acute and fulminant course in equids, especially in donkeys and mules, or a more chronic course, more often in horses. The case fatality rate is high, especially with more virulent strains of the organism.

Humans

The incubation period of glanders in humans can be as short as 1 to 5 days. Cases with apparent incubation periods of several months may have represented smoldering, unrecognized infection. The severity of disease can vary from mild to fatal, and the course can be acute and fulminant or chronic. Relapses can occur after quiescent periods of up to 10 years. As in horses, manifestations in humans usually involve the skin and respiratory tract. There may be pustular cutaneous eruptions, thick indurated lymphatics that may ulcerate, mucopurulent discharge from the eyes or nose, pneumonia, and metastatic abscesses in internal organs. Depending on the severity, the patient may have anorexia, fever, weight loss, headache, nausea, diarrhea, or septicemic shock. Lobar pneumonia, bronchopneumonia, or nodular densities may be seen on chest radiographs. Cases recently reported from Southeast Asia have been relatively mild, indicating that the local strain of the organism appears to have moderate pathogenicity for humans.

DIAGNOSIS

Clinical diagnosis in horses based on symptoms can be confirmed by reaction to mallein with a cutaneous hypersensitivity test. Mallein, a filtrate derived from culture of *B. mallei,* is injected into the eyelid of a horse. A positive reaction, read 48 hours later, consists of marked local swelling and purulent conjunctivitis. Several serologic tests are also available; CF is often used, although dot-ELISA is a more sensitive test.[361]

Clinical diagnosis in humans is based on consistent symptoms in an individual exposed to horses in an endemic area. The diagnosis can be confirmed by culture of the organism from lesions or tissues or by serologic testing, using CF or agglutination. Agglutination titers are often detectable by the second week of infection. The CF test is less sensitive but more specific than agglutination. CF tests become positive during the third week of infection.[274]

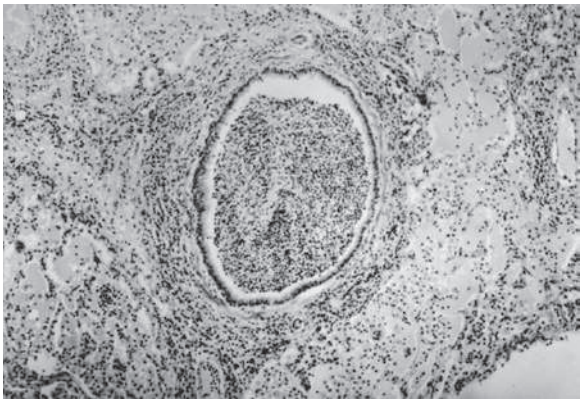

FIGURE 34-7 Bronchus filled with and surrounded by pus in the lung of a horse with glanders. (Hematoxylin-eosin stain, ×100.)

Laboratory diagnosis can be made by injection of infected material intraperitoneally into male guinea pigs or hamsters. The animals develop peritonitis that extends into the scrotal sac with severe inflammation known as the Strauss reaction.

In acute phases of glanders, abscess formation occurs. Later, the inflammatory focus is surrounded by a granulomatous reaction, but central karyorrhexis remains a prominent feature of the lesion. The lungs are the internal organs most typically involved (Figures 34-7 and 34-8), although septicemic glanders can involve the liver, spleen (Figure 34-9), bone, or brain. With chronic infection, multiple subcutaneous and intramuscular abscesses may develop.

TREATMENT

Studies indicate that sulfadiazine, 100 mg/kg/day in three divided doses for 3 weeks, is effective. Treatment with tetracyclines and streptomycin is also recommended.[274] *B. mallei* is sensitive in vitro to sulfamethizole, sulfathiazole, TMP-SMX, gentamicin, kanamycin, streptomycin, and tetracycline.[5] Ciprofloxacin and ofloxacin, but not norfloxacin, were found to be effective in treating experimentally infected guinea pigs and hamsters.[22] Therapy should be based on culture and sensitivity testing of isolates and clinical response to treatment.

Acute untreated septicemic cases are almost uniformly fatal within 7 to 10 days.[274] The prognosis is better in chronic forms of glanders, which can last for years, but deaths are still likely without adequate treatment.

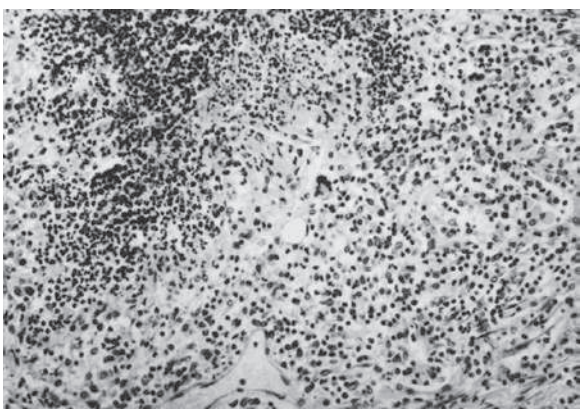

FIGURE 34-8 Gangrenous pneumonia with characteristic karyorrhexis in the lung of a horse with glanders. A multinucleated giant cell is in the center of the figure. (Hematoxylin-eosin stain, ×250.)

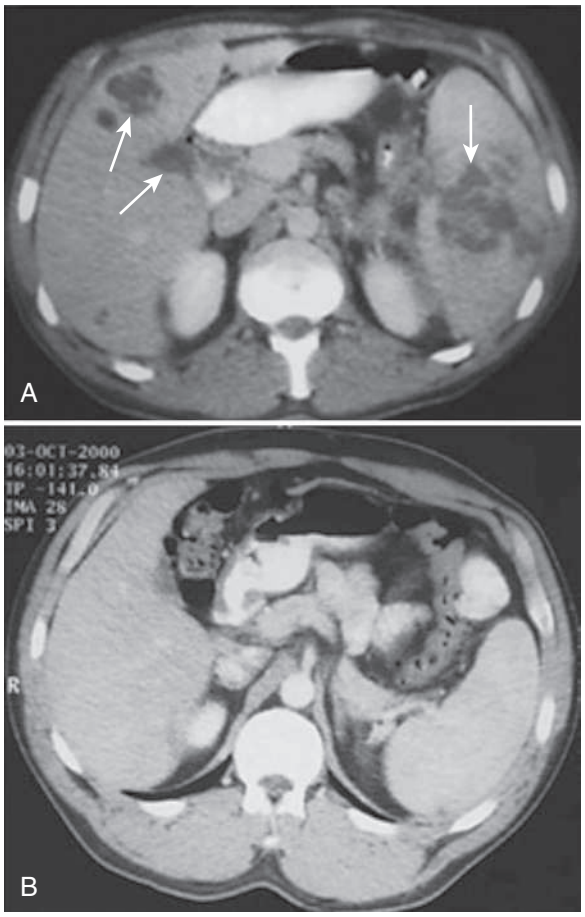

FIGURE 34-9 Abdominal computed tomographic scans from a patient with glanders. **A,** Before treatment, multiple hepatic and splenic abscesses (*arrows*). **B,** After treatment, almost complete resolution of the abscesses. *(From Srinivasan A, Kraus CN, DeShazer D, et al: Brief report: Glanders in a military research microbiologist,* N Engl J Med *345:256, 2001.)*

PREVENTION AND CONTROL

The only significant reservoir of *B. mallei* infection in nature is equids. If glanders were eradicated in them, it would disappear. National programs should be instituted in enzootic countries to eradicate the infection, by mallein or serologic tests of all horses, donkeys, and mules, followed by slaughter of reactive animals. People who handle horses in enzootic countries, including trekkers who pack gear into the wilderness on these animals, should be advised of the signs of glanders in equids and warned to avoid contact with sick animals.

Glanders can be transmitted from one person to another. Strict infection control should be exercised with suspected infected patients. Personnel should avoid contact with all secretions and respiratory droplets. Transmission is also a risk in the laboratory, so if this organism is being cultured, all work should be done under appropriate microbiologic hoods.

Some postulate that *B. mallei* could be an agent of bioterrorism in the future.

LEPTOSPIROSIS

Leptospirosis is an infectious disease caused by *Leptospira interrogans*. It can be acquired by animals and humans, usually by exposure to water contaminated with urine of wild or domestic animals. Adolf Weil first described the clinical picture of human leptospirosis in 1886. He described four febrile men with "particularities of an acute infectious illness with spleen tumor, jaundice, and nephritis." In addition, each had "severe nervous symptoms" and an enlarged liver. All recovered, and three had a biphasic clinical course with fever recurring after an afebrile period of 1 to 7 days. The term *Weil's disease* was coined by Goldschmidt in 1887. The carrier status was described in asymptomatic field mice by Ido and colleagues in 1915. Since then, the infection has been recognized both as a disease and as an asymptomatic carrier state in hundreds of animal species.

BACTERIOLOGY

Leptospira is a genus in the order Spirochaetales, an order characterized by thin, helical, gram-negative bacteria. There are nine pathogenic species, six nonpathogenic species that do not infect animal hosts, and five intermediate species with unknown pathogenicity. *L. interrogans* and *L. borgpetersenii* are the two species most often causing disease in animals and humans. More than 250 serovars, or serologically distinct strains of *Leptospira*, are known.[73] *Leptospira* organisms are spirochetes with hooked or curved ends, 6 to 20 µm long by 0.1 µm wide (Figure 34-10). They can grow on artificial media containing rabbit serum, such as Fletcher's semisolid and Stuart's liquid media, or on media containing albumin and fatty acids, such as Ellinghausen-McCullough-Johnson-Harris (EMJH) medium.[340] Because this requires special media, one should notify the laboratory of suspicion for *Leptospira* when sending cultures.

In describing outbreaks with shared epidemiologic or clinical features, several syndromes were originally ascribed to different serotypes, such as Fort Bragg fever caused by *Leptospira autumnalis*, swineherd's disease caused by *L. pomona*, and Weil's disease caused by *L. icterohaemorrhagiae*. Such terms are no longer commonly used because of overlap in the symptoms and epidemiology associated with various *Leptospira* serotypes.

EPIDEMIOLOGY

Leptospirosis is widespread throughout tropical and temperate areas of the world, with the incidence 10 times higher in tropical than in temperate climates. Leptospirosis is no longer a reportable condition, although it remains one of the most common zoonoses in the world and should be suspected in travelers with matching clinical syndromes. The disease is often underrecognized because of difficulties confirming the diagnosis and the many asymptomatic and oligosymptomatic infections in endemic

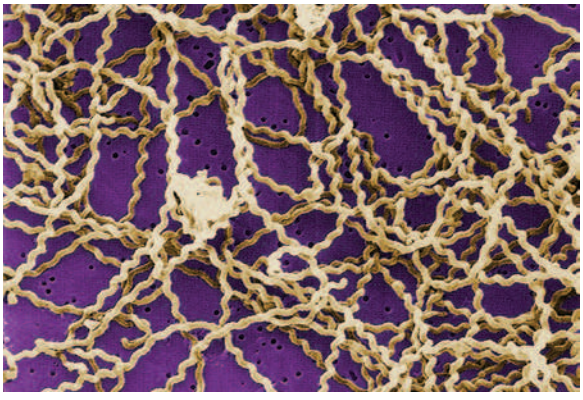

FIGURE 34-10 Scanning electron micrograph (SEM) of a number of *Leptospira* bacteria atop a 0.1-µm polycarbonate filter. Leptospires are long, thin, motile spirochetes that may be free living or associated with animal hosts; they survive well in freshwater, soil, and mud in tropical areas. Organisms are antigenically complex, with more than 200 known pathogenic serologic variants. Molecular taxonomic studies at the Centers for Disease Control and Prevention and elsewhere have identified 13 named and four unnamed species of pathogenic leptospires. Although some infected persons have no symptoms at all, leptospirosis can cause a wide range of symptoms, including high fever, severe headache, chills, muscle aches, and vomiting. Patients also may have jaundice (yellow skin and eyes), red eyes, abdominal pain, diarrhea, or a rash. *(From Centers for Disease Control and Prevention Public Health Image Library. Courtesy Janice Carr.)*

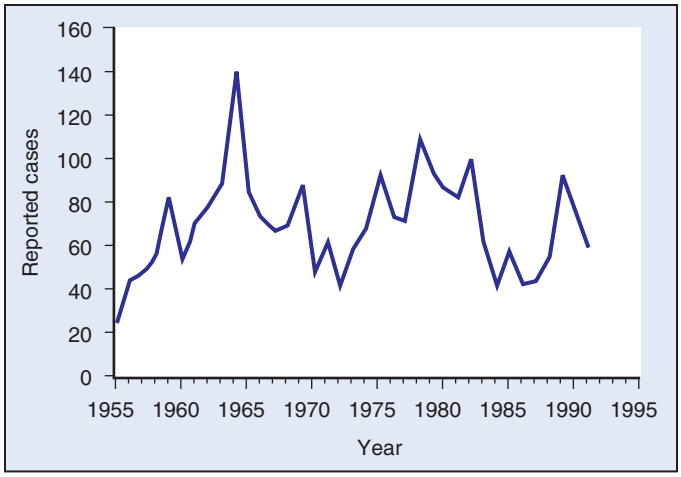

FIGURE 34-11 Reported annual cases of leptospirosis in the United States, 1955 to 1991. *(From Centers for Disease Control and Prevention: Reported annual cases of leptospirosis in the United States, 1955 to 1991,* MMWR *40, 1991.)*

areas.[262] It is particularly common in Southeast Asia and parts of Latin America, including some Caribbean islands.[121] Approximately 40 to 100 cases are reported annually in the United States (Figure 34-11), usually in the southern and Pacific coastal states, such as Hawaii. Active surveillance on Kauai and the east coast of the Big Island of Hawaii revealed a high incidence, accounting for a large proportion of flulike illness.[293] In 1996, five of 26 travelers returning from a white-water rafting trip in Costa Rica developed a febrile illness and were found to have leptospirosis.[63] In 1998, leptospirosis was implicated in an outbreak of acute febrile illness among athletes from 44 states and seven countries who participated in triathlons (which involve open-water swims in freshwater) in Springfield, Illinois, and Madison, Wisconsin.[64] In 2000, a leptospirosis outbreak was reported among adventure race participants in Florida.[335] These reports highlight the potential risk to those with exposure to contaminated freshwater.

Leptospirosis is a zoonosis in which certain serovars tend to have host specificity (Table 34-2). Dogs are usually associated with *L. icterohaemorrhagiae* and *L. canicola,* and swine and cattle are more frequently infected with *L. pomona* and *L. grippotyphosa,* although all four of these serovars or serotypes have been isolated from each host species. The major reservoir for *Leptospira* infections for humans and domestic animals is wildlife, principally wild mammals, although the organism has also been isolated from frogs and snakes, and serologically positive fish and turtles have been found.[218]

Leptospirosis infects both wild and domestic mammals. It may be asymptomatic, as is usually the case in wild animals, such as rodents, or may cause clinical infection, which can be fatal. Infected rodents are often the reservoirs for transmission, contaminating the environment, particularly water, with urine throughout their lifetime.[185] Animals that acquire clinical disease have fever, appear depressed, lose appetite, may become jaundiced, develop hemorrhages on mucous membranes, and in late stages of the disease may have renal failure.[154] In cattle, leptospirosis can cause stillbirths, hemoglobinuria, and thickened yellowish or blood-tinged milk. Leptospires have been isolated from the milk of cattle and goats. A theoretical risk exists that leptospirosis could be transmitted by consuming such milk. Pasteurization should destroy organisms. Stillbirths or delivery of weak piglets is a common sign of leptospirosis in swine. Cats are rarely affected by leptospirosis. They may be resistant to the disease because they are frequently exposed to infection through catching mice and other rodents. Leptospirosis has been suspected as a cause of recurrent uveitis in horses. This is of more interest in comparative pathology than in public health, because horses infrequently transmit the infection to humans.

TRANSMISSION

Animals are the major carriers of the disease and contaminate the environment by shedding organisms in their urine. Most human cases are environmentally acquired by indirect contact with contaminated water or soil and rarely transmit the disease themselves.[32] Usual ports of entry include nonintact skin, mucous membranes, or conjunctivae. Discovering the original animal source is often difficult. A wet, alkaline environment favors survival of *Leptospira,* with tropical, unpolluted, nonsaline water providing an optimum environment for infection. Heavy tropical rains increase infection risk by saturating soil, flushing leptospires into surface water, and drawing rodents and other small mammals into swampy areas. Infection can also be acquired by direct contact with infected animal blood and tissues, such as animal abortion products, or with infected animal urine.[200] Factors strongly associated with acquiring leptospirosis in Hawaii include household use of rainwater catchment systems and the presence of skin cuts at the presumed time of exposure.[293]

Leptospirosis is an occupational problem for veterinary, agricultural, sewer, slaughterhouse, laboratory, and military personnel.[120,159,293] Dairy farmers are at risk in milking parlors, probably through exposure to cow's urine.[9,170] Leptospirosis poses a vocational risk for hunters, trappers, hikers, and persons who swim in freshwater, such as ponds and streams, that may be contaminated with infected urine. Endemic leptospirosis is often a disease of poverty because of poor housing and sanitation.[277] Large-scale outbreaks are common during natural disasters, such as hurricanes and flooding, causing thousands of cases.[175,236]

SYMPTOMS

The incubation period for leptospirosis is usually 7 to 12 days (range, 2 to 26 days).[292] The disease is classically biphasic, although it may manifest with a variable clinical course.[172,280] The primary stage lasts 4 to 7 days and is characterized by organisms in blood, cerebrospinal fluid (CSF), and various body tissues. During the initial phase, more than half of victims have sudden onset of fever, chills, severe malaise, myalgias, headache, lymph

TABLE 34-2 Animal Reservoirs of Leptospires Isolated from Humans

Serogroup (Serovar)	Domestic Animals	Wildlife
Icterohaemorrhagiae (Icterohaemorrhagiae)	Dogs, cattle, swine	Brown rat, house rat, cotton rat, Pacific rat, house mouse, muskrat, gray fox, red fox, opossum, striped skunk, woodchuck, nutria
Canicola (Canicola)	Dogs, cattle, swine	Striped skunk, raccoon, armadillo, mongoose
Pomona (Pomona)	Dogs, cattle, swine, goats, sheep, horses	Striped skunk, raccoon, wildcat, opossum, woodchuck, red fox, deer, armadillo
Grippotyphosa (Grippotyphosa)	Dogs, cattle, swine	Muskrat, fox squirrel, gray squirrel, bobcat, cottontail rabbit, swamp rabbit, raccoon, striped skunk, red fox, gray fox, vole, opossum
Hebdomidis (Hardjo)	Cattle	None

Modified from Hanson LE: Leptospirosis in domestic animals: The public health perspective, *J Am Vet Med Assoc* 181:1505, 1982.
*Isolated in the United States.

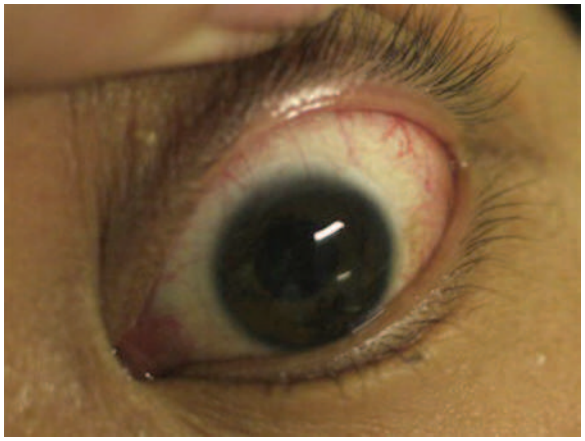

FIGURE 34-12 Conjunctival injection. *(From Kutsuna S, Kato Y, Koizumi N, et al: Travel-related leptospirosis in Japan: A report on a series of five imported cases diagnosed at the National Center for Global Health and Medicine,* J Infect Chemother *21:218-223, 2014.)*

node enlargement, and conjunctival injection, usually without exudate. Nausea, vomiting, and abdominal pain may occur. A nonproductive cough is common. The initial clinical differential diagnosis is broad and includes meningitis, hepatitis, influenza, encephalitis, and viral illness. The rickettsioses, typhoid fever, brucellosis, relapsing fever, toxoplasmosis, dengue fever, malaria, yellow fever, septicemia, Kawasaki syndrome, and toxic shock syndrome are also differential diagnoses.[159] The conjunctival injection seen in more than half of patients with leptospirosis is not typical of many other diseases and may help narrow the differential[358] (Figures 34-12 and 34-13).

The primary stage is usually followed by an afebrile period of 1 to 2 days. The onset of the second stage coincides with development of IgM antibodies. The organisms usually cannot be cultured from blood or CSF during this phase but can be isolated from urine for weeks or months. During the second stage, the patient may have fever, but the temperature is lower than in the primary stage. Headache is persistent, severe, and unresponsive to analgesics. It often heralds the onset of meningitis, one of the common complications of the secondary stage.

Myalgias, abdominal pain, nausea, and vomiting can occur in the second as well as in the primary stage. In addition to the conjunctival injection seen in the primary stage, uveitis (iridocyclitis) can be seen in the secondary stage. This can cause long-term ocular damage.[320] Occasionally, pharyngitis and a macular, purpuric, or ecchymotic rash occur (Figure 34-14). Rarely, endocarditis or myocarditis occurs. In a clinical study of leptospirosis

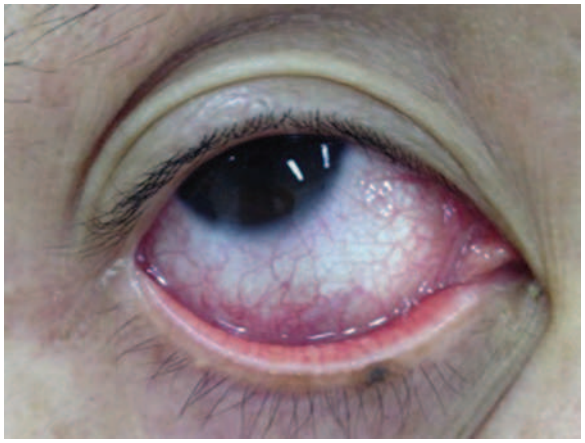

FIGURE 34-13 Conjunctival injection in leptospirosis. *(From Kutsuna S, Kato Y, Koizumi N, et al: Travel-related leptospirosis in Japan: A report on a series of five imported cases diagnosed at the National Center for Global Health and Medicine,* J Infect Chemother *21:218-223, 2014.)*

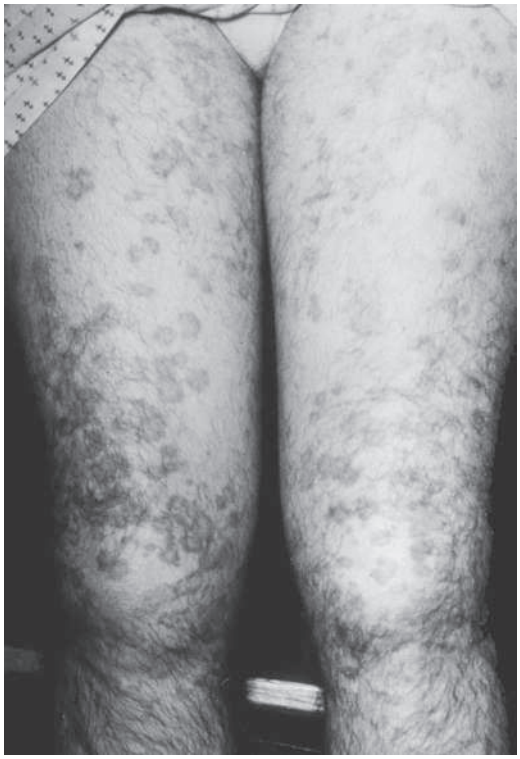

FIGURE 34-14 Hemorrhagic macular rash in a patient with leptospirosis. *(Courtesy University of Massachusetts Medical School.)*

in Barbados, cardiac arrhythmias and myocarditis occurred in 18% and pericarditis in 6% of patients.[111]

Splenic enlargement develops in approximately 20% of patients in the second stage. Hepatomegaly is sometimes found, especially if the patient is icteric. "Weil's disease" describes severe illness characterized by jaundice and renal disease that occurs in a minority of patients.[367] Mortality in cases with jaundice exceeds 15% but is rare in anicteric cases; as such, jaundice is a serious prognostic sign. Mortality depends on the patient's prior condition and is higher in older individuals than in young adults, with an overall case fatality rate of approximately 5%. In hospitalized patients, mortality can reach 52%.[77] Death can occur from hemorrhagic manifestations as a result of vasculitis, renal or hepatic failure, cardiogenic shock, or myocarditis. Severe pulmonary hemorrhagic syndrome is the main cause of mortality.[13]

DIAGNOSIS

Laboratory findings in leptospirosis include moderate leukocytosis, usually caused by an increase in neutrophils, elevated ESR, and less often thrombocytopenia. Thrombocytopenia is an indicator of severe disease and increases the risk for bleeding. Elevated bilirubin level (up to 65 mg/dL, mainly direct bilirubin), greatly increased serum creatine kinase level (often five times normal), and a less-than-fivefold increase in aspartate transaminase may suggest the diagnosis. An elevated blood urea nitrogen level is a common finding. Serum amylase concentration may also be elevated.

Definitive diagnosis of leptospirosis can be made by culture of the organism from clinical specimens or a positive microscopic agglutination test (MAT). Culture is performed on Fletcher's, Stuart's, EMJH,[340] or Tween 80–albumin medium. Blood and CSF should be cultured during the first week of illness; urine should be cultured thereafter. Blood cultures are insensitive and may take up to 2 to 3 weeks to multiply to a level sufficient to obtain detectable densities.[156] The likelihood of obtaining a positive culture is greatly diminished once antibiotics have been given. Oxalated blood samples can be sent to the laboratory for culture because the organisms can remain viable in oxalated blood for up to 11 days.

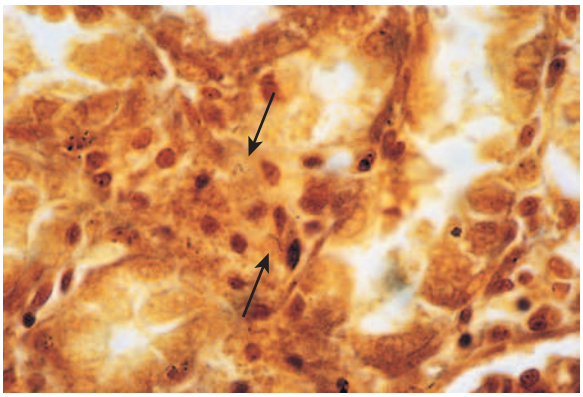

FIGURE 34-15 *Leptospira icterohaemorrhagiae (arrows)* in the kidney of an experimentally infected dog. (Warthin-Starry silver stain, ×1000.)

Some physicians have relied on darkfield examination for identification of the organisms, but this method is not considered reliable. Artifacts such as fibrin are readily mistaken for leptospires. The spirochetes can be demonstrated in tissue sections with silver stains (Fig. 34-15).

The MAT is the gold standard serologic test for leptospirosis and is considered positive if there is a fourfold rise in antibody titer.[368] The test uses live organisms and is available in relatively few reference laboratories. A genus-specific MAT employs a single, broadly reactive antigen.[374] An IgM-specific dot-ELISA is comparable to MAT in ability to detect recent exposure to leptospires and is rapid and simpler.[260] Latex agglutination and indirect hemagglutination have high specificity and sensitivity and are especially useful early in the infection.[265] A urine dipstick is available as a rapid screening test for the diagnosis of leptospirosis; if positive, a serum specimen can be sent to a reference laboratory for the MAT for confirmation.[313]

TREATMENT

Treatment of leptospirosis with antibiotics is most effective when begun during the first week of illness, preferably within 4 days of symptom onset. Although antibiotics were thought to have little value after this time, more recent studies indicate that they may still have some usefulness.[375] The treatment of choice is doxycycline, 100 mg orally (PO) twice daily for 7 days, or for children 8 years or older, 2 mg/kg/day in two equally divided doses, not to exceed 200 mg daily.[229] Azithromycin, 10 mg/kg PO on day 1 (maximum 500 mg/day), followed by 5 mg/kg/day PO once daily on subsequent days (maximum 250 mg/day), or amoxicillin, 25 to 50 mg/kg in three equally divided doses (maximum 500 mg/dose), can also be used, especially for children less than 8 years old and pregnant women. Alternative regimens for hospitalized patients include penicillin, 250,000 to 400,000 units/kg/day IV in four to six divided doses (maximum 6 to 12 million units daily); ceftriaxone, 80 to 100 mg/kg IV once daily (maximum 2 g daily); cefotaxime, 100 to 150 mg/kg/day IV in three to four equally divided doses; or doxycycline, 4 mg/kg/day IV in two equally divided doses (maximum 200 mg/day, not in children or pregnant women). Several studies have demonstrated comparable efficacy for doxycycline, penicillin, ceftriaxone, cefotaxime, and azithromycin.[39,268]

A Jarisch-Herxheimer reaction may occur after treatment. This is a response to release of endotoxins, usually occurring within 2 to 6 hours after initiating therapy, with sudden onset of fever, chills, malaise, headache, tachycardia, and hypotension. The reaction typically resolves spontaneously within 24 hours.[150]

Other than antibiotic treatment, therapy for leptospirosis is supportive, including fluid therapy, dialysis for renal failure,[177] and transfusion for hemorrhagic complications. Recovery from leptospirosis apparently leaves serovar-specific immunity. Individuals can become infected with other serovars. Assuming that the infection and hemorrhagic complications can be controlled, the long-term prognosis after successful treatment is good. Renal and hepatic function usually return, but headache and ocular damage may persist.[320]

PREVENTION

Prevention of human leptospirosis is based on avoiding infected animal tissues and areas contaminated by animal urine, blood, or tissue. Individuals at particularly high risk should be educated about prevention and encouraged to wear protective clothing, such as rubber gloves, when handling infective material. Swimming in freshwater ponds and streams likely to be heavily contaminated by urine from livestock or wildlife should be discouraged.

Doxycycline, 200 mg once a week, effectively prevented infection in U.S. soldiers training in Panama.[344] Such prophylactic treatment could be given to individuals at unusually high risk.

Although *Leptospira* vaccines have been experimentally produced for human use and are available in several other countries, no product is approved or commercially available in the United States.[156] Vaccines are available for animals. Immunization of domestic animals has primarily a veterinary benefit, in that the animals are protected from clinical disease. Immunity lasts about 6 months, but immunization does not guarantee that the animal cannot become infected. Several human cases have been traced to immunized dogs that apparently were still able to shed organisms.[122] Since then, some veterinary vaccines have been shown experimentally to reduce the renal carrier state.[179]

MELIOIDOSIS

Melioidosis is an infection caused by the bacterium *Burkholderia* (formerly *Pseudomonas*) *pseudomallei,* which lives freely in soil and water.[399] Disease is spread from the environment to both humans and other animals. Whitmore and Krishnaswami[380] first described the causative agent and disease process in humans in Rangoon, Burma, in 1912.[198]

BACTERIOLOGY

B. pseudomallei is a bipolar, gram-negative, aerobic rod approximately 0.5 to 1 μm in width and 3 to 5 μm in length. It grows readily on standard laboratory media at 37°C (98.6°F). After 48 to 72 hours of growth, distinctive wrinkled colonies with a "daisy head" appearance are formed. These give off a pungent, putrefactive odor.[197] The organism is oxidase positive and nonpyocyanogenic. It is resistant to colistin and gentamicin in vitro.[149] In 1992, Yabuuchi and co-workers proposed that seven species, formerly of *Pseudomonas* RNA group II, should be transferred to a new genus, *Burkholderia,* with *B. cepacia* as the type species.[399]

EPIDEMIOLOGY

Most cases of melioidosis have been reported in areas between 20 degrees north and 20 degrees south of the equator.[148] A majority of cases have been reported from Southeast Asia and tropical Australia. However, cases of melioidosis have been increasingly reported outside of classic endemic areas, possibly attributed to global warming.[78] The most heavily endemic areas include Myanmar (Burma), Malaysia, Vietnam, Singapore, Cambodia, Thailand, Java, Borneo, New Guinea, and northern Australia. Occasional human and animal cases have been reported from Central India, Sri Lanka, Niger, Madagascar, Ecuador, Panama, Aruba, and Mexico. Cases from the western hemisphere have been reviewed.[17]

Melioidosis is an especially important cause of disease in the northeast provinces of Thailand and northern Australia. It is implicated in 20% of community-acquired septicemic cases in Thailand and is the most common cause of fatal community-acquired bacteremic pneumonia in northern Australia.[76,96] In Australia, it manifests seasonally. *B. pseudomallei* survives during Australia's dry season in the clay layer of the soil, 25 to 30 cm (10 to 12 inches) below the surface, and can be brought to the

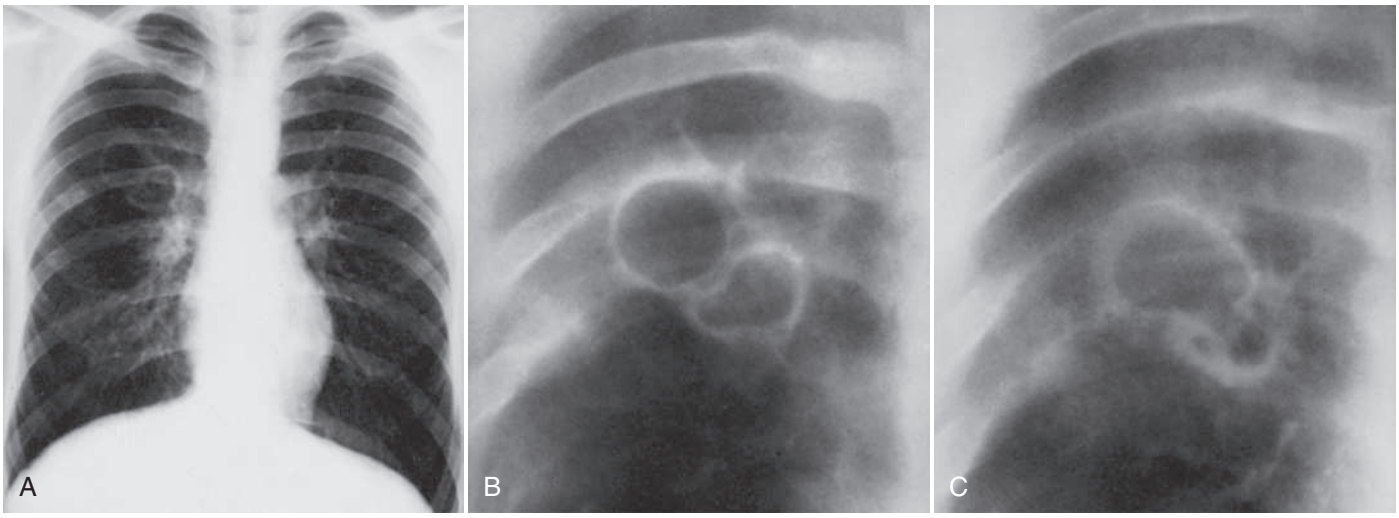

FIGURE 34-16 Subacute melioidosis with thin-walled cavities in the right upper lobe of the lung simulating tuberculosis in an American soldier serving in Vietnam. Sputum cultures were positive for *Burkholderia pseudomallei* and negative for acid-fast bacilli. The patient had a fever; cough with purulent, blood-streaked sputum; chest pain; and weight loss. **A,** Posteroanterior view of the chest, and **B,** anteroposterior (AP) tomogram of the right upper lobe, showing two thin-walled cavities with virtually no surrounding inflammatory reaction in the posterior segment of the right upper lobe. **C,** AP tomogram of the right upper lobe obtained 3 weeks later shows slight diminution in size of the lower, more medial cavity, which has merged with the larger cavity above it. The patient was treated with tetracycline for 2 months with subsequent clearing of his cavitary melioidosis. The subacute or subclinical forms of melioidosis must be considered in the differential diagnosis of thin-walled lung cavities in addition to other entities, such as tuberculosis, coccidioidomycosis, and bullae. *(From Palmer PES, Reeder MM, editors: The imaging of tropical diseases: With epidemiological, pathological and clinical correlation, Berlin, 2000, Springer. Reprinted with permission from Springer Science and Business Media.)*

surface and distributed by water seeping through this layer during the wet season.[149] Melioidosis is rare in the United States, with about five cases reported annually, usually in travelers or visitors, such as cases in Florida in 2005 traced to recent travel from Honduras.[69]

TRANSMISSION

Melioidosis is a saprozoonosis transmitted to animals and humans from the environment; transmission does not generally occur between living organisms. Rare cases of transmission from sheep to humans in Australia have been described.[82] There is a single case of presumed transmission by the venereal route.[230] Disease is reported much more often in adults than in children.

Clinical and subclinical infections occur in a variety of animals, most often sheep, goats, and swine. Infections in animals offer no direct threat to human health but are epidemiologic indicators that the organism is in a given geographic area.[148] Transmission is thought to occur by direct percutaneous inoculation through wounds contaminated with soil or water, ingestion, aspiration, or inhalation of infective droplets. A high incidence of pulmonary melioidosis in helicopter crew members in Vietnam was ascribed to inhalation of dust and aerosols raised by the helicopters operating in highly endemic areas.[148] However, the predominant route of transmission is percutaneous inoculation.[96]

SYMPTOMS

Most human *B. pseudomallei* infections are asymptomatic, as indicated by the high prevalence of seropositivity without clinical melioidosis within endemic areas. Active disease is most likely to be seen in individuals with predisposing conditions, particularly diabetes mellitus, alcoholism, neoplasms, malnutrition, and various forms of immunodeficiency.

Clinical disease can occur in acute, subacute, or chronic forms. Approximately half of patients become bacteremic, and up to a quarter develop septic shock.[97] The lungs are the organs most frequently involved. Pulmonary melioidosis can mimic TB in that the upper lobes are most frequently involved, cough is productive, sputum often contains blood, and patients complain of chest pain and fever (Figure 34-16). However, calcifications in the lungs and hilar lymph nodes typically seen in TB are rarely seen with melioidosis. An entire lobe or major segment of a lobe may be consolidated, and multiple pulmonary abscesses may be scattered in the lung parenchyma.

Septicemia can develop in the acute form of melioidosis and may mimic other forms of gram-negative sepsis in its manifestations. Skin ulcers and abscesses are also very common. Multiple abscesses can form in skin, lungs, liver, spleen, kidneys, and bone, but the CNS is rarely involved. Without treatment, the case fatality rate exceeds 90%.

In the subacute and chronic forms of disease, abscesses can form in internal organs and may drain through sinus tracts. Melioidosis has been referred to as a "medical time bomb" because infection can lie dormant for months or years, only to become manifest when resistance is lowered. An incubation period as long as 26 years has been reported.[227] The infection should be suspected in anyone with a compatible clinical picture, including fever of unknown origin, who has resided in or visited an endemic area.

DIAGNOSIS

The only definitive diagnostic procedure is culture of the organism from blood, bone marrow, sputum, pus, or infected tissue. *B. pseudomallei* readily grows on blood culture media but can be misidentified as *Pseudomonas* or other *Burkholderia* species in nonendemic locations.[205] Gram stain may reveal gram-negative bacilli and a characteristic bipolar staining with a "safety pin" appearance. Several serologic tests are available but are not reliable, because many individuals from endemic areas have antibodies to the organism without any evidence of clinical disease. An indirect hemagglutination antibody titer of 1:40 or greater is considered compatible with infection, as is a CF titer of 1:10 or greater. Rising titers by IgM IFA are probably the best immunologic indication of infection.[323]

No pathognomonic lesions are seen histologically. The abscesses consist of central areas of necrosis without unique or

distinctive features that would permit definitive histopathologic diagnosis.

TREATMENT

All patients with melioidosis should be treated with IV antibiotics for at least 2 weeks, followed by oral therapy for a minimum 3 months. Ceftazidime, 50 mg/kg up to 2 g IV every 6 hours, has historically been the preferred treatment. However, meropenem, 25 mg/kg up to 1 g IV every 8 hours, and imipenem, 25 mg/kg up to 1 g IV every 6 hours, may also be used, and it has been suggested that meropenem may produce better outcomes in severe disease.[79] Current oral recommendations include high-dose TMP-SMX, 8 mg/kg TMP and 40 mg/kg SMX up to 2 double-strength tablets (320/1600 mg) twice daily, with or without doxycycline, 2.5 mg/kg up to 100 mg twice daily. It is sometimes recommended to add folic acid, 0.4 mg PO daily, to the TMP-SMX regimen because of folic acid antagonism from this medication. For children younger than 9 years or pregnant women, recommended treatment is amoxicillin-clavulanate extended-release tablets twice daily for 20 weeks. Even with compliance, relapse rate is up to 10%. In vitro sensitivity tests do not always correlate with clinical response to antibiotics. Therapy must be given at sufficient dosage and duration to avoid recurrence of infection and emergence of resistant organisms.

PREVENTION AND CONTROL

In the field, prevention consists of avoiding ingestion or inhalation of potentially infective soil or water. Wounds, burns, and other injuries should be thoroughly cleaned to avoid infection through contamination. Reasonable care and precautions should be taken in handling purulent drainage of blood, sputum, and other materials from patients with melioidosis. Preliminary studies have included a variety of vaccine candidates that could have substantial benefits for persons in endemic areas.[381]

RAT-BITE FEVER

Rat-bite fever is a systemic illness characterized by two distinct syndromes caused by infection with either *Streptobacillus moniliformis* or *Spirillum minus*. *S. moniliformis* causes most cases in the United States, and *S. minus* mostly causes the disease in Asia. Rat-bite fever, also known as Sodoku and Haverhill fever, has been present for more than 2000 years. Long known in the Indian subcontinent, the first clinical U.S. report was in 1839, but the pathogen was unknown until isolated from a rat-bitten man by Schottmuller in 1914 and identified as *Streptothrix muris ratti*. It was renamed in 1925 to *Streptobacillus moniliformis*. In 1926, an outbreak in the milk supply in Haverhill, Massachusetts, led to the name Haverhill fever. Originally thought to be a different bacterium, it was named *Haverhillia multiformis* but was later found to have the same DNA. The second bacterium causing rat-bite fever was originally discovered in the early 19th century and named *Sporozoa muris*. It was renamed in 1924 to *Spirillum minus*. It is also referred to as Sodoku (*so*, "rat"; *doku*, "poison").

EPIDEMIOLOGY

Streptobacillus moniliformis and *Spirillum minus* are parts of the normal oral flora of rodents, including squirrels, and infection results from bites, scratches, or handling infected animals.[211] Rat-bite fever may also result from contact with wild and domestic carnivores, such as weasels, dogs, cats, and pigs, which may have been infected when hunting rats and mice.[317] Almost all domestic and wild rats carry *S. moniliformis*.[114] Fewer than 70 cases have been reported in North America, with at least half caused by *S. moniliformis* in laboratory workers. Rat-bite fever is not a reportable disease; therefore these numbers are likely underestimated.

At least 10% and up to 100% of rats are nasopharyngeal carriers of *Streptobaccillus*.[8,59,143] Risk of infection after a rat bite appears to be 10%, with 13% mortality if untreated. Patients with disease caused by *S. minus* are primarily children of lower socioeconomic groups exposed to poor sanitation and heavy rodent populations.[251] Demographics of the disease are shifting; rat-bite fever is now being seen in pet owners and people who work in pet stores. In a series of cases from California from 2000 to 2012, more than 90% were associated with pets.[2] Rare cases can occur in any setting and can easily be fatal, particularly when the proper diagnosis is not suspected.[68]

STREPTOBACILLARY TYPE

Streptobacillary rat-bite fever (Haverhill fever) is caused by *S. moniliformis*, an aerobic, nonmotile, gram-negative bacillus. The onset of symptoms usually occurs within 1 week of the bite, but the incubation period may extend to several weeks, during which time the original wound usually heals completely. A bite need not be present, because the disease can also be transmitted by contaminated food, milk, or water.[125] *S. moniliformis* has also been transmitted by simply playing with pet rats, without history of bite or injury.[288]

Symptoms

Although many rats may become colonized with *S. moniliformis*, few show symptoms of the disease. In humans, the initial incubation period is less than 7 days, and initial symptoms include fever, chills, migratory arthralgias, cough, malaise, headache, and less frequently, local lymphadenitis and septic arthritis (which in rare cases can be a presenting symptom).[101] These are followed by nonpruritic morbilliform or petechial rash, which often involves the palms and soles. Migratory polyarthritis develops in approximately 50% of patients and may last several years. Generalized lymphadenitis may be present; splenomegaly and hepatomegaly are rare.[341] Patients who acquire the disease through ingestion have more vomiting and an increased rate of pharyngitis. Rare complications include pericarditis, endocarditis, pericardial effusions, bronchopneumonia, pneumonitis, periarteritis nodosa, volvulus, and septicemia.[113,186] Because rate-bite fever is a rare but potentially fatal disease, it should be considered in patients with a history of rodent exposure presenting with rash, fever, and joint pain.[2]

When a history of animal bite is lacking, differential diagnosis must include rickettsial and viral infections. Fever and rash may suggest meningococcemia, but meningeal signs are lacking in rat-bite fever.

Diagnosis

Suspecting clinicians should notify the laboratory staff of the possibility of *S. moniliformis* because microbiologic diagnosis is difficult and identification by culture requires experienced laboratory workers who seek the organism.[2] Definitive diagnosis requires demonstration of rising antibody titers or culture of the bacillus from blood, joint fluid, pustules, or original bite location. Leukocytosis with left shift is common, and agglutinating antibodies for the bacillus appear during the course of the disease. The Venereal Disease Research Laboratories (VDRL) test shows a false-positive result for 25% of patients with rate-bite fever. Culture of the bacteria is difficult because the commercial aerobic blood culture anticoagulant (Liquoid) inhibits growth of the bacteria. Anaerobic cultures may show growth because this anticoagulant is not added. Panmede (a papin digest of ox liver) supplemented into a brain-heart infusion of cysteine broth in an anaerobic culture media has shown promise for culturing the bacteria.[319] On autopsy, interstitial pneumonia, fibrinous endocarditis, mononuclear meningitis, hepatosplenomegaly, and mononuclear cell infiltrates in regional lymph nodes have been found.[316]

Treatment

Untreated, rat-bite fever runs a course of several weeks; prolongation of symptoms should raise the suspicion for endocarditis. Mortality in untreated persons is up to 25%, with most deaths caused by endocarditis and pneumonia.[211] The disease can be fulminant. Two previously healthy adults died within 3 to 6 days after exposure to rats,[152] and an infant bitten by a wild rat died 4 days after the bite.[316] The treatment of choice is IV penicillin

G, 200,000 units every 4 hours for 7 to 10 days, followed by an oral course (penicillin V, 500 mg PO four times daily, ampicillin (500 mg four times daily), or amoxicillin (500 mg three times daily) to complete a 14-day course of therapy.[341] Effective alternatives for penicillin-allergic patients are doxycycline, 100 mg IV or PO twice daily; tetracycline, 30 mg/kg/day PO in four divided doses; or streptomycin, 15 mg/kg/day IM in two divided doses. Erythromycin is not effective. Complications such as endocarditis should be treated with high-dose IV potassium penicillin G, 10 to 20 million units/day, as well as streptomycin or gentamicin for 4 weeks.[286] Vancomycin and gentamicin can also be used in patients sensitive to penicillin.[211] The organism has both a bacillary and a cell wall–deficient L phase, which is thought to account for some of the antibiotic failures. The bacterial phase responds to penicillin, streptomycin, and tetracycline, whereas the L phase is resistant to penicillin.

SPIRILLAR TYPE

Mainly found in Asia, spirillar rat-bite fever is caused by *Spirillum minus*, a gram-negative, tightly coiled, spirillar microorganism. It is usually transmitted by infected wild rats, although cats have also been implicated. The general setting of socioeconomic deprivation in which this disease occurs is the same as in the streptobacillary form; cases in laboratory animals are unusual. The incubation period is 7 to 28 days, during which the bite lesion often heals.[143]

Symptoms

After the incubation period, the original wound can exacerbate with local development of pain, erythema, purplish discoloration, and swelling. An ulcer may develop, followed by chills, fever, lymphadenitis, and dark-red macular rash. Myalgias are common, but arthritis is absent, which helps in the differentiation from streptobacillary fever. Leukocytosis and a false-positive VDRL test are often present. The disease is episodic and relapsing, with a 24- to 72-hour cycle. The differential diagnosis includes rickettsial and viral diseases when the history of animal bite is not present. *S. minus* infection is differentiated from *S. moniliformis* infection by a longer incubation period, relapsing fever and illness, absence of arthritis, large macular or papular rash, and manifestations at the bite site, usually involving lymphadenitis, and still present when systemic illness occurs.[341]

Diagnosis and Treatment

Definitive diagnosis of the spirillar type rests on demonstrating the presence of *S. minus* in a darkfield preparation of exudate from an infected site. The patient's blood can be inoculated into mice, which may be tested for subsequent infection. The mortality from untreated disease is considerably lower than that from streptobacillary fever. The untreated course spans several months. Antibiotic therapy is the same as for streptobacillary fever.[129,143]

PLAGUE

Plague, a bacterial disease caused by *Yersinia pestis* and transmitted by the bites of infected fleas, has occurred in explosive epidemics. Humans are incidental hosts when they contact rodent fleas or handle infected animals, and they do not contribute to the natural disease cycle. Probable epidemics of plague occurred during the Peloponnesian War, as described by Thucydides, in approximately 400 BC. It ravaged the Roman Empire and western Europe during the age of Justinian and continued through the 7th century. The best-known and most devastating epidemic started in 1348. Known as the Black Death, the infection spread from Asia throughout western Europe, killing one-third of the population (Figure 34-17).[133] Having gained notoriety from three major pandemics that killed hundreds of millions of people, plague is now a concern for bioterrorism. Plague is a category A bioterrorism agent and is a reportable disease under the International Sanitary Regulations.[202]

The first person to characterize the disease microscopically was Yersin, during the third plague pandemic in the late 19th century, after the disease ravaged the port of Hong Kong. The rodents escaping from that pandemic spread the highly virulent *Yersinia pestis orientalis* into North and South America.[384]

FIGURE 34-17 Burial of plague victims.

Plague is carried by various rodent reservoir hosts and transmitted by rodent fleas. Most of the outbreaks in Europe have been ascribed to importation of plague from enzootic foci in Asia, by ships bringing infected rats and people to port cities. A matter of considerable historical and epidemiologic interest is how and why the various epidemics eventually subsided. Theories include development of mutant bacteria; changes in patterns of shipping, building, and hygiene; replacement of *Rattus rattus* by *Rattus norvegicus,* in the case of the Black Death (Figure 34-18); and development of immunity in animals and humans.[112] Improvement in urban hygiene, rodent-proof housing, and protective clothing have helped decrease the incidence of this disease in the past century.[46]

BACTERIOLOGY

Yersinia pestis is a gram-negative, nonmotile, nonsporulating rod with a bipolar, or "safety-pin," appearance in smears with Giemsa or Wayson stain (Figure 34-19).[51] The appearance is somewhat variable by Gram staining. Most standard bacteriologic media support the growth of the organism aerobically or under facultative anaerobic conditions. Optimal in vitro growth occurs at 28°C (82.4°F), at which temperature colonies become visible on plain agar in approximately 48 hours.

The disease harbors three virulence plasmids that encode several virulence factors. These include surface capsular material that is antiphagocytic, the ability to synthesize purines even if phagocytosed, resistance to complement-mediated lysis,[202] and a

FIGURE 34-18 Norway rat (*Rattus norvegicus*) in a corn storage bin in Kansas City, Missouri. *R. norvegicus* is known to be a reservoir of bubonic plague (transmitted to humans by the bite of a flea or other insect), endemic typhus fever, rat-bite fever, and a few other dreaded diseases. *(From Centers for Disease Control and Prevention Public Health Image Library.* http://phil.cdc.gov/Phil/home.asp.*)*

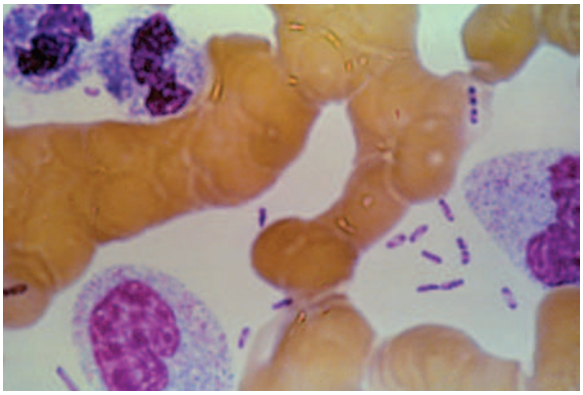

FIGURE 34-19 Wayson stain of *Yersinia pestis*. Note the characteristic "safety pin" appearance of the bacteria. *(From* http://www.cdc.gov/ncidod/dvbid/plague/wayson.htm.*)*

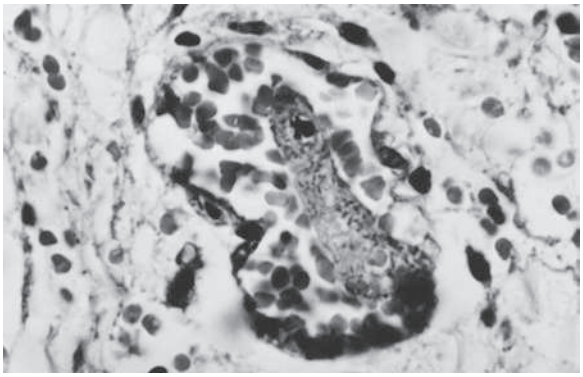

FIGURE 34-21 Thrombus in a vein in the subcutis of a prairie dog naturally infected with plague. Many organisms (*fine stippling*) are present in the thrombus. (Hematoxylin-eosin stain, ×1000.)

surface component needed for iron uptake. Virulence factors mediated by a plasmid include dependence on environmental calcium for growth at 37°C (98.6°F) and production of v and w[212] antigens. The relationship between calcium dependence and virulence is under investigation.[133]

EPIDEMIOLOGY

The epidemiology of plague is complex. Various fleas can transmit the infection between reservoir rodent hosts and humans. In major epidemics the prominent carriers were the tropical rat flea (*Xenopsylla cheopis*) (Figure 34-20) and the black rat (*Rattus rattus*), although many other flea and rat species are known to transmit plague. Children and males have a slight preponderance for the disease.[45]

Smoldering foci of infection are maintained in nature in wild rodents and their fleas. In the United States, enzootic (maintenance) hosts include deer mice (*Peromyscus maniculatus*) and various voles (*Microtus* spp.). Epizootic (amplifying) hosts include the prairie dog (*Cynomys* spp.) (Figure 34-21) and ground squirrel (*Spermophilus* spp.). Other rodents and lagomorphs that maintain infection include chipmunks (*Eutamias* spp.), marmots (*Marmota* spp.), wood rats (*Neotoma* spp.), rabbits (*Sylvilagus* spp.), and hares (*Lepus* spp.).[269] Conditions that provide adequate food and shelter for plague-susceptible rodents put humans at increased risk for acquiring the disease.[62]

Enzootic foci of plague remain in parts of Asia, Africa, and South America,[48,269] as well as in the western United States. From 2000 to 2009, cases of plague reported to the World Health Organization (WHO) from 16 countries found that African countries were responsible for more than 97% of the world's 21,725 cases. Recent outbreaks have occurred in the Democratic Republic of Congo (2005, 2006), China (2009), and Peru (2010).[11]

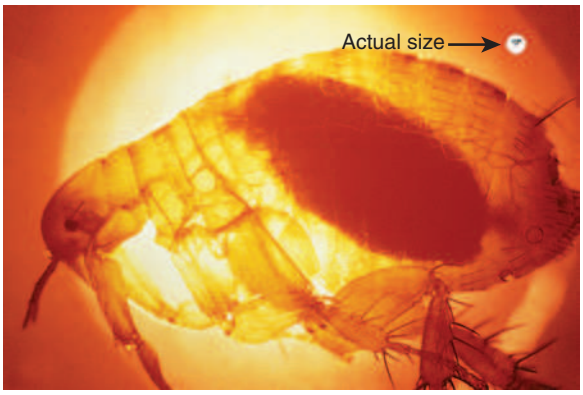

FIGURE 34-20 Male *Xenopsylla cheopis* (Oriental rat flea) engorged with blood. This flea is the primary vector of plague in most large plague epidemics in Asia, Africa, and South America. Both male and female fleas can transmit the infection. *(From* http://www.cdc.gov/ncidod/dvbid/plague/index.htm.*)*

The major enzootic U.S. states are New Mexico, Arizona, California, Colorado, Oregon, Nevada, and Utah. Plague season tends to run from February through August in North America and is related to the presence and prevalence of the vectors and hosts.[45] Between 1900 and 2012, there have been 1006 reported plague cases in the United States. Overall U.S. geographic distribution of plague has corresponded to roughly three distinct epidemiologic phases (Figure 34-22). Between 1900 and 1925, 496 reported plague cases were mostly restricted to the port cities of the Pacific Coast and Gulf Coast, with more than 90% of cases coming from California. Between 1926 and 1964, there were only 42 cases, mostly acquired in western states such as California (52%) and New Mexico (29%). There were 468 cases reported between 1965 and 2012, mostly in the Southwest. The majority of cases now occur in New Mexico, followed by Arizona and Colorado.[190] There were two cases in Oregon in 2010.[12] Bubonic plague has accounted for the majority of U.S. cases, with septicemic and pneumonic plague being less common. In 2005, the WHO reported that human plague can cause severe disease, with a case-fatality rate of 30% to 60% if left untreated.[389]

In many foreign areas, the exact species of rodents and fleas involved in transmission and maintenance are not known. However, it is known that the distribution of the plague is linked to the geographic distribution of its natural foci.[389] Vietnam is the only country considered a threat for the international introduction of plague (Figure 34-23).

In the United States the major epidemiologic factor associated with acquiring plague is living in a rural or suburban area where the enzootic disease occurs. People who hike, camp, or perform field studies in such areas are vulnerable. Its diagnosis should be considered in anyone with a compatible history who has recently been in an enzootic area.

More recently, a fundamental question in disease ecology has arisen in relation to plague: what happens to the pathogens between the periods of epidemics that allows the disease to persist? A group of researchers at Stanford University looked into this in a set of prairie dogs and found that grasshopper mice carry the fleas during interepizootic periods as alternate hosts. The grasshopper mice show heterogeneity to mortality, allowing for periods of quiescence between outbreaks as well as transmission between groups of prairie dogs that are relatively dispersed. This is the first time the theory of "percolation-threshold phenomenon" with alternate hosts as the key element determining outbreaks has been shown.[291]

TRANSMISSION

Plague is normally a flea-borne disease of rodents, although other animals, including humans, can become infected. Humans are generally infected by the bite of an infected flea; however, direct contact with and percutaneous inoculation of *Y. pestis* organisms

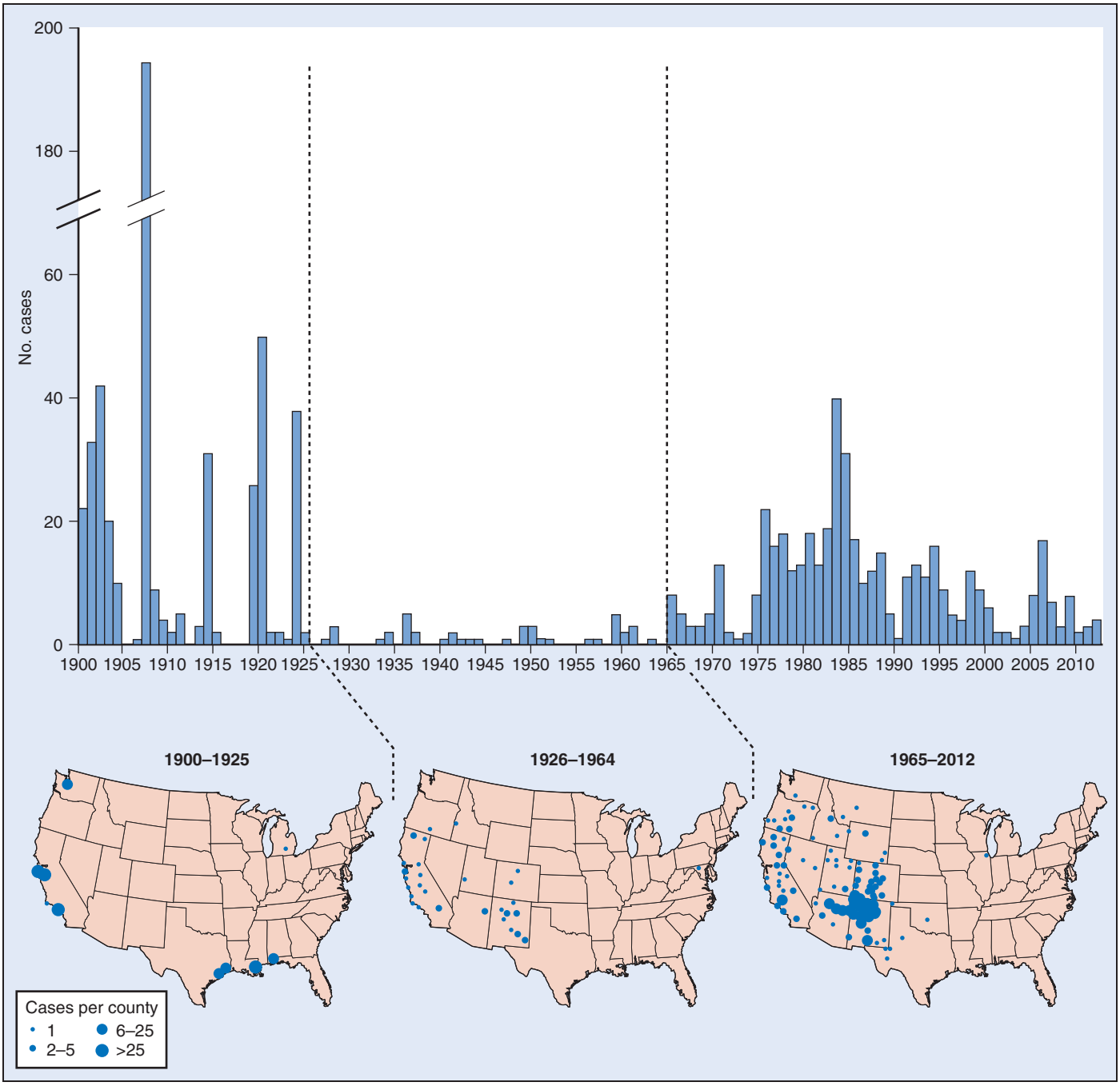

FIGURE 34-22 Frequency and geographic distribution of human plague cases in the United States, 1900-2012. Three periods reflect different epidemiologic and geographic patterns: 1900-1925, 1926-1964, and 1965-2012. *(From Kugeler KJ, Staples JE, Hinckley AF, et al: Epidemiology of human plague in the United States, 1900-2012,* Emerg Infect Dis *21:16-22, 2015.)*

can lead to disease. Rarely, inhaled infective droplets cause pulmonary plague; human-to-human transmission can occur. In 1997 an outbreak in Madagascar affected 18 persons, with eight deaths. These cases were attributed to a healer sucking bacteremic blood out of an infected patient and subsequently developing pneumonic plague.[45]

The black rat is highly susceptible to plague and dies with severe septicemia. The concentration of organisms in the rat's blood ensures infection of the biting flea. When the rat dies, the flea leaves to seek other hosts. This cycle is unusual in that the infection kills the reservoir host and the vector, but the nature of the infection in the flea and rat guarantees further transmission and survival of the microorganism.

The bacteria multiply so extensively in the *X. cheopis* flea that they block its proventriculus, or foregut. The flea cannot feed effectively, becomes ravenously hungry, and regurgitates large numbers of bacilli when it bites. There are multiple theories as to the survival of the bacteria during periods between outbreaks. The most popular hypothesis is that *Y. pestis* can persist by maintaining a benign relationship within adapted rodents or fleas.[117] Another hypothesis is that it may be able to survive in the soil for limited periods within the carcasses of infected animals.[384]

Carnivorous mammals can acquire plague by ingesting infected rodents or by being bitten by their fleas. Dogs usually do not become very ill with plague, but cats can acquire severe, often fatal forms of infection, resembling syndromes seen in humans. Cats can transmit plague to humans by bite, respiratory droplets, or carrying fleas to people. Plague is an occupational risk for veterinarians who handle sick cats or their tissues.[174,284] Although dogs are usually not as severely affected as cats, at least

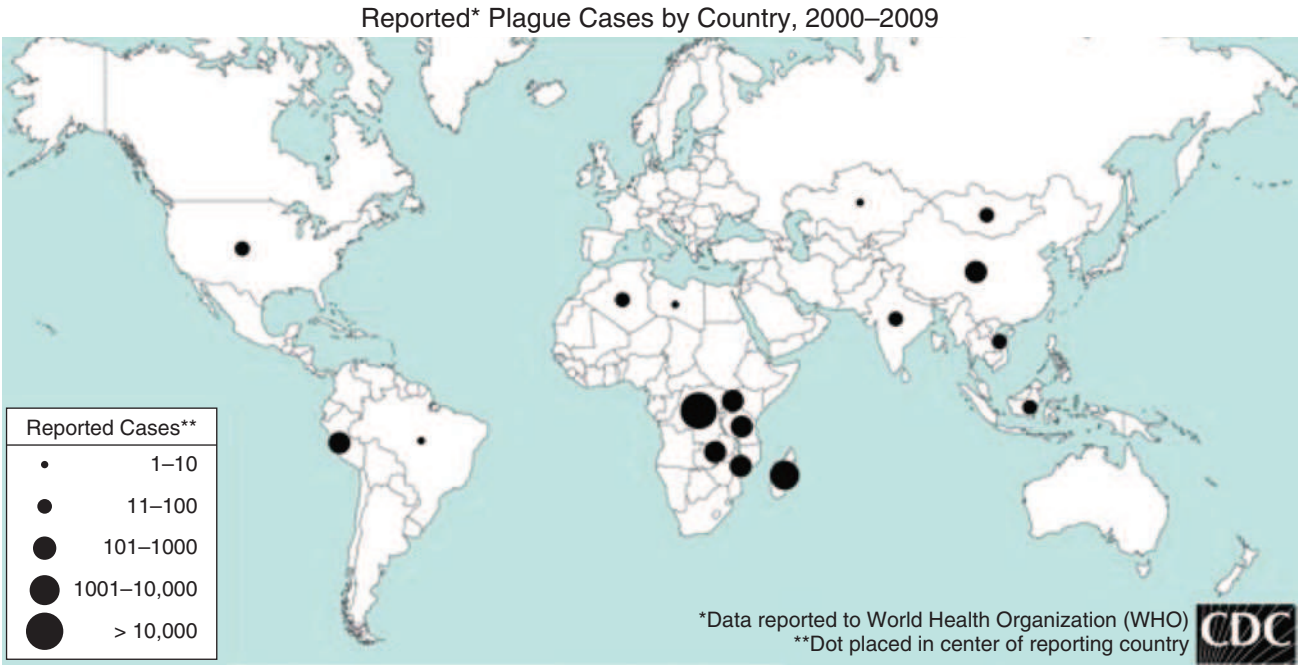

FIGURE 34-23 Reported cases of plague by country, 2000-2009. (http://www.cdc.gov/plague/maps/index.html.)

one human case was associated with a dog that apparently died of plague.[287] In the United States, one person acquired plague while skinning an infected coyote[53] and two while skinning bobcats.[56] Other carnivores, such as skunks, badgers, and raccoons, have been found with antibody to the plague bacillus and presumably were exposed while hunting infected rodents. Exposure to infected rabbits, their fleas, or both has been associated with human plague.[51] Plague is not generally recognized as a disease of farm animals in modern times, although a recent report ascribed one outbreak of plague in a Libyan village to contact with a sick camel and another to contact with two goats.[83]

SYMPTOMS

The three most common forms of plague are bubonic, septicemic, and pneumonic. Less common forms are meningeal, pharyngeal, and ophthalmic.

In the most common form, *bubonic plague,* buboes develop. These are greatly enlarged and very tender lymph nodes proximal to the point of percutaneous entry, such as a flea bite or a cut infected by handling infected tissues. Inguinal nodes are most often involved because fleas usually bite on the legs. Skinning an infected animal or handling its tissues often results in axillary buboes. Frequently, cervical, hilar, or mesenteric lymph nodes are enlarged. Skin lesions at the site of inoculation are usually not apparent. However, some patients have necrotic lesions or eschars.[378]

The incubation period for bubonic plague is usually 2 to 6 days but can be up to 10 days before clinically apparent infection is present.[45] In mild or early stages of infection, seeding of the blood occurs intermittently, causing a low sensitivity to blood culture testing. Later, if disease becomes severe, all blood cultures are positive. Patients usually have sudden onset of high fever, chills, severe malaise, headache, and myalgias, associated with intense pain and swelling in the affected lymph nodes. The inguinal region is most often involved, most likely from drainage of extremity lesions. The word "bubo" is derived from the Greek word for "groin." Toxicity, cardiovascular collapse with shock, and hemorrhagic phenomena may occur. Blackened hemorrhagic skin lesions gave rise to plague being called the "Black Death" during the 14th-century pandemic.

Patients with bacteremia and significant symptoms but no buboes are considered to have *septicemic plague.* Such cases may be difficult to diagnose unless the physician suspects plague based on epidemiology. As with other forms of gram-negative sepsis, patients have fever, chills, malaise, headache, and GI symptoms such as nausea, vomiting, and diarrhea. The disease can result in cardiovascular collapse. Thrombosis and disseminated intravascular coagulation may be present (see Figure 34-21). Untreated septicemic plague progresses to pulmonary involvement and death. However, transmissible pneumonic infection is estimated to occur in only 5% of patients with septicemic plague, because victims die before alveolar pneumonitis and the potential for spread of droplets.

Pneumonic plague can be primary and can result from inhalation of droplets from another pneumonic patient or can be secondary from pulmonary seeding from the blood. The secondary form is more common.[369] Pneumonic plague runs an acute and fulminant course and is almost uniformly fatal if not treated. The incubation period is 2 to 3 days, and disease is characterized by the sudden onset of fever, cough, bloody sputum, headache, and shaking chills. Radiographs reveal progressive consolidation of pneumonic patches in the lungs, often with pleural effusion (Figure 34-24). Patients are usually critically ill by the time they are symptomatic from the disease.[202]

Plague should be suspected in patients who have various combinations of lymphadenopathy, high fever, malaise, tachycardia, tachypnea, hypotension, and abdominal symptoms and who have come from an endemic area. If the suspicion is reasonable, antibiotic therapy should be instituted immediately. Treatment should not be delayed to await laboratory confirmation of the diagnosis.

Rare forms of plague include pharyngeal, meningeal, and ophthalmic. Pharyngeal and ophthalmic plague can be acquired by exposure to droplets expelled by a pneumonic patient. Endophthalmitis can also be secondary to septicemia. Meningitis is acquired by direct seeding while the patient is bacteremic.

DIAGNOSIS

Routine laboratory studies do not provide findings specific for plague. Leukocytosis and thrombocytopenia are present in approximately half of cases. As such, the combination of thrombocytopenia and WBC count greater than 20,000 cells/mm^3 has been used as an indicator of plague in endemic areas.[47] Chest radiology is not specific.

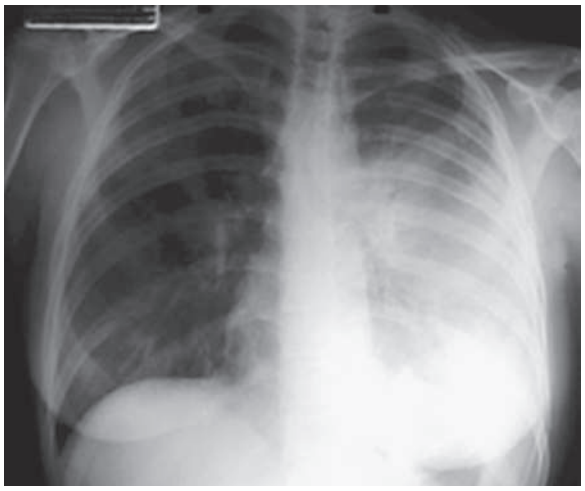

FIGURE 34-24 Pneumonic plague. *(From* http://er1.org/docs/photos/Plague/pneumonic%20plague.jpg.*)*

Definitive diagnosis is based on culture of the organism from body fluids such as sputum, CSF, blood, or aspirates of buboes. The cultures require a minimum of 4 days for growth. The best staining technique to demonstrate bipolar morphology of the organism is the Giemsa or Wayson technique.

Direct fluorescent antibody (DFA) stain of aspirates and smears provides a reasonably rapid diagnostic technique (Figure 34-25). Although cross-reactions with *Yersinia pseudotuberculosis* have been recorded, and occasional strains of the plague bacillus do not stain well with DFA, a positive DFA test in a patient with a compatible epidemiologic and clinical picture is a reasonable basis for making a diagnosis of plague and instituting therapy. A positive test is defined as an at least fourfold rise in antibody titers to the F-1 antigen of *Y. pestis*.[61] ELISA tests are also used and provide rapid diagnosis, and PCR has shown to be reproducible and highly sensitive; however, neither test lends to ease of use in remote situations.[391]

Material from buboes should be obtained by fine-needle aspiration rather than excision or incision and drainage. This reduces risks of transmission to medical personnel and iatrogenic septicemia.

TREATMENT

Widespread use of antibiotics in the 1940s allowed for adequate treatment of plague.[391] Patients with suspected plague should be treated immediately without awaiting definitive laboratory studies. Whichever drug combination is selected, antibiotic therapy should be given for at least 10 days, or for 3 or 4 days after clinical recovery.

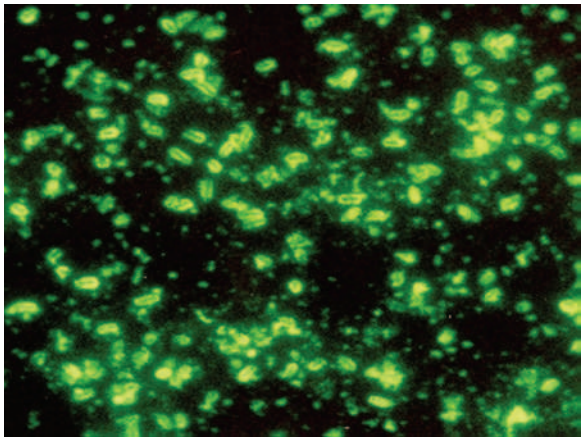

FIGURE 34-25 *Yersinia pestis* seen on direct fluorescent antibody staining. *(Courtesy Centers for Disease Control and Prevention.)*

Streptomycin was the original agent used in treatment, but because of availability, the generally preferred drug is gentamicin, 5 mg/kg IV or IM once or 2-mg/kg loading dose, followed by 1.7 mg/kg IV or IM three times daily for 10 days. Aminoglycosides penetrate poorly into the CSF and therefore are not recommended for use in persons with meningeal plague.[391] An acceptable alternative is doxycycline in a loading dose of 200 mg IV, followed by 100 mg IV twice daily for 10 days.[389] A randomized clinical trial in Tanzania demonstrated good efficacy of a 7-day course of either doxycycline (100 mg PO or IV twice daily) or gentamicin (2.5 mg/kg IM twice daily) as single-agent therapy for plague.[245] Although limited clinical trials have been done on humans, animal studies suggest that fluoroquinolones are effective agents against plague.[266] As such, levofloxacin is also an acceptable alternative, but it should only be used in patients who cannot tolerate aminoglycosides or tetracyclines.

Chloramphenicol or TMP-SMX may also be used. Chloramphenicol is administered in a loading dose of 25 mg/kg PO up to 3 g total, followed by 50 to 75 mg/kg/day PO in four divided doses for 10 to 14 days. If the patient does not tolerate oral therapy, chloramphenicol can be given IV, 25 mg/kg as a loading dose followed by 60 mg/kg in four divided doses every 6 hours until PO therapy is tolerated. It is preferable to use chloramphenicol in the event of meningitis or endophthalmitis because of good penetration into affected tissues. Use of chloramphenicol is decreasing because of severe adverse effects, including bone marrow suppression, aplastic anemia, and "gray baby" syndrome.[391] TMP-SMX (320/1600 mg) twice daily for 10 to 17 days was found effective in treating plague.[3] Recent literature shows that sulfonamides should be used in the treatment of bubonic plague only.[389,391]

Infants born to plague-infected mothers may have congenital infection. They can be treated with kanamycin, 15 mg/kg/day IV or IM in four divided doses every 6 hours, or streptomycin, 10 to 20 mg/kg/day in four divided doses every 6 hours. Some experts recommend treatment of children with TMP-SMX, 4 mg/kg of trimethoprim twice daily for 7 to 10 days.

The recent discovery of a multidrug-resistant strain of *Y. pestis* in Madagascar is of concern.[132] Resistance to all first-line antibiotics, to the principal treatment alternatives, and to prophylactic drugs was mediated by a transferable plasmid. However, these isolates were susceptible to cephalosporins, quinolones, and trimethoprim.

The greatest risk of contagion is by aerosol transmission from patients with the pneumonic form of plague. All persons with suspected plague should be placed in strict quarantine and isolation for a minimum of 48 hours of specific antibiotic treatment. If no respiratory signs develop within 48 hours, wound and skin precautions will suffice for the remainder of the hospitalization. Patients with plague pneumonia or pharyngitis should be kept under strict respiratory quarantine for at least 4 days of antibiotic treatment, until the pharyngeal culture is negative for the organism or respiratory signs abate. Contact personnel should wear gloves, gowns, masks, and eye protection. Strong[339] dramatically illustrated effective protective clothing during a pneumonic plague epidemic in Manchuria in 1911.

The greatest risk of acquiring plague from a patient with the septicemic or bubonic form is by inoculation of blood or exudate; therefore, strict needle precautions should be undertaken. Buboes should not be incised and drained. In theory, fleas harbored by a septicemic patient should be capable of transmitting the disease, but the CDC recommendations for control of plague do not cover eradication of fleas from human patients.[379] No pesticides have been approved by the U.S. Food and Drug Administration (FDA) for this use. Products effective against lice have limited effectiveness, because most fleas do not remain long on a human host.

PROPHYLAXIS

Household contacts and individuals exposed within 1 m (3.3 feet) to patients with pneumonic plague who have not received antibiotics for at least 48 hours should be prophylactically treated with antibiotics.[272] Tetracycline, 500 mg PO every 6 hours for 6 days, or doxycycline, 100 mg PO for 7 days, can be given to adults. TMP-SMX can be given to children younger than 8 years

(8 to 12 mg/kg of the trimethoprim component twice daily) and to most pregnant women. Levofloxacin, streptomycin, chloramphenicol, and sulfadiazine are alternative prophylactic medications, given in therapeutic doses for 1 week to 10 days.

Household contacts of individuals with bubonic plague do not need to be treated prophylactically. They should have their temperature recorded twice daily, and if it exceeds 37.7°C (99.86°F) orally, they should report immediately to a physician for evaluation. Careful surveillance is indicated for persons who have had face-to-face contact with patients with pneumonic plague. Their well-being should be confirmed daily.

The incubation period for primary pneumonic plague is 1 to 3 days and for pharyngeal plague, 3 to 6 days. Precautionary follow-up observation of contacts should be maintained throughout this time. All cases of suspected or confirmed plague should be reported to the state health department.

PREVENTION

Residents and visitors to plague-endemic areas should be advised of the risks of infection. They should avoid contact with rodents and other possible animal reservoirs of infection that are found sick or dead in the wild. Disposable plastic or rubber gloves should be worn when skinning or dressing a possibly infected animal. Cats and dogs should be kept indoors, leashed, or otherwise restrained. Owners of pets that have access to wild rodent populations must maintain flea control. Veterinary personnel working on animals that could have plague should follow strict infection control procedures.

Health departments in enzootic areas should maintain surveillance for plague in local reservoir species. At times of increased plague activity, insecticide sprays and powders can be applied to rodent burrows. Ectoparasite control is essential before any attempt is made to kill the rodents, because killing the rodents without control of their ectoparasites causes fleas to seek other hosts, including dogs, cats, and people.

A killed bacterial vaccine has been developed but is not commercially available in the United States and is rarely used. Much of the experience with it has been with military personnel deployed to endemic areas. The vaccine has short-term (6- to 12-month) efficacy and has a significant incidence of side effects, such as fever, malaise, and pain at the site of injection.[57]

Clinical and epidemiologic assistance for problems relating to plague can be obtained from the CDC's Bacterial Disease Branch.

TULAREMIA

Tularemia was first described in 1837 by Homma Soken, a Japanese physician who wrote of a febrile illness with generalized lymphadenopathy in persons who had eaten infected rabbit meat. In 1911, McCoy described a disease resembling plague in California ground squirrels. In the following year, McCoy and Chapin isolated the organism from rodents in Tulare County, California; this geographic site gave rise to the name of the disease. Edward Francis did much of the landmark bacteriologic and clinical investigation, and the genus of the causative organism, *Francisella*, is named after him. The role of ticks as vectors of the disease was discovered by Parker and Spencer in 1924. In 1929, they described transovarial transmission of the bacterium in ticks.

BACTERIOLOGY

Francisella tularensis is a nonmotile, gram-negative coccobacillus measuring 0.2 by 0.3 to 0.7 μm. It may be grown aerobically on a medium containing cysteine or other sulfhydryl compounds. The organism is best grown on glucose cysteine agar with thiamine or on cysteine glucose blood agar. The organism has also been isolated in thioglycolate broth, charcoal yeast extract, and Thayer-Martin agar.

Two varieties of the organism are recognized in North America. Type A, *F. tularensis tularensis*, can ferment glycerol and has citrulline ureidase activity. Type B, *F. tularensis holarctica*, does not ferment glycerol and does not have citrulline ureidase activity. Type A generally causes more severe disease than does type B. Type B is found in streams, ponds, lakes, and rivers in Europe, Asia, and North America and is often recovered from water voles, muskrats, and beavers.[392] Type A is more frequently recovered from rabbits and various bloodsucking arthropods. The two varieties sometimes share an ecologic niche.[223]

EPIDEMIOLOGY

The CDC reports a 2:1 male/female incidence of tularemia, thought to result from increased outdoor activities and male contact with animals. The disease is also more common in the summer months among children. Anyone involved in outdoor activities is at risk in endemic areas.[71] The reported incidence of tularemia has been steadily decreasing in the United States since its peak at 2291 cases in 1939 (Figure 34-26). Other tick-borne

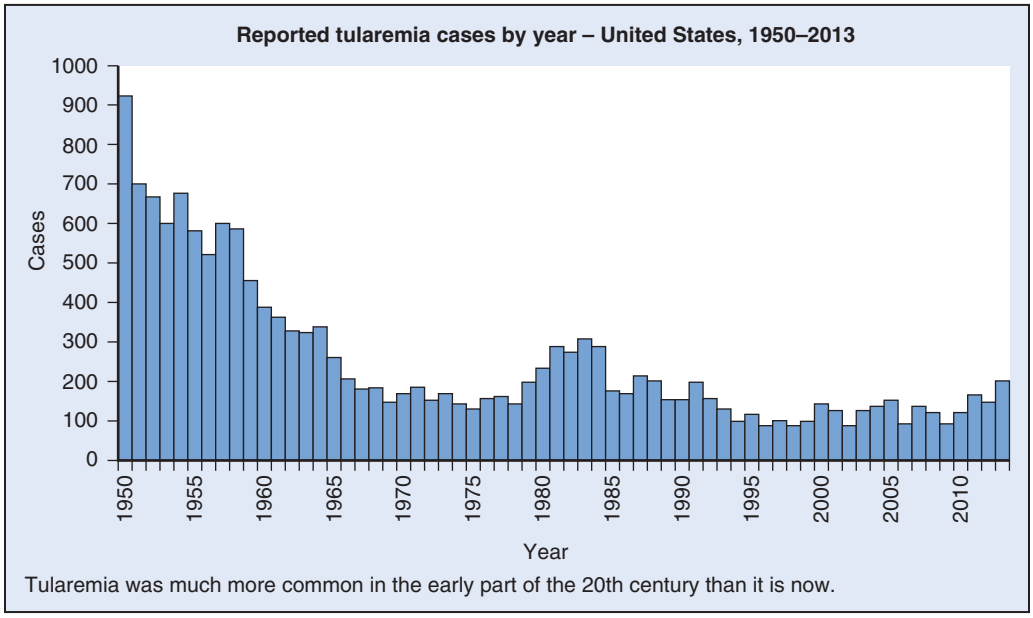

Figure 34-26 Reported cases of tularemia in the United States, 1950 to 2013. *(From* http://www.cdc.gov/tularemia/statistics/year.html.*)*

infections, such as Rocky Mountain spotted fever and Lyme disease, have increased.

Most cases of tularemia in the United States have been reported from the South and Midwest, particularly Arkansas, Missouri, Massachusetts, Oklahoma, South Dakota, and Kansas.[71] The disease is also widespread in Europe, Canada, the Middle East, Russia, and Japan. Transmission by ticks and other arthropods usually occurs in the spring and summer. Transmission from rabbits most often occurs during the fall and winter hunting seasons. An outbreak of 39 patients with tularemia was reported in Germany after a hare hunt in 2005.[158] About 200 U.S. cases are reported every year, and although tularemia is a reportable disease, it is likely that the actual number is higher, because the empirical use of antibiotics may have aborted undiagnosed cases. In a series of patients from the endemic region of Missouri, ulceroglandular tularemia was the most common type among all patients; by age breakdown, children more often had ulceroglandular tularemia and adults more often developed pneumonic tularemia.[353]

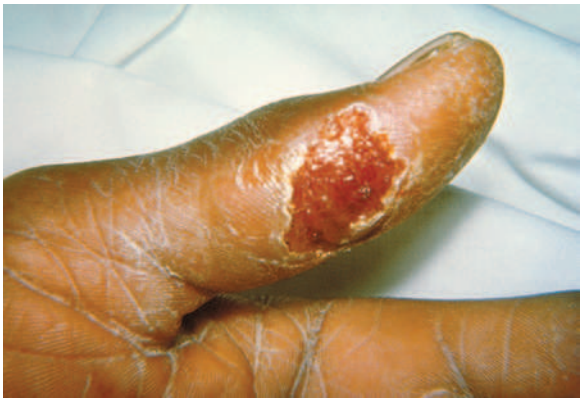

FIGURE 34-27 Cutaneous tularemia. Thumb with skin ulcer of tularemia. *(From Centers for Disease Control and Prevention Public Health Image Library. Courtesy Dr. Thomas Sellers, Emory University.)*

TRANSMISSION

Before 1950, most reported cases of tularemia were associated with direct contact with rabbits. Tularemia is now most frequently transmitted by ticks.[35] Many different species of ticks are potential or proven vectors. A common vector in the United States is the dog tick, *Dermacentor variabilis*. The lone star tick, *Amblyomma americanum,* is the main vector in southern states. In the Czech Republic and Austria, *Dermacentor reticulatus* ticks are the main vector of tularemia, whereas in the former Soviet Union, the vector is mosquitoes (*Aedes*, *Culex*, and *Anopheles*) and the *Ixodes* species of tick.[115] Because the infection can be transmitted transovarially, ticks are an important natural reservoir. Ticks may transmit the bacteria through their feces, since the organism has not been isolated from their salivary glands. Deerflies and other biting flies may also be suitable vectors.[183] In the United States the second most common source of human infection is rabbits. The infection can be acquired by skinning, eviscerating, or handling the tissues of infected rabbits or by eating improperly cooked infected meat or contaminated vegetables.[255] Transmission can also occur by direct contact with or ingestion of infected soil, water, or fomites. Infection can occur by inhalation of dust or water aerosol[98] or in the laboratory. Organisms remain viable in mud samples stored as long as 14 weeks, in tap water for 3 months, in dry straw for 6 months, and in salted meat for 31 days.[25]

Occasional cases of tularemia have been transmitted by cat bite[58,273] or by handling infected tissue from animals other than rabbits, such as bear,[55] deer,[54] beaver, and muskrat.[402] There is no evidence for human-to-human transmission.[392]

Given the low numbers (10 to 50) of bacteria needed to cause disease, in the 1950s the U.S. military evaluated tularemia as a potential biologic weapon, with the idea that it could be aerosolized and cause a severe life-threatening pneumonia in any exposed person. According to the CDC, this was never accomplished. Concern remains that tularemia may be developed into a biologic weapon.[71]

SYMPTOMS

Classically, tularemia occurs in one of six clinical presentations: glandular, ulceroglandular, oculoglandular, oropharyngeal, pneumonic, or typhoidal.[25,223] Evans and colleagues[119] simplified this classification into two major categories: ulceroglandular and typhoidal. Patients are considered to have *ulceroglandular* tularemia if they have lesions of the skin or mucous membranes (Figure 34-27), with or without associated lymphadenopathy, with affected lymph nodes at least 1 cm (0.4 inch) in diameter. Patients without lesions of the skin or mucous membranes and with lesser enlargement of lymph nodes are considered to have *typhoidal* tularemia. In this classification, pharyngitis or pneumonia can occur in either the ulceroglandular or the typhoidal form of the disease.

The *ulceroglandular* form accounts for approximately 80% of tularemia cases. The typical skin lesion begins as an erythematous papule or nodule that indurates and ulcerates. It is frequently painful and tender. Ulcers associated with handling infected animals are usually located on the hand, with associated lymphadenopathy found in the epitrochlear or axillary regions. Infections transmitted by tick bites are usually located on the lower extremities, associated with inguinal or femoral lymphadenopathy.

Glandular tularemia is characterized by the presence of enlarged, tender lymph nodes without an associated skin lesion. However, the skin lesion may have healed or gone unnoticed before development of lymphadenopathy.

In the *oculoglandular* form, unilateral conjunctivitis occurs with concentration of inflammatory response in and around ulcers and nodular lesions on the conjunctiva, with enlargement of the ipsilateral preauricular lymph node.[153] The oculoglandular form constitutes 1% to 2% of tularemia cases. It is thought to be spread to the eye by a finger.[334]

Gastrointestinal or *oropharyngeal* tularemia may be acquired by eating foods contaminated with bacteria. The patient often presents with ulcerative–exudative stomatitis and pharyngitis with significant cervical lymphadenopathy. Interestingly, lymphadenopathy is usually unilateral.[392]

The *typhoidal* form occurs in approximately 10% of tularemia cases. It is characterized by fever, chills, and debility with no noticeable lymphadenopathy. As the disease progresses, weight loss may be significant. Hepatosplenomegaly can occur, especially in children.[168] Pericarditis occurs rarely.[119] Exudative pharyngitis can occur with either the typhoidal or the ulceroglandular form. There is usually associated cervical lymphadenitis.

Pneumonia is a fairly common complication of tularemia (*pneumonic* form). The pulmonary infection can be acquired by inhalation of aerosol, usually from stirring up the dirt while farming. Symptoms include fever, cough, chest pain, shortness of breath, production of sputum, hemoptysis, nausea, and vomiting. In the severe form of the disease, it may imitate typhoid fever with pulse-temperature dissociation and mental deterioration.[392] Radiographic abnormalities of the chest may be found in patients without pulmonary symptoms. Chest x-ray film may reveal infiltrates, most often of the lower lobe, hilar lymphadenopathy, and pleural effusion. Tularemia patients with pneumonia are more likely to be older, less likely to have a known source of infection, and more likely to die than those without pulmonary infection.[310] Before the advent of antibiotics, the pulmonary form of tularemia resulted in mortality rates of 30% to 60%.

Severe complications of tularemia, such as bacteremia, pneumonia, and rhabdomyolysis, are most likely to be seen in patients with significant underlying disease, such as lymphoma, other forms of cancer, or diabetes.[264] According to WHO, without treatment, mortality rates have been as high as 30% to 60% for the type A disease. With treatment, mortality rates are 2% to 5% (WHO/CDC).[392]

DIAGNOSIS

Ulceroglandular tularemia can be confused with cat-scratch disease, streptococcal or staphylococcal skin diseases, sporotrichosis, and plague. Typhoidal tularemia can mimic septicemic plague, brucellosis, salmonellosis, typhoid fever, other forms of gram-negative sepsis, and leptospirosis. Tularemic pneumonia can appear similar to other forms of bacterial and nonbacterial pneumonia, including Q fever, psittacosis, legionnaires' disease, and tuberculosis.[285,310]

Oculoglandular tularemia resembles Parinaud syndrome (granulomatous conjunctivitis with preauricular lymphadenitis) caused by other bacteria (e.g., *Leptothrix* spp., *Mycobacterium tuberculosis*), syphilis, and cat-scratch disease.[153]

The differential diagnosis of oropharyngeal tularemia includes infectious mononucleosis, streptococcal pharyngitis, and plague pharyngitis. The disease most likely to be confused with tularemia is plague, because both diseases occur under similar epidemiologic circumstances and are characterized by similar clinical syndromes.[52,324] The bacteria causing plague and tularemia share morphologic and cultural features but can be differentiated serologically and with appropriate microbiologic techniques.

Blood chemistries tend to be normal, but other tests reveal elevated WBC, ESR, and C-reactive protein (CRP) levels. The CRP can remain elevated for months after the disease.[392] Definitive diagnosis of tularemia is usually based on antibody studies, which are best obtained 10 to 20 days after infection.[189,343] The most common test is agglutination, either tube agglutination or microagglutination.[298] ELISA is also used for diagnosis. An advantage of ELISA is identification of IgM, IgA, and IgG antibodies.

Diagnosis of tularemia is established serologically by demonstrating a fourfold or greater rise in titer between acute and convalescent sera taken 1 week or more apart. Titers of 80 or greater are generally considered significant in the agglutination test. Values rarely reach that level during the first week of infection, but usually reach or exceed that by day 16 of infection. Agglutinating antibodies remain detectable for 10 to 30 years after infection. IgM, IgA, and IgG antibodies also remain detectable by ELISA for at least 11 years after infection. Because of the long persistence of antibody, single titers cannot be used for definitive diagnosis.

Tularemia can also be definitively diagnosed by isolation and identification of the organism from blood, skin lesions, and lymph node biopsies or aspirates.[392] Samples for culture, however, are not routinely taken in suspect cases, and they are not encouraged because of the high frequency of contamination and infective risk to laboratory workers handling *F. tularensis*.

TREATMENT

For moderate to severe infection, streptomycin, the original drug of choice, should be given, 30 to 40 mg/kg/day IM in two divided doses every 12 hours for 3 days, followed by half that dosage for another 4 to 7 days. A meta-analysis of various antibiotics used to treat tularemia reported a cure rate for streptomycin of 97%, with no relapses.[116] For gentamicin and tetracycline, respectively, the cure rate was 86% and 88%; relapse rate, 6% and 12%; and failure rate, 8% and 0%. The duration of therapy with gentamicin and a delay in its initiation may have affected outcome in severe cases.[264] For chloramphenicol and tobramycin, the cure rate was 77% and 50%; relapse rate, 21% and 0%; and failure rate, 2% and 33%, respectively. Treatment with imipenem-cilastatin was successful in one case and with ciprofloxacin or norfloxacin, in six cases; therapy with ceftriaxone was ineffective in eight cases.[116] For mild infections, doxycycline, 100 mg twice daily for 14 days in adults, and for children over 8 years old, 2 to 4 mg/kg/day PO in two divided doses for 14 days (daily dose not to exceed 200 mg), or ciprofloxacin, 500 to 750 mg twice daily for 14 days, is appropriate.

PREVENTION

Prevention of tularemia involves avoidance of ectoparasites such as ticks and appropriate hygiene in the handling of infected animal tissues. Insect repellents should be applied when going into areas where ticks, deerflies, and other possible vectors are found. Persons walking in tick-infested brush should wear long pants, with the bottoms of the trouser legs tucked into socks or boot tops. Individuals should check frequently for the presence of ticks while in the field. Ticks should be removed as quickly as possible, preferably with pointed forceps grasping the mouthparts, taking care not to break the mouthparts or to squeeze the body of the tick.

Persons handling suspect animals should wear rubber or plastic gloves. Reservoir animals, such as rabbits or muskrats that appear ill, should not be handled. When it is necessary to handle sick animals, infection control procedures should include the use of gloves, face masks, and disposable gowns.

Culturing the organism should be attempted only in laboratories that have appropriate containment facilities for handling such dangerous organisms. Laboratory work with *F. tularensis* should always be conducted under an appropriate microbiologic hood. Standard halogen-containing phenol or alcohol-based antiseptics can be used for disinfecting surfaces.

Although person-to-person transmission is rare, reasonable infection control measures should be taken to reduce exposure to aerosols from patients with oropharyngeal or pneumonic tularemia, and exposure to exudates should be avoided.

A live-attenuated vaccine previously developed is no longer available, given questions of efficacy and stability. Other vaccines are under development and may be indicated eventually for those who are at high risk, such as laboratory personnel who frequently work with *Francisella tularensis*.[294-297]

AVIAN/SWINE INFLUENZA

Influenza pandemics have occurred throughout history and remain a threat today. Originally, influenza was not a reportable disease. Until discovery of the virus in 1930, the influenza illness was thought to be caused by a bacterium now known as *Haemophilus influenzae*.[354] There have been five influenza pandemics over the last 100 years. Each has been caused by a novel virus from the combination of avian, swine, and human strains, including H2N2 in 1957, H3N2 in 1968, and H1N1 from 2009-2010. The most memorable pandemic was the "Spanish flu" of 1918, which killed more people in 1 year than the bubonic plague and is thought to have been an adapted swine strain.[350]

In 2009 the H1N1 swine flu spread around the globe in a new pandemic. The first reported cases of the novel H1N1 strain were in Mexico in late March; soon thereafter it was found in the United States and Canada. By October 2009, H1N1 influenza was reported in more than 200 countries,[233] likely the result of air travel. In June 2009, WHO raised its pandemic alert to the highest level, indicating widespread transmission on at least two continents. According to the CDC, approximately 61 million cases of pandemic H1N1 influenza occurred in the United States between April 2009 and April 2010, causing 12,470 deaths.[321] Most deaths were from severe respiratory failure from pneumonia and acute respiratory distress syndrome (ARDS).[393] The pandemic was declared over in August 2010.[123]

The first confirmed human infections by avian influenza H5N1 virus were reported in Hong Kong in 1998; 6 of 18 patients died.[403] No additional cases were reported until February 2003, when one of two people infected with avian influenza died in Hong Kong.[251] In December 2003, several Asian countries reported an outbreak of avian influenza in poultry.[70] Although only 32 cases were laboratory confirmed, mortality reached 70%.[349] Since that time, H5N1 has been reported in more than 660 humans and has prompted concerns that a new pandemic might emerge with significant potential global mortality.[242] The predominance of children and young adults affected by the disease and high mortality rate are particularly concerning.[20]

VIROLOGY

Avian influenza H5N1 and swine influenza H1N1 are subtypes belonging to the family orthomyxoviridae, all of which are single-stranded RNA viruses (Figure 34-28). Other subtypes known to

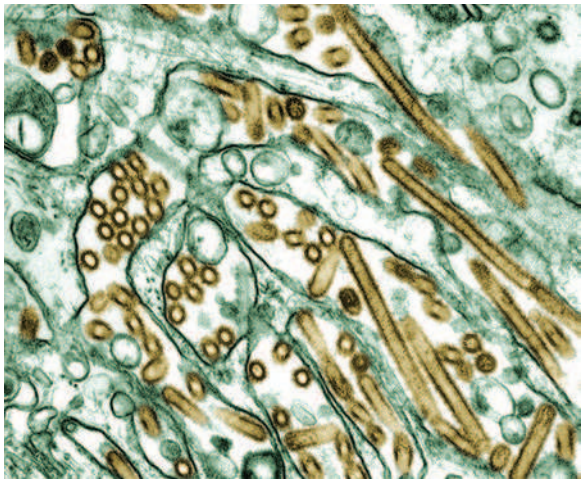

FIGURE 34-28 Avian influenza. Colorized transmission electron micrograph (TEM) of avian influenza A H5N1 viruses (seen in *gold*) grown in MDCK cells (seen in *green*). *(From Centers for Disease Control and Prevention Public Health Image Library. Courtesy C. Goldsmith, J. Katz, and S. Zaki, 1997.)*

have caused pandemics include H3N2 and H2N2. Subtype identifiers refer to the specific surface proteins present on the virus. *H* refers to the type of hemagglutinin protein, of which there are 16 subtypes known, and *N* refers to the type of neuraminidase protein, of which there are nine subtypes known. Hemagglutinin primarily facilitates binding to the target cell, whereas neuraminidase allows for the release of progeny virions from infected cells.[349]

Antigenic drift occurs when, because of poor proofreading of genetic material, errors in transcription and translation result in variants of the original strain. Over time, this leads to strains sufficiently different to evade humoral immunity and cause illness in persons who were infected with the original strain. This is why people are susceptible to the flu every year and retain only partial immunity. The more concerning antigenic shift is thought to cause pandemic outbreaks of influenza. *Antigenic shift* occurs when two or more different viruses infect a host and combine genetic information to create a novel strain to which humans have little immunity. The pig is implicated in aiding in this reassortment of genetic material, because the pig trachea has receptors for both avian and human strains and can support the growth of both viruses.[354] It is believed that this antigenic shift is responsible for severe global outbreaks of influenza.

The Spanish flu of 1918 had the same subtype H1N1 as did the 2009 swine flu and caused 20 to 50 million deaths worldwide. The more recent H1N1, a likely descendant of the Spanish flu, was feared during its initial outbreak because it was found to be a quadruple reassortment of two swine strains (one of which appears to be related to the 1918 strain), one human strain, and one avian strain of influenza.[233,354,355] The protein divergence of the novel H1N1 is about 20% to 24% from the seasonal flu.[393]

EPIDEMIOLOGY

Endemic reservoirs for influenza are swine, migratory aquatic wildfowl, and many mammalian and avian species. The 2009-2010 "swine flu" originated in Mexico and is thought to have led to human-to-human spread months before the outbreak was recognized in early March 2009 as a novel strain of influenza. It spread quickly to the United States and by May 2009 was found in a herd of pigs in Alberta, Canada.[393] This spread was thought to result from a farmer who had traveled to Mexico and on returning home transmitted the virus to the pigs.

The highly pathogenic H5N1 avian influenza has been confined to poultry outbreaks in Asia. The first association occurred in Hong Kong in 1997. H5N1 reemerged in Hong Kong in 2003 and since then has become endemic in poultry in Eurasia.[348] The first case reported in North America was in January 2014 in Canada, when a woman who had returned from Beijing, China, died of the disease.[382] Since 2003, there have been more than 660 human cases with a case fatality rate of 60%.[70] Fortunately, avian influenza H5N1 is not easily transmitted between humans.

Several other subtypes have been linked to human disease. Avian influenza H9N2 occurred in Hong Kong in 1999, 2003, 2007, and 2009.[370] Subtype H7N7 occurred in humans, primarily as conjunctivitis, in The Netherlands (2003) and Canada (2004).[127,187] One of the 83 infected patients in The Netherlands died. Several other avian subtypes that have caused human disease, all in 2013, include H7N9, H6N1, H10N8, and H10N7.

TRANSMISSION

Most H5N1 infections in humans result from contact with infected birds or their contaminated feces. However, several cases of limited human-to-human transmission have been reported in the literature, one believed to be in Indonesia in 2006, where eight family members were affected by the illness and seven died, only one of whom had been exposed to infected poultry.[40,70,187,390] Most cases are in people sharing living facilities with the index case. No spread outside this range has been seen. Unlike previous outbreaks of other swine influenza viruses, the 2009-2010 pandemic of H1N1 demonstrated sustained human-to-human transmission. Transmission between hospitalized patients and health care providers also occurred.[203] Because of the genetic similarity of the strains, the entire pandemic likely started from an isolated case.[70]

SYMPTOMS AND DIAGNOSIS

The incubation period for influenza is 2 to 4 days. Infected persons may shed the virus 1 day before symptom onset and for 5 to 7 days after symptom resolution.[393] Symptomatology for all influenza viruses have remained constant, with patients typically presenting with a febrile respiratory illness within days of exposure. Myalgias, arthralgias, cough, sore throat, shortness of breath, wheezing, headache, rhinorrhea, and chills are common complaints.[26] GI manifestations (e.g., nausea, vomiting, diarrhea) may also occur and have been found to be more common in patients with swine flu.[398] The majority of swine infected with influenza exhibit symptoms of the flu similar to those in humans.[393] Notably, H5N1 outbreaks tend to affect children and young adults.

Chest radiographs show infiltrates of varying patterns, with 66% of patients having infiltrates suggestive of pneumonia or ARDS in hospitalized patients.[204] Hepatic dysfunction and anemia are common. Laboratory tests may demonstrate renal insufficiency, coagulopathy, leukopenia, and lymphopenia.[169,349] Laboratory testing can be performed on a nasopharyngeal aspirate or swab, preferably within 3 days of symptom onset.[251] Diagnostic tests available for influenza include viral culture, serology, rapid antigen testing, PCR, and immunofluorescence. Sensitivity and specificity of these tests vary by the laboratory that performs the test, type of test used, and type of specimen tested. In suspected cases of avian or swine influenza, it is critical to collect specimens for viral culture. Only culture isolates can provide information regarding the specific influenza subtypes and strains.

TREATMENT AND PREVENTION

More than 99% of influenza isolates during the 2009-2010 pandemic were the H1N1 influenza A strain, most of which were susceptible to the neuraminidase inhibitors oseltamivir and zanamivir. The CDC recommended treatment for children, adolescents, and adults with suspected or confirmed H1N1 influenza who required hospitalization; those who had progressive, severe, or complicated illness; and those at risk for severe disease (children <5 years, adults ≥65 years, pregnant women or those <2 weeks postpartum, and persons with severe medical conditions).[394] During the H1N1 pandemic, the FDA issued an emergency use authorization (EUA) for IV peramivir to be used for

life-threatening cases. However, the EUA expired in June 2010, and large clinical trials have not yet been done.

Avian influenza H5N1 is susceptible to oseltamivir and zanamivir in vitro. It is resistant to amantadine and rimantadine.[349] Oseltamivir is the recommended treatment and dosed at 75 mg twice daily for 5 days in uncomplicated disease. Weight-based dosing for children age 1 to 12 years varies by weight, all 5-day courses (≤15 kg, 60 mg/day divided twice daily; >15 to 23 kg, 90 mg/day divided twice daily; >23 to 40 kg, 120 mg/day divided twice daily; >40 kg, 120 mg/day divided twice daily). Children 13 years and older receive adult dosing.

A higher dose of 150 mg twice daily and a longer duration of 10 days may be considered in patients with higher acuity. Inhaled zanamivir should not be used. IV zanamivir and peramivir are in clinical development.[397] The H5N1 virus is killed by heat and disinfectants such as alcohol. However, the influenza virus can survive in feces for months.

Persons coming into contact with patients suspected of avian or swine influenza should observe strict hand hygiene and respiratory and contact precautions (including wearing a particulate respirator, gloves, gown, and goggles).[67] WHO recommends that household contacts of patients with H5N1 avian influenza receive postexposure prophylaxis with oseltamivir, 75 mg once daily for 7 to 10 days.[397] Persons visiting countries with endemic H5N1 should take extra care if visiting farmland or having exposure to poultry. Persons living with someone diagnosed with H5N1 should immediately be tested for H5N1 and prophylactically treated.

COWPOX AND MONKEYPOX INFECTIONS

Poxviruses are large DNA viruses that are implicated in a variety of human diseases, including smallpox, monkeypox, cowpox, and molluscum contagiosum. Historically, immunization against smallpox was performed with an injection of vaccinia virus, which resulted in a local skin lesion. As a result, pox infections are rare, because this immunization provided cross-protection against other poxviruses. At present, however, because smallpox has been eradicated and immunization is no longer recommended, cases of monkeypox, cowpox, and catpox may increase.[362]

Epidemiologic evidence suggests that *cowpox* is not enzootic in cattle, that the cow has a minor role, that feline cowpox is important as a source of human infection, and that wildlife, principally rodents, are virus reservoirs.[23] Although poxvirus infection in the domestic cat has only recently been described, the incidence has increased steadily, and cats are now the most frequently reported hosts of poxvirus in England.[362] The infection occurs mostly among hunting cats in the late summer and early autumn; infection in humans is usually reported after close contact with or a scratch from a sick cat, although transmission from rats has also been reported.[385] The infection is manifested as an inflamed vesicular nodule with lymphadenitis, systemic symptoms (e.g., fever), and a rapid but self-limited course, similar to the orf poxvirus carried by sheep, cattle, and goats. This disease has not yet been reported in immunosuppressed persons. No effective treatment is available, but normally the disease is self-limited.

Monkeypox is endemic to central and west Africa, with the first reported case in laboratory monkeys in Copenhagen in 1958.[366] In 2003 the first community-acquired outbreak of monkeypox occurred in the central United States. There were no fatalities, and the reservoir was believed to have been infected prairie dogs.[275] Initial symptoms include fever, headache, lymphadenopathy, myalgias, and malaise. Within days, a maculopapular rash erupts, usually spreading in a centrifugal pattern and progressing through several stages before crusting over and sloughing (Figure 34-29).[105] In the United States the mode of transmission is believed to have been through respiratory droplets or direct contact.[105] Diagnosis is based on serum samples and scrapings from lesions. As with cowpox, there is no known effective treatment for monkeypox, and the disease is self-limited.

FIGURE 34-29 Monkeypox lesions on the arm and leg of a 4-year-old child in Bondua, Grand Gedeh County, Liberia. This infection was caused by a poxvirus of the vaccinia, variola, monkeypox type. *(From Centers for Disease Control and Prevention Public Health Image Library.* http://phil.cdc.gov/Phil/quicksearch.asp.*)*

HANTAVIRUS PULMONARY (CARDIOPULMONARY) SYNDROME

Reports in the Middle Ages from China and England described clinical entities similar to what we now know as *Hantavirus*. During the Korean conflict in 1951, almost 3000 United Nations and American soldiers were affected by an acute febrile illness with renal failure and shock, with a mortality rate nearing 7%.[195] This illness became known as Korean hemorrhagic fever.[194,195] In 1978, Lee and colleagues[195] identified the causative agent, naming it *Hantavirus* because most cases in the troops developed near a small river called Hantann. About the same time, other causes of hemorrhagic fever with renal syndrome (HFRS) were identified in Korea and Europe as the Seoul virus and the Puumala and Dobrava viruses, respectively. Until 1993, hemorrhagic infections associated with *Hantavirus* strains were thought to be limited to Asia and Eastern Europe, and they largely lacked respiratory symptoms. In 1993, an outbreak of severe respiratory illness with high mortality occurred in the southwestern United States. This outbreak was subsequently investigated and described as the hantavirus cardiopulmonary syndrome (HCPS), or hantavirus pulmonary syndrome (HPS), caused by a novel *Hantavirus*.[110] Although rare, there has also been a small number of human cases of HFRS caused by Seoul virus in the United States.[282]

VIROLOGY

Hantaviruses are in the Bunyaviridae family and are trisegmented RNA viruses with a lipid envelope.[307] They cause HFRS as well as HCPS (HPS). The genus *Hantavirus* comprises two main groups: Old World and New World.

Humans are not part of the natural host range of Hantaviruses. Human infection occurs accidentally in those exposed to the virus by inhalation or by contact with urine, feces, or saliva of infected rodents.[240] One exception is the *Hantavirus* strain "Sout" in Argentina, which has been reported to have sporadic human-to-human transmission.[224] The Sin Nombre virus, also known as the Four Corners virus, is the primary *Hantavirus* causing HCPS in the United States, with the deer mouse (*Peromyscus maniculatus*) as the predominant carrier (Figure 34-30).[65] Other small mammals, such as piñon mice, brush mice, and western chipmunks, may also be infected. Wild rodents are also the vectors of Hantaan, Puumala, Prospect Hill, and Seoul viruses, all members of the *Hantavirus* genus. Hantaviruses have also been isolated from the lung tissues of bats.[180]

EPIDEMIOLOGY

Approximately 150,000 to 200,000 cases of *Hantavirus* syndromes occur throughout the world each year, with the majority in China.[305] Seoul virus is the etiologic agent in the majority of

FIGURE 34-30 The deer mouse, *Peromyscus maniculatus*, a *Hantavirus* carrier that becomes a threat when it enters human habitation in rural and suburban areas. All Hantaviruses known to cause hantavirus pulmonary (or cardiopulmonary) syndrome are carried by New World rats and mice of the family Muridae, subfamily Sigmodontinae. This subfamily contains at least 430 species, which are widespread in North and South America. *(From Centers for Disease Control and Prevention Public Health Image Library. Courtesy James Gathany.)*

the Chinese cases. Case fatality rates in China are 1%.[182] Several thousand cases of HFRS from Puumala and Dobrava viruses occur every year throughout Europe, with the case fatality rate up to 10%. Although most cases of HCPS have been clustered in the western United States, particularly the Four Corners area (Arizona, New Mexico, Colorado, and Utah), the virus is present across the entire United States as well as the majority of the Americas.[250,270] As of February 2013, 617 cases of HCPS have been documented in the United States, with increased numbers of cases in 2006, 1999-2000, and 1993-1994.[72] In summer 2012, an outbreak in Yosemite National Park affected 10 visitors and caused three fatalities. Rodent infestations were found in the walls of insulated tent cabins.[254]

The 1993 outbreak in the Four Corners area was thought to result in part from the El Niño effect, creating a surge in the infected rat population by increasing the food supply.[307] Since 1994, the CDC has sponsored continuous monitoring studies of rodent populations at nine sites in Arizona, Colorado, and New Mexico. Spikes in the host population correlate with HCPS outbreaks among humans. *Hantavirus* antibody prevalence in deer mouse populations surveyed since 1994 shows a 10% baseline prevalence, increasing up to 40% prevalence during rodent population peaks. During the 1993 outbreak, a prevalence of 30% was detected.[80] Many outbreaks have occurred among persons of lower socioeconomic status, thought to be caused by the poor living facilities that may favor increased encounters with rodents.

TRANSMISSION

Hantaviruses appear to have co-evolved with the rodent reservoir host species over many thousands of years, likely leading to the lack of illness in the hosts.[305] Host animals shed virus in saliva, urine, and feces for weeks. The greatest shedding of the virus takes place 3 to 8 weeks after infection.[65] Human infection probably occurs when infective saliva or excreta are inhaled as aerosols, or when excreta are directly inoculated through the skin or perhaps ingested. Humans have also been infected with *Hantavirus* through rodent bites. Human-to-human transmission of the Sin Nombre virus in the United States does not appear to occur; however, there has been human-to-human transmission of *Hantavirus* strains in Chile and Argentina. For this reason, it is considered a potential bioterrorism agent by the CDC.[65,224]

SYMPTOMS

Hantavirus renal syndrome (HFRS) has an incubation period ranging from 10 days to 6 weeks and consists of five stages that may overlap: febrile, hypotensive, oliguric, diuretic, and convalescent. The onset is sudden, with intense headache, petechial rash, fever, and chills. Ocular symptoms such as refraction abnormalities may occur, and hemorrhage may manifest as injection of the conjunctive and mucosa.[217] About day 4 of disease, hypotension and acute renal failure develop. The mortality from HFRS is 1% to 40% (depending on the strain), and recovery may take months.[305]

Hantavirus cardiopulmonary syndrome (HCPS) begins with an incubation period up to 17 days, followed by prodrome of fever, myalgia, and variable respiratory symptoms (e.g., cough, shortness of breath with minimal bronchospasm) that last up to 5 days. Acute respiratory distress rapidly follows, with acute noncardiac pulmonary edema and hypotension within 2 to 15 days.[240] Other early-phase symptoms include headache, chills, abdominal pain, nausea, and vomiting. Abdominal pain may be severe and is occasionally misdiagnosed as acute abdomen.[217] Patients often demonstrate hemoconcentration, thrombocytopenia, leukocytosis, hypoalbuminemia, and lactic acidosis.

Rapid deterioration occurs, coincident with marked bilateral pulmonary infiltrates identified on chest radiograph (Figure 34-31). One percent of patients experience severe neurologic manifestations, including seizures.[240] Fever, hypoxia, and hypotension may culminate in death; survivors usually recover within 5 to 7 days and have few or no sequelae. Autopsies have demonstrated intense pulmonary infiltration, with marked accumulations of *Hantavirus* antigens in endothelial cells.

DIAGNOSIS

The causative agent has been identified by serologic tests, PCR to RNA, and immunohistochemistry[64,193] (Figure 34-32). Laboratory evidence of acute *Hantavirus* infection can be obtained by IgM antibodies to *Hantavirus* antigens, fourfold or greater increase in antibody titers to *Hantavirus* antigens in paired serum specimens, positive immunohistochemical stain for *Hantavirus* antigen in formalin-fixed tissues (Figure 34-33), or positive PCR from frozen-tissue specimens (usually lungs). ELISA testing for *Hantavirus* was developed by the CDC and is available only in state health departments.[234] Typical clinical laboratory findings include hemoconcentration, neutrophilic leukocytosis, thrombocytopenia, and circulating immunoblasts.

Any person with a severe and sudden respiratory illness should be suspected to have *Hantavirus* infection. CDC screening criteria include febrile illness with temperature higher than 38.3°C (101°F) in a previously healthy person characterized by unexplained ARDS or bilateral interstitial pulmonary infiltrates developing within 72 hours of hospitalization, with respiratory compromise requiring supplemental oxygen.[65]

TREATMENT

Treatment is supportive because no cure has been developed. Previously isolated Old World Hantaviruses have demonstrated in vitro sensitivity to ribavirin, although there has been no demonstrated benefit of ribavirin for the New World strains.[90] The

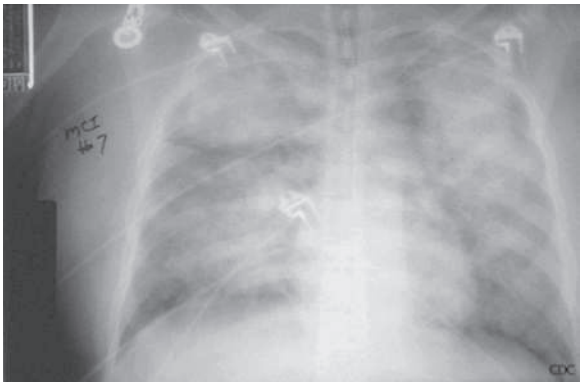

FIGURE 34-31 Hantavirus pulmonary syndrome as shown on chest radiograph. *(From* http://www.bt.cdc.gov/agent/plague/trainingmodule/3/12hantavirus.htm.*)*

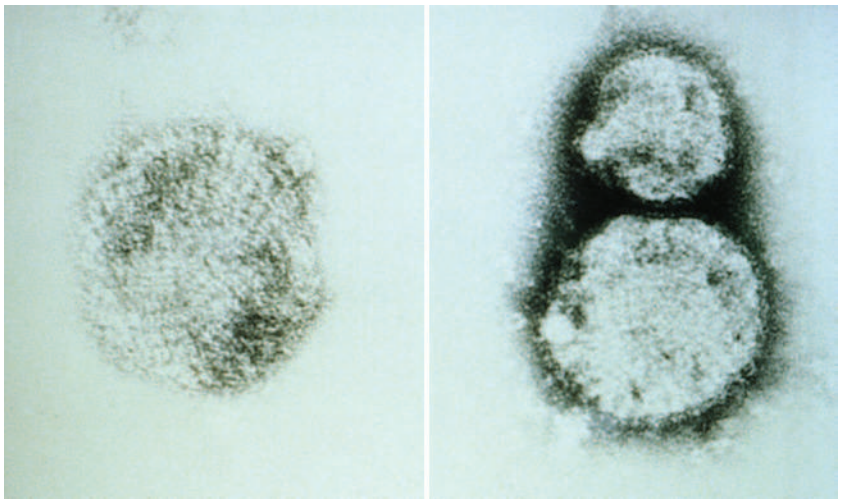

FIGURE 34-32 Electron micrographs of the *Hantavirus* virions responsible for causing hantavirus pulmonary (or cardiopulmonary) syndrome. *(From Centers for Disease Control and Prevention Public Health Image Library.* http://phil.cdc.gov/Phil/home.asp.*)*

CDC has stated that the drug is of no use with HCPS and is not available for use under any existing research protocol as of 2004. Intensive care unit management of symptoms is recommended with pressors, avoidance of fluid overload, and possible use of extracorporeal membrane oxygenation (ECMO) in the most severe cases. Glucocorticoids are not recommended for treatment of patients with HCPS. A randomized controlled trial in Chile found no difference between treatment and placebo groups.[364] Studies are evaluating the use of neutralizing antibodies, because it was noted that patients with the more severe form of HCPS had significantly lower antibody titers than those with less severe forms.[234] Preliminary evidence suggests that antisera administration from patients who recovered from HCPS appears to reduce severity of illness.[363]

PREVENTION

According to the CDC, *Hantavirus* transmission to humans may be epidemiologically associated with planting or harvesting field crops, occupying previously vacant dwellings, disturbing rodent-infested areas while hiking or camping, inhabiting dwellings with indoor rodent populations, or residing in an area with an increasing rodent density. Most persons with HCPS (HPS) who had high-risk exposure are thought to have been infected in and around their homes. Limiting opportunities for domestic exposure is important. Measures to prevent HCPS can be divided into four areas (Box 34-1).

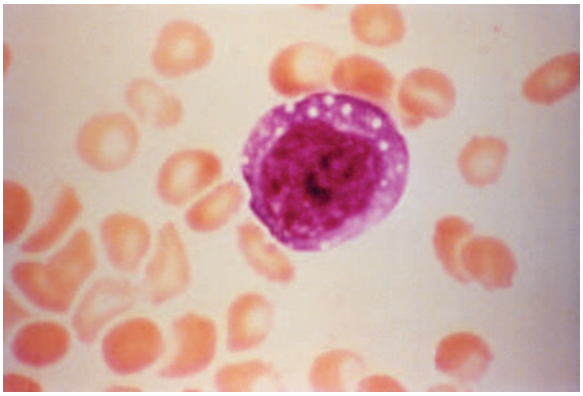

FIGURE 34-33 Micrograph depicting an atypical, enlarged lymphocyte found in the blood smear from a patient with hantavirus pulmonary syndrome (HPS). The laboratory finding of this lymphocyte, combined with a bandemia and dropping platelet count, is characteristic of HPS. *(From Centers for Disease Control and Prevention Public Health Image Library.* http://phil.cdc.gov/Phil/home.asp.*)*

HENDRA VIRUS

Hendra virus was first described after a September 1994 outbreak of a severe respiratory illness among a group of horses and humans in Queensland, Australia. Of 21 affected horses, 14 died of respiratory failure, and of the two humans affected—a trainer and a stable hand—one died of severe interstitial pneumonia.[241] In a second and unrelated outbreak 13 months later, a farmer died of severe meningoencephalitis after contact with a horse infected with Hendra virus.[257]

BOX 34-1 Centers for Disease Control and Prevention Recommendations for Preventing Hantavirus Pulmonary (Cardiopulmonary) Syndrome

1. Eliminate rodent harborage.
   a. Keep cooking, eating, and food storage areas clean.
   b. Cover human food and animal feed.
   c. Contain and elevate garbage.
   d. Seal holes and cracks in dwellings to prevent entrance by rodents.
   e. Clear brush and trash from around homes and outbuildings.
2. Control rodent populations by maintaining snap traps and using rodenticides; in areas where plague occurs, control fleas with insecticides.
3. Safely clean up rodent-infested areas.
   a. Air out infested spaces before cleanup.
   b. Spray areas of infestation and all excreta, nesting, and other materials with household disinfectant or 10% bleach solution. Then, clean up, seal in bags, and dispose.
   c. Avoid sweeping, vacuuming, or stirring dust until the area is thoroughly wet with disinfectant.
   d. Wear rubber gloves; disinfect gloves before removal, and wash hands afterward.
   e. In areas where plague occurs, spray insecticide on trapped rodents and nesting materials to prevent fleas from abandoning rodents to find new hosts.
4. Avoid rodents when outdoors.
   a. Do not disturb rodent droppings or camp or sleep near burrows or areas where trash is present.
   b. Avoid feeding or handling rodents, even if they appear friendly.

VIROLOGY

Hendra virus is a paramyxovirus that shares 70% to 78% of its nucleotide sequencing with the closely related Nipah virus.[84,209,281] Formerly called "equine morbillivirus," Hendra virus was further sequenced and classified as a paramyxovirus after the 1994 outbreak in Australia.[146]

EPIDEMIOLOGY AND TRANSMISSION

The outbreaks of Hendra virus have all been reported among horses and humans in close contact in the Australian states of Queensland and New South Wales.[214] The natural reservoir for Hendra virus is thought to be the fruit bat (*Pteropus* spp.); however, the mode of transmission to horses is unknown.[243] Although the virus is found in a large portion of the fruit bat population, human bat handlers have had no reported cases of the virus.[315] Horse-to-horse transmission has been documented.[214] The documented human cases of Hendra virus are thought to be acquired through close contact with infected horses. No human-to-human transmission has been documented.

SYMPTOMS

The equine form of Hendra virus manifests as a severe respiratory infection. There have been seven identified infections in humans, four of whom died. Clinical symptoms have included fever, respiratory symptoms and meningoencephalitis with subsequent seizures, coma, and death. The incubation period for human infection appears to range from 5 to 21 days. In addition, there is evidence to suggest that the virus may reactivate after latency or persist after initial infection.[214]

DIAGNOSIS AND TREATMENT

Definitive diagnosis can be accomplished by viral culture or by ELISA of the CSF and serum samples. Supportive measures are the mainstay of treatment of Hendra virus infection because there are no approved effective antiviral drugs for human or animal infections.[6]

PREVENTION AND CONTROL

Early identification of equine cases and quarantine of affected animals is the key to preventing human cases. A Hendra virus vaccine has been approved for use in horses in Australia.[41]

NIPAH VIRUS

The Nipah virus is a chilling example of emerging zoonotic infections; a highly contagious swine-associated virus with a human mortality rate of 75%.[278] The original outbreak of Nipah virus in humans occurred in September 1998 in northern Malaysia and spread to farms south of this original epicenter and into Singapore by June 1999. It is believed that spread within Malaysia resulted from sale of infected pigs.[237] In Malaysia, there were 265 reported cases with 105 deaths, and in Singapore there were 11 reported cases with one death. The outbreak was contained in Singapore once importation of pigs from Malaysia ceased; in Malaysia, more than 1 million pigs from the outbreak area were destroyed before the illness disappeared.[191] The virus derives its name from Kampung Sungai Nipah, the village where patients supplied the first viral isolates.[386] In 2004, an outbreak of 36 patients with Nipah virus occurred in Bangladesh.[151] This outbreak was notable for person-to-person transmission and a 75% mortality rate. There was also an outbreak of acute Nipah encephalitis in the neighboring district of Siliguri in India in 2001.[74]

VIROLOGY

The Nipah virus is a paramyxovirus closely related to Hendra virus, a paramyxovirus that caused an outbreak of respiratory disease in horses in Australia (see previous section). Hendra and Nipah viruses are classified under the genus *Henipavirus*.[371] Nipah is a single-stranded RNA virus encapsulated into a helical core surrounded by a lipid membrane containing two distinct viral glycoproteins.[399]

TRANSMISSION

Nipah virus is transmitted to humans by contact with infected pigs or fresh pig products. In the past, there had been isolated suggestions of human-to-human transmission, but this was not confirmed by epidemiologic studies until the 2004 outbreak in Bangladesh.[86,345,346] Since 2001, there have been recurrent outbreaks in Bangladesh thought to be caused by human-to-human transmission, because none was associated with clusters of ill animals or contact with a potential animal host, such as a pig.[206] As such, Nipah infection in Bangladesh is believed to be contracted from human-to-human transmission and possibly also bat-to-human transmission.[299] There is evidence that fruit bats of the species *Pteropus hypomelanus* may serve as a host reservoir for Nipah virus, as they do for Hendra virus. Nipah virus has been isolated from the urine of *P. hypomelanus* on Tioman Island, just off the Malaysian coast, and neutralizing antibodies have been detected in two species of fruit bats (*P. hypomelanus*, *P. vampyrus*).[85,400] If fruit bats serve as the reservoir, it is unclear how transmission then occurs to pigs.

SYMPTOMS

Nipah virus infection is characterized by encephalitic symptoms. Onset of symptoms occurs within 2 weeks, and patients present with a wide range of symptoms, ranging from nonspecific fever and headache to rapidly progressive encephalitis.[141,196] The largest population with Nipah virus that has been studied was 94 patients in 1999 at the University of Malaya Medical Center in Kuala Lumpur, Malaysia.[141] More than half of patients had decreased level of consciousness (Glasgow Coma Scale [GCS] score <15) at presentation and signs of brainstem dysfunction, including abnormal doll's eye reflex, segmental myoclonus, vasomotor instability, and pinpoint pupils. Few patients presented with both neurologic and respiratory symptoms or abnormal chest radiograph. The fatality rate in patients with febrile encephalitis was 32%. A study of 92 patients with Nipah infection from the 2001-2004 Bangladesh outbreaks identified fever, altered mental status, headache, cough, respiratory difficulty, vomiting, and convulsions as the most common signs and symptoms. Patients who died were more likely than survivors to have fever, altered mental status, difficulty breathing, and abnormal plantar reflexes.[164]

DIAGNOSIS AND TREATMENT

Nonspecific laboratory findings include thrombocytopenia, leukopenia, transaminitis, and CSF with either elevated WBC count or elevated protein level, similar to other viral encephalitides.[141] Definitive diagnosis can be accomplished by viral culture or ELISA of CSF and serum samples.[386] There is no established treatment other than supportive measures.

Because of its broad spectrum of activity against RNA and DNA viruses, ribavirin was given to 140 patients in the Malaysian outbreak and reported to be associated with fewer deaths compared with controls. However, treated patients were identified later in the outbreak and may have benefited from better overall care rather than directly from ribavarin.[81] Survivors of Nipah virus encephalitis typically have neurologic abnormalities.[314]

CYSTICERCOSIS (TAENIASIS)

The encysted larvae, or *cysticerci,* of the tapeworm *Taenia solium* in the flesh of pigs, known as "measly pork," were well known to the ancient Greeks. Aristotle (384-322 BC) referred to these cysticerci in the section on diseases of pigs in his *History of Animals,* describing "bladders that are like hailstones."[252] These tapeworms have been described throughout the centuries and across the globe.

PARASITOLOGY AND TRANSMISSION

Taenia is a genus of cestodes, or tapeworms, belonging to the family *Taeniidae.*[241] The two species causing infection in humans are *Taenia solium,* the pork tapeworm, and *Taenia saginata,* the beef tapeworm. Both cause an intestinal form of tapeworm infection. *T. solium* alone produces the more significant clinical syndrome of cysticercosis, involving neural and other tissues in the human body.

Taenia solium

The life cycle of *T. solium* involves pigs and humans (Figure 34-34). Humans are infected by ingesting insufficiently cooked pork containing larval tapeworms, or cysticerci. Ingested cysticerci attach to the small intestine with four muscular suckers and a crown of hooklets. Over the next few days, these worms produce proglottids, or segments, which elongate to form a mature tapeworm that can be several meters in length. These proglottids are gravid and release embryonated eggs.

Gravid proglottids or eggs are released from human feces into the environment, where they contaminate water or vegetation and then are ingested by pigs. Once ingested, the eggs become a six-hooked larval form called an *oncosphere,* which penetrates the intestinal wall of the pig and migrates via the lymphatic or venous system into tissues to complete the cycle and become a cysticercus.

Human cysticercosis develops when humans ingest the embryonated eggs or gravid proglottids that normally infect pigs. The infection is also initiated when humans ingest vegetation or water contaminated with human feces containing *T. solium* eggs, which may be the most common mode of transmission. It is hypothesized that carriers of *T. solium* tapeworms can ingest eggs through reverse peristalsis and autoinfection, but this has not been proved. Once ingested, these eggs release oncospheres, which, as in the pig, invade the intestinal mucosa and migrate hematogenously into tissues. Once in the tissues, most frequently brain and muscle, the larval form develops into a cysticercus over

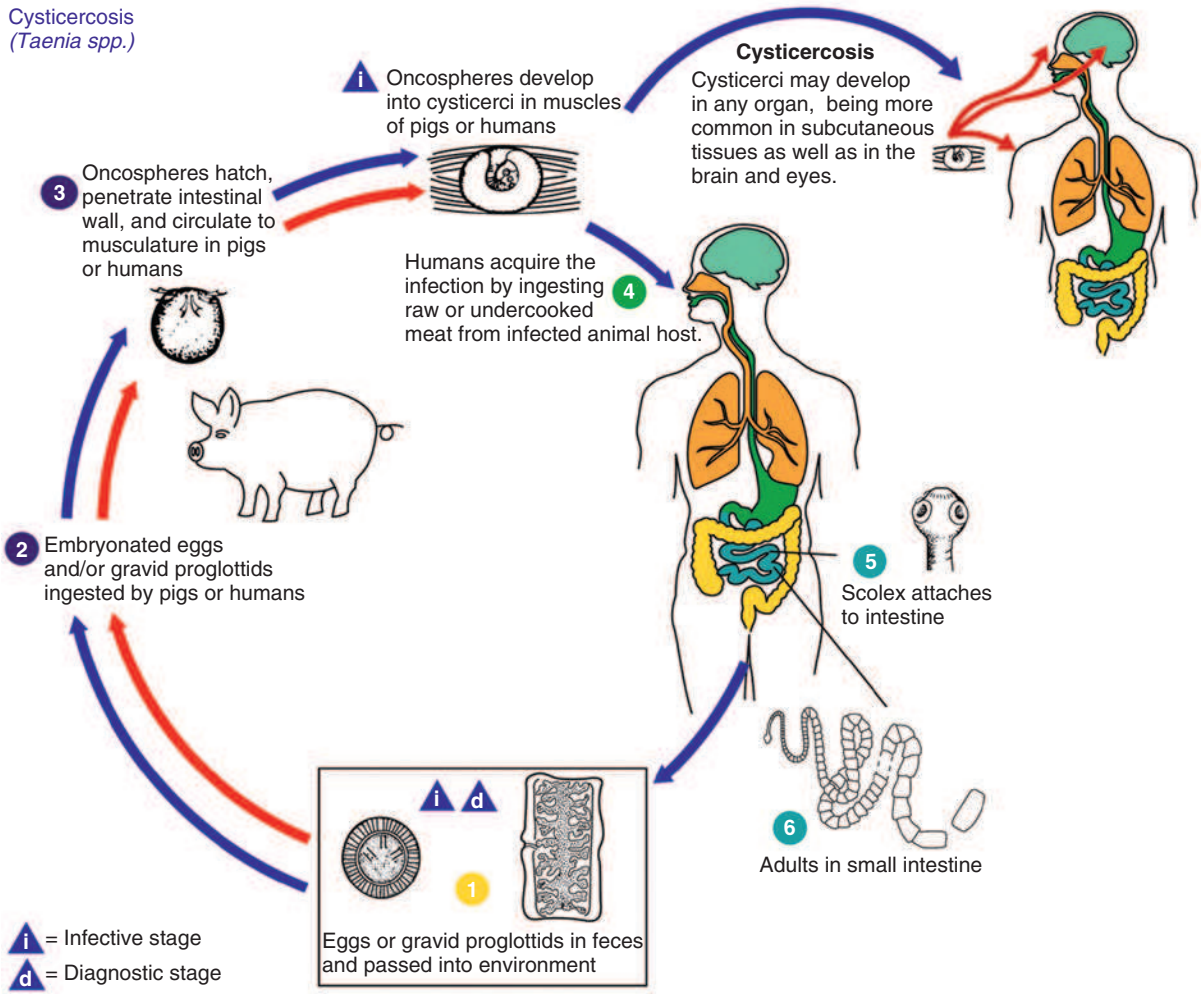

FIGURE 34-34 Cysticercosis is an infection of both humans and pigs with the larval stages of the parasitic cestode, *Taenia solium.* This infection is caused by ingestion of eggs shed in the feces of a human tapeworm carrier (**1**). Pigs and humans become infected by ingesting eggs or gravid proglottids (**2**). Humans are infected either by ingestion of food contaminated with feces or by autoinfection. In the latter case, a human infected with adult *T. solium* can ingest eggs produced by that tapeworm, either through fecal contamination or possibly from proglottids carried into the stomach by reverse peristalsis. Once eggs are ingested, oncospheres hatch in the intestine (**3**), invade the intestinal wall, and migrate to striated muscles, as well as to brain, liver, and other tissues, where they develop into cysticerci. In humans, cysts can cause serious sequelae if they localize in the brain, resulting in neurocysticercosis. The parasite life cycle is completed, resulting in human tapeworm infection, when humans ingest undercooked pork containing cysticerci (**4**). Cysts evaginate and attach to the small intestine by their scolices (**5**). Adult tapeworms develop (2 to 7 m [7 to 23 feet] in length); produce less than 1000 proglottids, each with approximately 50,000 eggs; and reside in the small intestine for years (**6**). *(From* http://www.dpd.cdc.gov/dpdx/HTML/Cysticercosis.htm.*)*

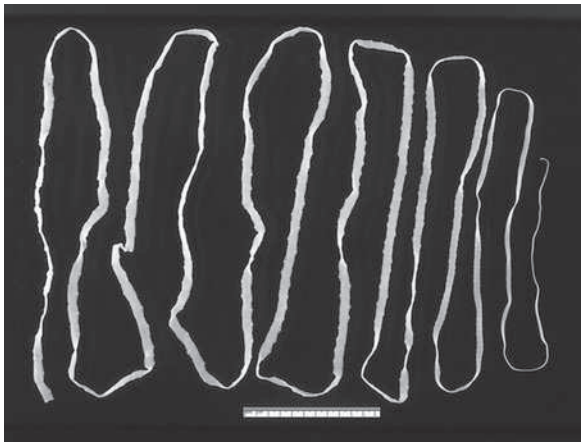

FIGURE 34-35 Adult *Taenia saginata* tapeworm. Humans become infected by ingesting raw or undercooked infected meat. In the human intestine, the cysticercus develops over 2 months into an adult tapeworm, which can survive for years, attaching to and residing in the small intestine. *(From Centers for Disease Control and Prevention Public Health Image Library.* http://phil.cdc.gov/Phil/home.asp.*)*

3 to 4 months. These cysticerci may remain viable for several years.

Taenia saginata

The life cycle of *T. saginata* involves humans and cattle. Humans ingest larval tapeworms, or cysticerci, from insufficiently cooked beef. Ingested cysticerci attach to the small intestine with four muscular suckers and a crown of hooklets. These worms then produce proglottids, or segments, elongating to form a mature tapeworm that can parasitize the small intestine of a human for as long as 25 years and grow up to 10 m (33 feet) in length (Figure 34-35). The proglottids release eggs, which are released through human feces into the environment. These eggs are ingested by cattle, where they form oncospheres, penetrate the intestinal wall, and migrate to other tissues to form a cysticercus and complete the cycle.

EPIDEMIOLOGY

Taenia solium infection is directly associated with eating undercooked pork. It is prevalent in Africa, India, Southeast Asia, China, Mexico, and Central and South America. It is seen infrequently in the Middle East.

It is important to note that cysticercosis also results from ingestion of water or vegetation contaminated by human feces containing *T. solium* eggs; therefore, human cysticercosis can occur in populations where pork is not consumed and where people are not in close contact with pigs.[303] Cysticercosis is estimated to affect 50 million people worldwide, although this may be an underestimate, because many cases are undiagnosed.[302] Prevalence is higher in rural areas and areas where pigs are raised; seroprevalence in endemic regions in South America is as high as 25%.[136]

In the United States, many cases of cysticercosis are seen in immigrants from endemic areas. In one study, 10% of patients in Los Angeles presenting to emergency departments with a seizure had a diagnosis of neurocysticercosis; in New Mexico, it was 6% of patients.[256] People can be infected when traveling to endemic areas and by ingesting produce or water contaminated with *T. solium* eggs.

Taenia saginata occurs worldwide. Its life cycle is perpetuated by humans and cattle.

SYMPTOMS

The presentations of intestinal infections caused by *T. solium* and *T. saginata* are similar, with mild abdominal discomfort, chronic indigestion, hunger pains, and/or diarrhea. Many patients are asymptomatic and present only after discovering a length of the tapeworm in their feces.

The symptoms of cysticercosis are related to the tissues involved. The syndrome is usually classified as either *neurocysticercosis* or *extraneural cysticercosis*. Neurocysticercosis, the more common form, is further divided into parenchymal and extraparenchymal neurocysticercosis.[50]

The more common form of neurocysticercosis is *parenchymal*. Cysticerci in the brain often locate to the cortex or basal ganglia, and patients most often present with either focal or generalized seizures. Cysts are typically less than 1 cm (0.4 inch) in diameter. In endemic areas, neurocysticercosis is the most common cause of epilepsy, and the prevalence of epilepsy is higher than in nonendemic areas.[134] Other symptoms of parenchymal neurocysticercosis include headaches, nausea, and vomiting as well as psychiatric presentations. Over time, parenchymal cysticerci calcify as they degenerate and may serve as foci for the seizures.

One complication of parenchymal neurocysticercosis is cysticercal encephalitis, which is caused by an intense immune reaction resulting from a massive number of cysts in the brain parenchyma. This reaction can be spontaneous, or it may be provoked by medical therapy that causes degeneration of a large number of cysts simultaneously. Patients present with fever, headache, vomiting, impaired visual acuity, altered mental status, and even seizures. For unknown reasons, this is more common in children and young women.

Extraparenchymal neurocysticercosis includes subarachnoid cysts, racemose cysticercosis, ventricular cysticercosis, and spinal cysticercosis. Patients with subarachnoid cysts may present with cranial nerve palsies and hydrocephalus because of mass effect and inflammation associated with large cysticerci at the base of the brain.

Racemose cysticercosis is an infrequent but serious form of extraparenchymal neurocysticercosis. It is characterized by proliferating lobulated cysts resembling a cluster of grapes that are typically lodged in the ventricular system. The presentation consists of arachnoiditis, basilar meningitis, and hydrocephalus and is associated with a poor prognosis.

A more common form of extraparenchymal neurocysticercosis involves the presence of ventricular cysts, free floating or attached to the choroid plexus. These cysts cause inflammation in the ventricles, and patients present with obstructive hydrocephalus and elevated intracranial pressure. Symptoms include focal neurologic symptoms, seizures, and dementia. An atypical presentation of a ventricular cyst is Bruns syndrome, which presents with episodes of sudden loss of consciousness associated with head movements; these episodes are caused by intermittent obstruction from mobile cysts in the fourth ventricle.[290]

Spinal cysticercosis, in which cysticerci are located in the subarachnoid space or intramedullary region, is less common. These cysts can lead to inflammation and demyelination. Patients present with radicular pain or paresthesias in the affected area. Thoracic lesions are most common.

Extraneural cysticercosis may involve muscles, the eye, and subcutaneous tissues. Ocular cysticercosis, which occurs in 1% to 3% of all cases of cysticercosis, can involve the anterior chamber, subretinal space, or vitreous humor.[137] These cysticerci can cause inflammation when they degenerate, so a thorough ophthalmologic examination should be performed in patients with cysticercosis before starting treatment.

Other sites of extraneural cysticercosis include muscles and subcutaneous tissues. Cysticerci in these locations are often asymptomatic but may be seen incidentally as nodules or calcifications on radiographs. Rare cases of cysticerci in cardiac muscle have been reported, with resulting conduction disturbances and cardiomyopathy.[34]

DIAGNOSIS

Stool samples from humans harboring *Taenia* tapeworms may reveal proglottids and eggs. Eggs are spherical, 30 to 40 μm in diameter, and have a thick, radially striated shell. *T. solium* and

T. saginata eggs are identical. Proglottids of *T. solium*, however, are smaller than those of *T. saginata*.

Diagnostic testing for cysticercosis depends on the clinical presentation. Routine blood counts and hepatic panels are normal in typical patients with cysticercosis. The most sensitive serologic test is an enzyme-linked immunoelectrotransfer blot (EITB) assay, with a sensitivity of 98% and a specificity of 100% for patients with active cysticercosis.[138,352] Other serologic tests, including ELISA, CF, radioimmunoassay, and other immunoblots, have been used but are less sensitive and specific. The sensitivity of all tests is lower in patients with inactive cysticercosis or only isolated lesions. The EITB is more sensitive in serum than in CSF.[383] As with any antibody test, a positive test does not indicate active infection.

A lumbar puncture can be useful in the diagnosis of neurocysticercosis, although it is not necessary. CSF findings include normal glucose, normal to mildly elevated protein and WBC counts, and occasional eosinophilia. Serologic tests can be done on CSF but are not as sensitive as serum serologies.

Imaging modalities are useful in diagnosing cysticercosis. Plain films may demonstrate calcified cysticercal lesions (Figure 34-36). CT and magnetic resonance imaging (MRI) are more useful in diagnosing neurocysticercosis. CT findings include nonenhancing hypodense lesions of viable cysts and calcified lesions of old cysts. Degenerating lesions may have some surrounding inflammatory edema. CT may also demonstrate extraparenchymal cysts in the ventricles or subarachnoid space and may demonstrate the resultant hydrocephalus. CT is preferred over MRI for serial examinations to follow progress. MRI is more sensitive than CT in detecting small lesions and extraparenchymal lesions. MRI is also better at characterizing the scolex and evaluating degenerative changes in the parasite. For spinal cord lesions, MRI is the preferred imaging modality.

Diagnosis of cysticercosis can also be made on pathology, either by brain biopsy (rarely) or by biopsy of muscle or subcutaneous nodule. Cysticerci are 5 to 10 mm (0.2 to 0.4 inch) in diameter and resemble a fluid-filled bladder containing a small larval scolex (Figure 34-37).

TREATMENT

For intestinal involvement of either *T. solium* or *T. saginata*, the treatment of choice is albendazole or praziquantel.

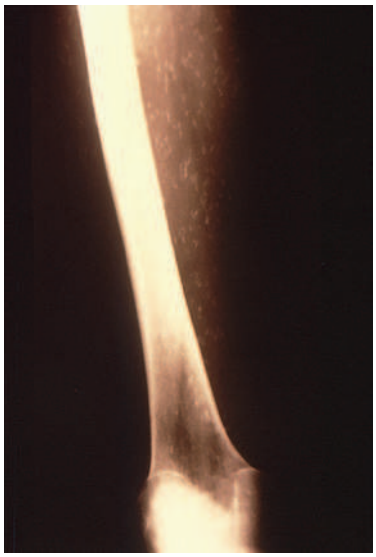

FIGURE 34-36 This x-ray film reveals cysticercosis of the muscle caused by the presence of the cestode *Taenia saginata*, or beef tapeworm. Humans are the only definitive hosts for *T. saginata* and *T. solium*. Eggs or gravid proglottids are passed with feces; the eggs can survive for days to months in the environment. *(From Centers for Disease Control and Prevention Public Health Image Library.* http://phil.cdc.gov/Phil/home.asp.*)*

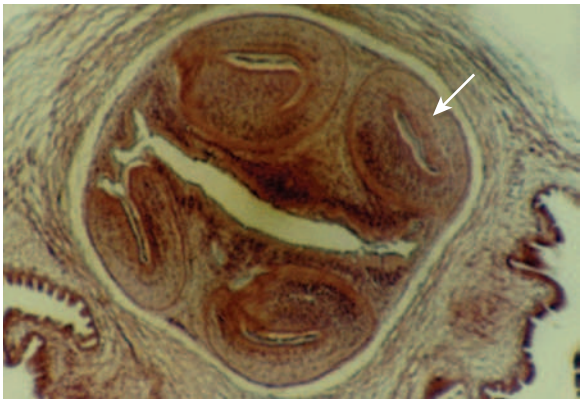

FIGURE 34-37 Cysticercosis in muscle section. Note sucker (*arrow*) of bladderworm. The fluid-filled cyst contains an inverted scolex. The worm larva is inverted and as such, the rugose tegument is on the inside of the bladder. The rugose tegument will become the adult worm's body surface. *(Courtesy Department of Pathology, University of Texas Southwestern Medical Center.* http://pathcuric1.swmed.edu/MicroBiology/LabRef/Parasites/Platyhelminth/SlideC4.html.*)*

Treatment for neurocysticercosis depends on the presentation, and options include anticonvulsant therapy, anthelminthic therapy with albendazole or praziquantel along with corticosteroids, and surgery.[16,135]

Anticonvulsant therapy is indicated and extremely important for patients who present with seizures and neurocysticercosis. Drugs of choice include phenytoin and carbamazepine. Length of therapy depends on recurrence of seizures.

Anthelminthic (anthelmintic) therapy is not always indicated in neurocysticercosis.[329] Calcified asymptomatic cysts do not require anthelmintic therapy. For parenchymal neurocysticercosis, latest guidelines support albendazole plus steroid treatment.[16] For extraparenchymal neurocysticercosis, there is a risk of complications from swelling and inflammation provoked by anthelmintic therapy, and therapy must be considered on a case by case basis.

The anthelmintic drug of choice is albendazole, 15 mg/kg/day divided twice daily for 8 days, or praziquantel, 75 to 100 mg/kg in three divided doses 2 hours apart. Praziquantel shows reduced serum levels in the presence of phenytoin, phenobarbital, or corticosteroids because of cytochrome P-450 induction, so albendazole has a more favorable profile in these patients.

Steroids are administered along with anthelmintic therapy to decrease adverse effects of an inflammatory response from degenerating cysts resulting from therapy. The drug of choice is prednisolone, 1 mg/kg/day, or dexamethasone, 0.1 mg/kg/day, starting 2 days before treatment and continuing for 4 to 6 days after therapy is completed. Additionally, for intraventricular cysts or neurocysticercosal encephalitis, steroids alone are indicated to decrease the inflammatory response and risk of obstruction and edema.

Surgery may be required in the case of obstructive neurocysticercosis. Patients with obstructive hydrocephalus require ventriculoperitoneal shunting. Rarely, patients with intraventricular or subarachnoid cysts may require surgical excision.

Extraneural cysticercosis does not require treatment if it is asymptomatic. Patients with extraneural cysticercosis should be evaluated for neurocysticercosis.

PREVENTION AND CONTROL

Prevention of infection with *T. solium* and *T. saginata* involves good handwashing and hygiene to avoid fecal-oral infection. Prevention of primary infection with *T. solium* requires cooking pork until the interior of the meat is not pink, or freezing it to −20°C (−4.0°F) for at least 12 hours. Carriers of *T. solium* pose a public health risk and need to be identified and properly treated. Every effort must be made to avoid contact between human feces and the vegetation and water near pigs or livestock.

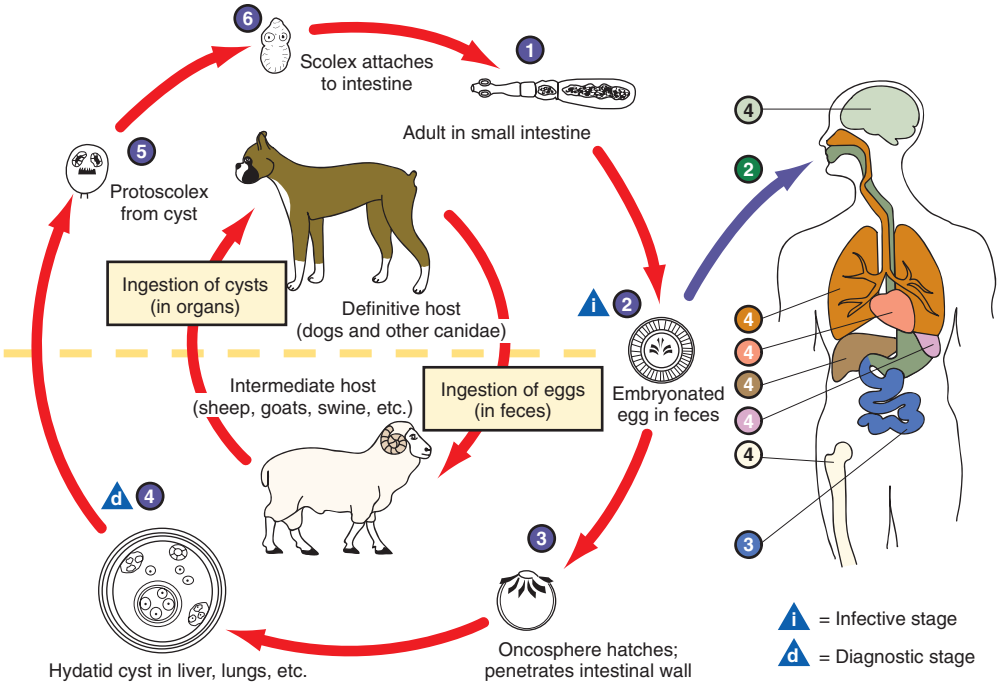

FIGURE 34-38 The adult *Echinococcus granulosus* (3 to 6 mm long) (**1**) resides in the small intestine of the definitive host (dogs or other canids). Gravid proglottids release eggs (**2**) that are passed in the feces. After ingestion by a suitable intermediate host (under natural conditions: sheep, goat, swine, cattle, horses, camel), the egg hatches in the small intestine and releases an oncosphere (**3**) that penetrates the intestinal wall and migrates through the circulatory system into various organs, especially the liver and lungs. In these organs, the oncosphere develops into a cyst (**4**) that enlarges gradually, producing protoscolices and daughter cysts that fill the cyst interior. The definitive host becomes infected by ingesting the cyst-containing organs of the infected intermediate host. After ingestion, the protoscolices (**5**) evaginate, attach to the intestinal mucosa (**6**), and develop into adult stages (**1**) in 32 to 80 days. The same life cycle occurs with *Echinococcus multilocularis* (1.2 to 3.7 mm), with the following differences: the definitive hosts are foxes, and to a lesser extent dogs, cats, coyotes, and wolves; the intermediate hosts are small rodents; and larval growth (in the liver) remains indefinitely in the proliferative stage, resulting in invasion of the surrounding tissues. For *Echinococcus vogeli* (up to 5.6 mm long), the definitive hosts are bush dogs and dogs, the intermediate hosts are rodents, and the larval stage (in the liver, lungs, and other organs) develops both externally and internally, resulting in multiple vesicles. *Echinococcus oligarthrus* (up to 2.9 mm long) has a life cycle that involves wild felids as definitive hosts and rodents as intermediate hosts. Humans become infected by ingesting eggs (**2**), with resulting release of oncospheres in the intestine and development of cysts (**4**) in various organs. *(From* http://www.dpd.cdc.gov/dpdx/HTML/Echinococcosis.htm.*)*

ECHINOCOCCOSIS

Echinococcosis (hydatidosis, or *hydatid disease*) is a parasitic disease found wherever sheep are herded and dogs are in close contact with humans. Sheep were first domesticated in the Neolithic era, and large herds of sheep were present during the Mesolithic era around the Caspian Sea during 5000 to 6000 BC.[253] Because dogs have long lived in close quarters with humans, feeding off scraps and offal from livestock and transmitting infection through close contact, echinococcosis is a disease that has likely been present in human populations since the beginning of humanity. Hydatid disease was well known in ancient times, and there are references to cysts in slaughtered animals in the Babylonian *Talmud,* by Hippocrates in the 4th century BC, by Arataeus in the 1st century AD, and by Galen in the 2nd century AD.[126] Echinococcosis is one of the most broadly spread parasitic zoonoses, with cases occurring in almost all countries and climates around the world.[108]

PARASITOLOGY AND TRANSMISSION

Echinococcus is a genus of cestodes, or tapeworms, belonging to the family Taeniidae.[161] Human echinococcosis is caused by infection with the larval stages of *Echinococcus.* Several species of *Echinococcus* are known to cause disease in humans. *E. granulosus* causes cystic echinococcosis, the most common form of the disease in humans. *E. multilocularis* causes alveolar echinococcosis, accounting for 5% of hepatic hydatid disease. *E. vogeli* and *E. oligarthrus* rarely cause echinococcosis in humans.

The life cycle of *Echinococcus* involves a definitive (e.g., dog) and an intermediate (e.g., sheep) host. Humans become infected as accidental hosts in this life cycle (Figure 34-38).[107] In the definitive host, the adult tapeworm inhabits the small intestine. These adult worms differ by species. *E. granulosus* worms are 2 to 7 mm (0.08 to 0.28 inch) long and consist of a scolex with hooks and suckers as well as at least three proglottids. *E. multilocularis* worms are up to 4 mm (0.16 inch) long with two to six proglottids. Proglottids are segments consisting of both male and female sexual organs that produce eggs, which contain oncospheres. These eggs are 30 to 40 µm in size.

The definitive host may harbor thousands of worms, each of which can produce thousands of eggs from the proglottids each day. These eggs are expelled in the feces of the definitive host. Intermediate hosts are infected by ingesting these eggs from the environment, as are accidental hosts such as humans. The eggs hatch within the intermediate host and release oncospheres, which then penetrate the intestinal mucosa, enter the blood and lymphatic systems, and migrate to visceral organs. After reaching these organs, most often the liver, the oncospheres develop into fluid-filled cysts, which then develop into the metacestode or hydatid cyst. Adult forms, or *protoscolices,* eventually develop within these hydatid cysts.

The adult protoscolices develop into secondary daughter cysts within the intermediate host (Figure 34-39). If infected organs

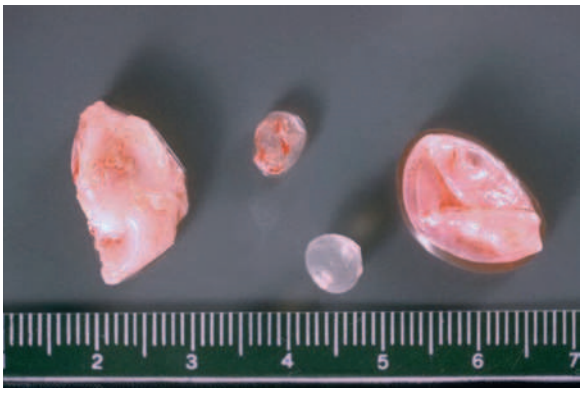

FIGURE 34-39 Gross pathology of membrane and hydatid daughter cysts from human lung. *(From Centers for Disease Control and Prevention Public Health Image Library.* http://phil.cdc.gov/Phil/quicksearch.asp*.)*

from the intermediate host are ingested by the definitive host, the protoscolices develop into mature worms within the definitive host's small intestine over 4 to 7 weeks to complete the life cycle. A definitive host is required for development of mature worms and thus the release of infectious eggs into the environment. Adult tapeworms do not develop in the intestines of humans or intermediate hosts; therefore, direct transmission of echinococcosis from human to human does not occur.[241]

EPIDEMIOLOGY

The epidemiology of *Echinococcus* differs by species:

Echinococcus granulosus

E. granulosus occurs nearly worldwide, and more frequently in rural, grazing areas where dogs ingest organs from infected animals. Human cystic hydatidosis is a significant public health problem in South and Central America, the Middle East, some sub-Saharan countries, China, and the former Soviet Union. Infection rates are highest in endemic rural areas, with prevalence rates of 2% to 6%.[301]

The definitive hosts for *E. granulosus* are dogs and other canids. The intermediate hosts are sheep, although other livestock can occasionally act as intermediate hosts. Human infection results from ingestion of eggs from the environment. These eggs may be ingested from contaminated water or vegetables or from direct contact with infected dogs through fecal-oral contact, which occurs more frequently in children.

Echinococcus multilocularis

E. multilocularis occurs in the northern hemisphere, including central Europe and the northern parts of Europe, Asia, and North America. *E. multilocularis* has a number of definitive hosts, including foxes, wolves, dogs, coyotes, and cats. Intermediate hosts are rodents, including voles, muskrats, and housemice.

Echinococcus vogeli and *E. oligarthrus*

E. vogeli and *E. oligarthrus* occur in Central and South America. The definitive hosts of *E. vogeli* are wild canids, and the intermediate hosts are rodents. The definitive hosts of *E. oligarthrus* are wild felids, and the intermediate hosts are rodents.

SYMPTOMS

Echinococcus granulosus (Cystic Hydatidosis)

E. granulosus in humans develops as a unilocular hydatid cyst. This cyst is a slow-growing, space-occupying cystic lesion enclosed by a laminated germinative membrane that produces protoscolices, or tapeworm heads (Figure 34-40). The cyst grows as it slowly accumulates fluid. Spillage of this fluid can result in severe reactions, including anaphylaxis and death, and it can also lead to dissemination of infection from the release of protoscolices.[241]

Because of the slow growth of the cysts, infections remain silent for many years before causing symptoms. Symptoms depend on the organs involved. The liver is most often affected, seen in two-thirds of patients. The lungs are involved in approximately 25% of patients, whereas other organs, including brain, bone, heart, muscle, and kidneys, are rarely involved. Single-organ involvement is found in 85% to 90% of patients, and more than two-thirds of patients have only a single cyst.

Hepatic involvement, the most common form of echinococcosis, can involve abdominal pain, an abdominal mass, or biliary ductal obstruction. Mass effect on the portal veins, hepatic veins, and inferior vena cava can result in portal hypertension, venous obstruction, or the Budd-Chiari syndrome.

Pulmonary involvement can manifest with cough, dyspnea, chest pain, and hemoptysis. Seizures or elevated intracranial pressure can indicate brain involvement. Bony cysts may present as pathologic fractures; the spine, pelvis, and long bones are most frequently involved. Spontaneous or traumatic rupture of cysts releases toxic fluid into involved areas and can produce fever, urticaria, eosinophilia, and anaphylactic shock.

Echinococcus multilocularis (Alveolar Hydatidosis)

E. multilocularis infection follows a more aggressive course than does *E. granulosus* infection. *E. multilocularis* forms cysts composed of a thin laminar layer without a limiting membrane or germinal layer. These cysts behave as a slowly growing, destructive, polycystic tumor. The lesions are made up of multiple irregular cysts, often with mixed solid and cystic components. This polycystic mass invades and destroys adjacent tissues and can metastasize to distant sites in the body.

The primary infection site in alveolar hydatidosis is almost always the liver, but spread to other organs such as the lungs and brain occurs frequently by direct extension or hematogenous or lymphatic dissemination. Manifesting symptoms include right upper quadrant discomfort, malaise, and weight loss. Biliary obstruction, portal hypertension, and the Budd-Chiari syndrome can also occur.

Alveolar hydatidosis is a more aggressive disease than cystic hydatidosis. Untreated, the patient with alveolar hydatidosis has a 10-year survival rate of less than 10% after the onset of symptoms, and a 15-year survival rate of less than 1%.[7]

Echinococcus vogeli and *E. oligarthrus*

E. vogeli and *E. oligarthrus* cause polycystic hydatid disease affecting the liver and occasionally the lungs. Both are rare causes of hydatid disease in humans.

DIAGNOSIS

The diagnosis of echinococcosis relies mainly on findings by ultrasonography or other imaging techniques supported by positive serologic tests. Serology testing should be used before invasive methods of diagnosing echinococcosis. In patients with negative serology but suspicious lesions on imaging, fine-needle

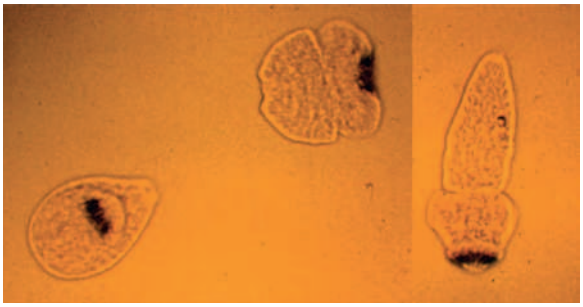

FIGURE 34-40 "Hydatid sand." Fluid aspirated from a hydatid cyst shows multiple protoscolices (approximately 100 µm), each of which has typical hooklets. The protoscolices are normally invaginated (*left*), and they evaginate (*middle*, then *right*) when put in saline. *(Image contributed by Georgia Division of Public Health.)*

biopsy by ultrasonographic guidance can be useful for confirmation of the diagnosis. However, precautions must be taken with this procedure to avoid leakage of toxic cystic fluid and to control any allergic reaction that results from this leakage.

False-negative serology results occur when the location, integrity, or vitality of the cyst is such that the patient has not mounted an antibody response to the cyst. Intact cysts result in the lowest rate of antibody response. Cysts in bone and the liver are more likely to elicit antibody response than those in the lungs or brain. Patients with calcified or dead cysts are generally seronegative. False-positive serology results may occur in patients with other tapeworm infections, cancer, and chronic immune disorders.

Echinococcus granulosus

Routine serum tests, such as CBC and hepatic panels, may demonstrate mild abnormalities but are not diagnostic. Eosinophilia is uncommon and usually present only if antigenic material has leaked from cysts.[124]

Serology tests for *E. granulosus* include ELISA, indirect hemagglutination (IHA), and IFA tests, with sensitivity ranging from 60% to 90%. The best sensitivity is obtained by using a combination of tests. These tests have limited usefulness for following the course of disease after treatment; imaging techniques are the modality of choice for monitoring disease progress.

Imaging is extremely useful in diagnosing cystic hydatidosis. Although plain radiographs may reveal calcified cysts, ultrasound, CT, and MRI are preferable for diagnosis. Ultrasound has the benefits of being easy to perform and less expensive than CT or MRI, and it is particularly useful for evaluation of intraabdominal cysts. These cysts most often appear as anechoic, smooth, round cysts that look similar to benign cysts. Septation can be seen when daughter cysts are present. The "hydatid sand" may be visible on ultrasound imaging.

The CT scan is useful for better defining the site, size, and composition of cysts and is better than ultrasound at detecting extrahepatic cysts. CT is also useful to monitor for recurrence during or after therapy. The sensitivity of CT is cited as 95% to 100%.[289] MRI is better than ultrasound for mapping extrahepatic cysts, particularly in the brain.[357] However, MRI has little benefit over CT for abdominal or pulmonary hydatid cysts, except for better delineating venous or biliary involvement. Other techniques, such as endoscopic retrograde cholangiopancreatography, are also useful in diagnosing biliary involvement of hydatid disease.

Echinococcus multilocularis

Nonspecific leukopenia or thrombocytopenia, mild eosinophilia, and nonspecific liver function abnormalities may be detected but are not diagnostic. Hypergammaglobulinemia and elevated serum IgE levels are typically present.

Serology tests in alveolar hydatidosis are much more sensitive than for cystic hydatidosis, with a higher proportion of patients having an antibody response to *E. multilocularis*. Immunoaffinity-purified *E. multilocularis* antigens used in ELISA have a sensitivity of 95%. In alveolar echinococcosis, serial serology is useful for following the disease course, given its increased sensitivity.

The preferred imaging modalities for alveolar hydatidosis are similar to those for cystic hydatidosis: ultrasound, CT, and MRI. These polycystic lesions typically have irregular borders, central necrosis, and irregular calcifications. They are often difficult to distinguish from a tumor. MRI is useful for delineating obstruction of the inferior vena cava or for brain lesions.

TREATMENT

Treatment is based on extent of disease and may include surgery, anthelmintic therapy, percutaneous therapy, and observation.[43] Traditionally, surgery is the most common form of treatment for echinococcosis and results in a 90% cure rate when the cysts are completely excised.[213] Cystic hydatidosis is more often curable with surgery than is alveolar hydatidosis, which tends to be more invasive. After surgery, medication may be necessary to keep the cysts from recurring. The drug of choice for treatment of cystic echinococcosis (*E. granulosus*) is albendazole. Albendazole or mebendazole is the recommended treatment for *E. multilocularis* infections.[178]

Not all patients with hydatid disease are surgical candidates. WHO recommendations for hydatid disease list the following contraindications for surgery: patients at the extremes of age, patients in very poor general condition, pregnant women, patients with multiple cysts or cysts that are difficult to access, and patients with dead or completely calcified cysts.[387] Patients who are not good candidates for surgery have two options: chemotherapy with albendazole or mebendazole and a newer treatment, percutaneous aspiration, introduction of a protoscolicidal agent, and reaspiration (PAIR).[173]

The PAIR procedure involves percutaneous puncture of cysts under ultrasound guidance, aspiration of cyst fluid, and injection of a protoscolicidal agent such as hypertonic saline or ethanol into the cyst cavity. The cyst is then reaspirated after 15 minutes. PAIR has been used primarily for cysts in the liver, although cysts in other sites have also been treated. WHO currently recommends PAIR for inoperable patients and for patients who refuse surgery. The indications for the PAIR procedure are expanding as experience with this modality grows. With appropriate patient selection, PAIR may be used more widely for initial treatment of echinococcosis.[103] PAIR is contraindicated in patients with inaccessible cysts or cysts with a high risk of spillage into the abdominal cavity. It is also contraindicated in inactive cysts and for cysts with biliary communication. Risks of the procedure include spillage of fluid and the resulting allergic reaction, bleeding, infection, chemical sclerosing cholangitis, and biliary fistulas. Treatment with albendazole or mebendazole is recommended before and after the procedure to decrease risks and increase success of therapy.

PREVENTION AND CONTROL

Prevention and control of echinococcosis involve disrupting the life cycle of the parasite.[94] Control measures include eliminating stray dogs and preventing dogs from consuming infected viscera by prohibiting home slaughter of sheep. Control programs are ongoing in Australia, Argentina, Chile, Brazil, Peru, China, Portugal, and many Mediterranean countries. Many of these programs include surveillance testing of dogs for *Echinococcus* and treating infected dogs with praziquantel. The most successful programs, in Iceland, New Zealand, and Tasmania, relied on regular repeated treatment with praziquantel of all at-risk dogs to eliminate the definitive host carriers of *E. granulosus*.[94]

For humans, prevention involves avoiding close contact with dogs and foxes and careful washing of vegetables and fresh produce when in endemic areas. The future may hold vaccination for humans as well.

TRICHINELLOSIS

Trichinellosis is an infection caused by nematodes in the genus *Trichinella*. In the past, only one species, *Trichinella spiralis,* was recognized. Isoenzyme and DNA analysis indicate that the genus is polyspecific.[271] Eight gene pools, T_1 through T_8, have been identified. T_1 is classic *T. spiralis*; the principal reservoir is in domestic swine, but some wild animals can also be infected. T_2, *Trichinella nativa,* is found primarily in terrestrial mammals such as the bear, walrus, or fox in Arctic and sub-Arctic regions. Most human infections are caused by T_1, and few by T_2. Relatively few data are available on how frequently the other species infect people. T_3 occurs in bears (Ursidae), and T_7 and T_8 occur in African Hyenidae and Felidae. Only T_4, *Trichinella pseudospiralis,* can infect mammals and birds. Unless stated otherwise, the rest of this discussion relates to trichinellosis caused by *T. spiralis*.

HISTORICAL ASPECTS

The Bible references swine as dirty animals, and some religions advocate not eating pork; it is hypothesized that part of this practice encouraged public health by preventing parasitic infections

such as trichinellosis and cysticercosis. *Trichinella* cysts were first noticed by Paget during an anatomic dissection in 1836, when distinct white lesions were found throughout a muscle specimen. The association between encysted organisms and ingestion of contaminated meat was not made until 1850. In 1862, Friedreich diagnosed and described the first clinical case of acute trichinellosis. Outbreaks in Germany in 1849 and 1865 were associated with mortality of 19% and 30%, respectively. Examination of diaphragmatic muscle samples in the United States between 1936 and 1941 revealed *Trichinella* organisms in one of every six samples tested (16.7%). National reporting of trichinellosis began in 1947. The incidence of this disease has decreased significantly since the passage of legislation (the Federal Swine Health Protection Act of 1980) prohibiting the feeding of raw sewage to swine, aided by the widespread freezing of pork and increasing public awareness of the dangers of eating inadequately cooked pork products (Figure 34-41).

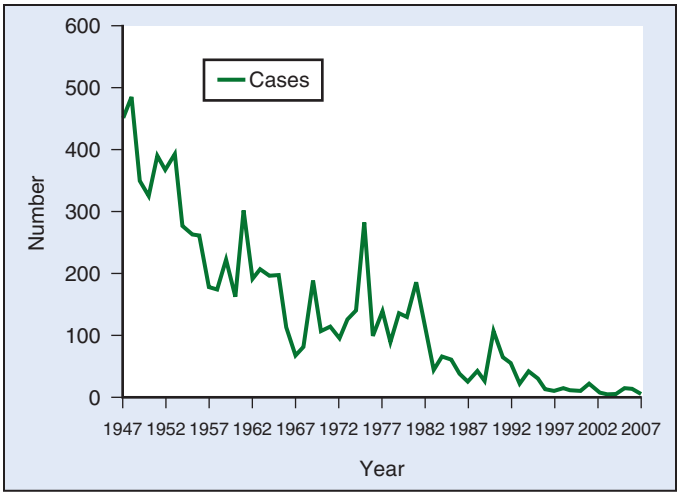

FIGURE 34-41 Reported cases of trichinellosis in the United States. *(Modified from Centers for Disease Control and Prevention: Reported cases of trichinellosis in the United States,* MMWR *58:1, 2009.)*

LIFE CYCLE

The life cycle of *Trichinella* organisms is unusual in that every host is necessarily both a definitive host, harboring the adult stage of the parasite, and an intermediate host, harboring the larval stage (Figure 34-42).

The infection is acquired by ingestion of larvae encysted in skeletal muscle. The worms mature within a few days in the small intestine. The female burrows into the mucosa and deposits larvae in tissue, starting around the fifth day after infection. Most larvae are deposited within 4 weeks, but they can be produced for as long as 4 months. The larvae enter the circulation and invade skeletal muscle within 7 to 14 days (Figure 34-43). They become encapsulated about day 21 and are then infective for the next host that ingests them.

EPIDEMIOLOGY AND TRANSMISSION

All carnivorous and omnivorous mammals are susceptible to trichinellosis, but most human infections are acquired by eating

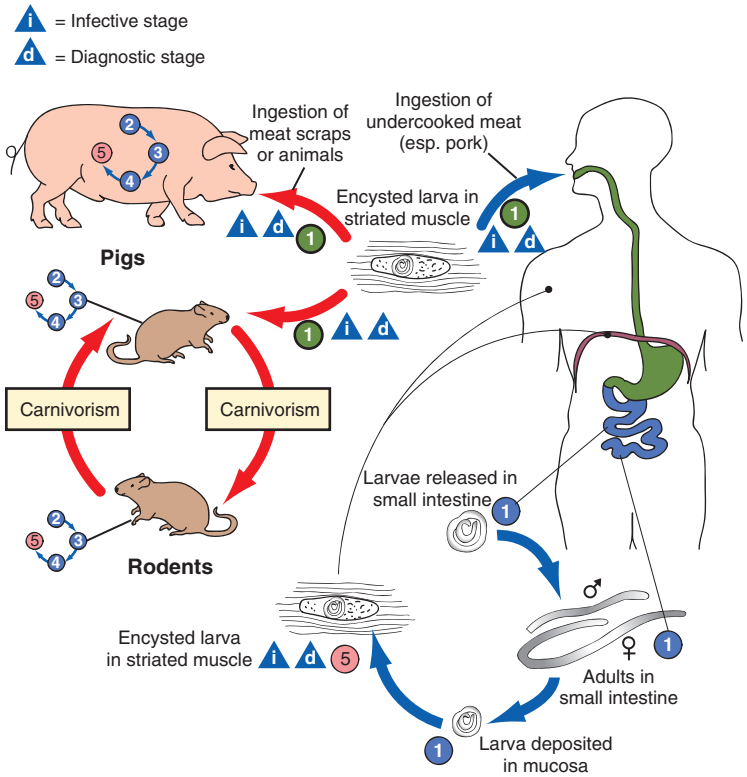

FIGURE 34-42 Trichinellosis is acquired by ingesting meat containing cysts (encysted larvae) (**1**) of *Trichinella*. After exposure to gastric acid and pepsin, the larvae are released (**2**) from the cysts and invade the small-bowel mucosa, where they develop into adult worms (**3**) (females, 2.2 mm in length; males, 1.2 mm; life span in small bowel, 4 weeks). After 1 week, the females release larvae (**4**) that migrate to the striated muscles, where they encyst (**5**). *Trichinella pseudospiralis*, however, does not encyst. Encystment is completed in 4 to 5 weeks, and the encysted larvae may remain viable for several years. Ingestion of the encysted larvae perpetuates the cycle. Rats and rodents are primarily responsible for maintaining the endemicity of this infection. Carnivorous or omnivorous animals, such as pigs and bears, feed on infected rodents or meat from other animals. Different animal hosts are implicated in the life cycle of the different species of *Trichinella*. Humans are accidentally infected when eating improperly processed meat of these carnivorous animals (or eating food contaminated with such meat). *(From* http://www.dpd.cdc.gov/DPDx/HTML/Trichinellosis.htm.*)*

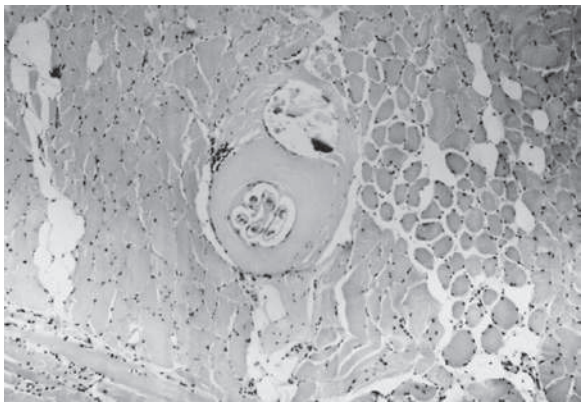

FIGURE 34-43 Trichinellosis in a polar bear. A larva is seen within a muscle fiber in the center of the picture. The parasite found in Arctic mammals is highly resistant to freezing and has been given a separate species status, *Trichinella nativa*. (Hematoxylin-eosin stain, ×100.)

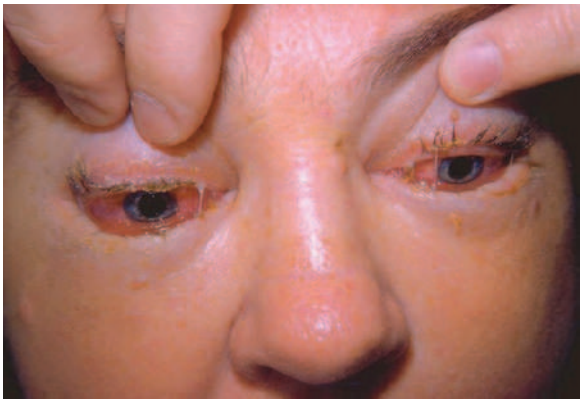

FIGURE 34-44 Clinical appearance of the eyes of a patient with trichinellosis. The patient had periorbital swelling, muscle pain, diarrhea, and 28% eosinophils. *(From Centers for Disease Control and Prevention Public Health Image Library. Courtesy Dr. Thomas Sellers, Emory University.)*

raw or undercooked pork. Game animals can harbor the parasite. Trichinellosis was found in 1.3% of black bears in New England.[162] It can infect other species of bears, raccoons, opossums, seals, walruses, peccaries, and wild swine.

Rodents, such as mice and rats, are frequently infected in nature. Except in certain cultures, these small rodents, unlike their larger cousins (e.g., squirrels, woodchucks, muskrats, agoutis, capybaras), are rarely eaten by people. These larger rodents are primarily herbivorous but are still an occasional source of human infection.

Although experimentally susceptible to trichinellosis, herbivores, such as members of the deer and antelope families, are almost never infected naturally, and consumption of their flesh is not associated with this infection. Some outbreaks of trichinellosis have occurred in people who consumed horseflesh.[60] The horses could have been infected by consuming mice, dead or alive, in their feed. Alternatively, larvae passed in the stool of infected rodents could have been ingested in the horses' grain or hay. Swine that are privately raised and slaughtered are a continuing source of human infections in many areas, including the northeastern United States.[15] Bears, walruses, and feral swine have been the principal nondomestic sources of trichinellosis in the United States.[228]

In the United States, there were 66 cases reported between 2002 and 2007.[176] Clusters of cases tend to occur from a common infected animal. Pork, bear meat, walrus meat, and cougar meat are common sources of U.S. infection, with sausage being a frequent implicated pork product. [239] Wild boars are a source of infection in Germany.[162] They have also been increasing as a source of U.S. infection.[147,163] Twenty-six cases of trichinellosis reported in the United States from 1975 to 1989 were acquired during foreign travel; 17 of these patients had traveled to Mexico or Asia.[228]

SYMPTOMS

The signs and symptoms of trichinellosis are closely related to the activities of the parasite in its life cycle. The severity of disease is directly related to the number of adult and larval worms present. GI symptoms predominate during the first week after ingestion of infected meat. The worms mate and invade the intestinal mucosa during the first 48 hours. The female worm is capable of producing up to 1500 larvae during its lifetime. Larvae are deposited starting on approximately the fifth day after ingestion. This activity results in bowel irritation, with nausea, vomiting, variable diarrhea, and abdominal pain. Fever may occur. These symptoms are often mistaken for various forms of food poisoning. GI symptoms may continue until the females are cleared from the intestinal tract at approximately 4 to 6 weeks after infection.

Larval production reaches a peak during the second week after infection, during which the cardinal clinical manifestation of trichinellosis occur as the larvae begin to invade skeletal muscle. As they invade, muscle pain, tenderness, swelling, and weakness develop and can even restrict breathing and tongue movement. During larval migration, direct capillary damage occurs, resulting in facial edema, especially involving the periorbital area, which may be accompanied by photophobia, blurred vision, diplopia, and complaints of pain on moving the eyes (Figure 34-44). Splinter hemorrhages may appear in the nail beds, and there may be cutaneous petechiae (Figure 34-45). Hemorrhagic lesions can also occur in the conjunctivae and retinae. Core body temperature may reach 40.5° C (105° F). Hepatomegaly is also common.[246]

Eosinophils start to increase in peripheral blood during the second week, often exceeding 20% of the total WBC count after the third week of infection. The eosinophil count normalizes from 6 to 12 months after infection. Gastroenteric symptoms may continue during this period, until the females are cleared from the intestinal tract, approximately 4 to 6 weeks after infection. During the second phase of infection, migrating larvae can cause pulmonary damage, resulting in cough, dyspnea, and pleuritic pain. There may be hemoptysis. Myocarditis can occur and may be life threatening.

Cardiac disease remains the most common cause of death in trichinellosis.[247] Damage to the brain or meninges by migrating larvae can cause encephalitic or meningitic symptoms in up to 24% of patients. A spinal tap may reveal eosinophils in the CSF. Headache is common and often worse with movement. In a

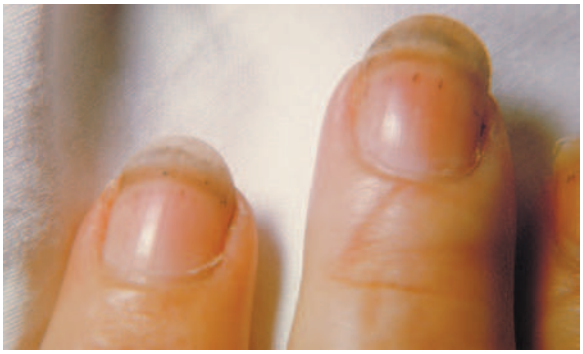

FIGURE 34-45 The parasitic disease trichinellosis is manifested by splinter hemorrhages under the fingernails. *(From Centers for Disease Control and Prevention Public Health Image Library. Courtesy Dr. Thomas Sellers, Emory University.)*

review of 77 patients with neurotrichinellosis, the mortality rate was 17%, with lower eosinophil counts associated with death.[249] Renal disease is uncommon, with findings such as renal failure occurring only in severe disease.[248]

The third phase of infection is encystment of the larvae within skeletal muscle, starting about the second or third week after infection. This can cause significant myalgias and stiffness in affected muscle groups. The final phase of infection occurs as the larvae die and become calcified. This is a period of convalescence, which is usually asymptomatic, and typically occurs between 6 and 18 months after infection.

In the Inuit population of northeastern Canada, trichinellosis is associated with eating raw walrus and is characterized by prolonged diarrhea and brief muscle symptoms. High peripheral eosinophilia and high *Trichinella* antibody titers occur. The disease is probably caused by *T. nativa,* and at least some cases may be associated with reinfection.[210]

DIAGNOSIS

Larvae are sometimes passed in the stool in the early stages of infection, but this occurs infrequently and inconsistently and cannot be used for diagnosis. Diagnosis is often based on clinical symptoms and confirmed by serology.

Trichinellosis is definitively diagnosed by biopsy of the gastrocnemius muscle or of clinically affected (painful, tender) muscles (Figure 34-46). The larvae are demonstrable in muscle beginning about the seventh day after infection. Diagnosis can also be made serologically, using the bentonite flocculation test (BFT), latex particle agglutination, or countercurrent immunoelectrophoresis. The BFT involves a suspension of aluminum silicate particles (bentonite) to which *Trichinella* antigen is bound and incubated with dilutions of serum from the patient. All these tests usually do not become positive until 3 to 4 weeks after infection. Newer ELISAs are available that measure reaction by different immunoglobulin classes. Most ELISAs offer greater specificity and sensitivity and become positive earlier than many of the other tests.[14,300,360] An ELISA for IgG, using the excretory-secretory antigen of *T. spiralis* larvae, had specificity and sensitivity of 100% at days 57 and 120 after infection, but was negative at day 23.[215] An experimental assay, the dissociated enhanced lanthanide fluoroimmunoassay (DELFIA), can detect as little as 1 ng of antigen per milliliter of serum. Circulating antigen was detected in mice as early as 7 days after infection.[184]

TREATMENT

Management of symptomatic *Trichinella* infection consists of anthelmintic therapy and corticosteroids. Albendazole and mebendazole are the primary anthelmintic drugs used. Albendazole is slightly preferred because it does not require as much monitoring as mebendazole.[145] The recommended dose for albendazole is 400 mg twice daily for 8 to 14 days. The recommended dose for mebendazole is 200 to 400 mg three times daily for 3 days, followed by 400 to 500 mg three times daily for 10 days.[258]

Steroids (e.g., prednisone, 30 to 60 mg/day PO for 10 to 30 days) can be given for relief of severe illness, such as myocarditis caused by migrating larvae or nervous system involvement.[181] Dosage and duration of treatment are individually determined by clinical response. Steroids reduce the inflammatory response to larvae but can also interfere with rejection of adult females in the intestine, thus prolonging the period of larva deposition.

As a general rule, the effectiveness of therapy depends on the time of administration. Early treatment before larvae have established themselves in the muscle is most effective. There is no satisfactory, safe, and effective drug for elimination of harbored larvae.[145]

PREVENTION

Trichinellosis is prevented by cooking meat to an internal temperature of 65.6° to 77° C (150° to 170° F). Most *Trichinella* larvae are killed by freezing. The time required depends on the thickness of the meat and the freezing temperature. Holding meat at −15° C (5° F) for 20 days, −23.3° C (−10° F) for 10 days, or −28.9° C (−20° F) for 6 days is recommended. Salting, drying, and smoking are not always effective. Note that *T. nativa* found in Arctic mammals is resistant to freezing.

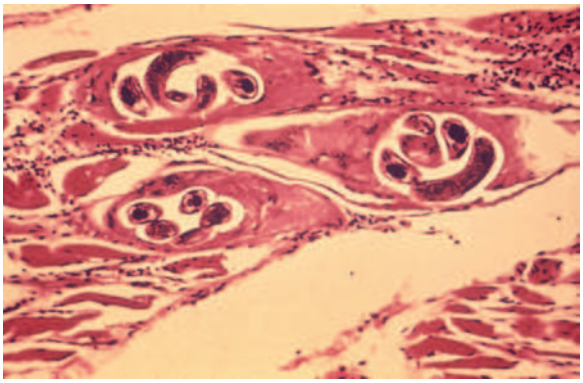

FIGURE 34-46 Micrograph of developing *Trichinella* cysts within human muscle tissue. *(From Centers for Disease Control and Prevention Public Health Image Library.* http://phil.cdc.gov/Phil/quicksearch.asp*.)*

VARIANT CREUTZFELDT-JAKOB DISEASE

Prion diseases include fatal degenerative diseases of the nervous system that affect humans and animals. In humans, prion disorders include Creutzfeldt-Jakob disease (CJD), kuru, Gerstmann-Sträussler-Scheinker syndrome, fatal familial insomnia, and variant Creutzfeldt-Jakob disease (vCJD). In animals, these include bovine spongiform encephalopathy (BSE), scrapie, chronic wasting disease, transmissible mink encephalopathy, and feline spongiform encephalopathy. BSE is unique in that it is the only animal-related prion disease believed to lead to a human prion disease, vCJD, through consumption of contaminated ruminant products.

HISTORICAL ASPECTS

The first diagnosis of BSE was reported by the Central Veterinary Laboratory in Weybridge, England, in December 1986.[377] In subsequent years, the number of reported cases rose steadily, and the British government initiated a series of escalating preventive measures to combat the epidemic. Incidence peaked in 1992, with 36,680 confirmed cattle cases that year. By 2000, fewer than 1500 cases had been reported, reflecting ongoing steady decline.[93]

In late 1995 and early 1996, CJD began appearing in Great Britain in a very unusual population—young adults. Further investigation revealed significant differences from previously documented CJD cases in histopathology, electroencephalography (EEG) waveforms, and MRI brain signal hyperintensities. These cases were named "new-variant CJD."

Classically, CJD has occurred sporadically without the clustering that occurred with this new variant, which led researchers to search for a new risk factor or cause. Given that the onset of symptoms of CJD after initial exposure can be delayed for up to a decade, the time between confirmation of the first case of BSE and the first case of the new vCJD raised suspicions for a bovine-to-human transmission.[306] Subsequent studies have demonstrated remarkably similar molecular characteristics, histopathology, and clinical features in BSE and vCJD patients.[88,192,312] It is now widely accepted that consumption of BSE-contaminated ruminant products can result in vCJD in humans. Many countries, including the UK, United States, and Canada, have developed vCJD watch groups aimed at identifying sources as they arise.

BIOLOGY

The infectious agent is believed to be an abnormal isoform of the prion protein (PrP), designated PrP^{Sc}.[87] A prion is an infectious protein that lacks nucleic acids. The human *PrP* gene is located on the short arm of chromosome 20 and spans 16 kilobases (kb).[87] PrP^{Sc} is derived, through an aberrant post-translational mechanism, from isoform PrP^{C}, which is found as a membrane-anchored glycoprotein in many cells throughout the body. If the PrP^{C} protein undergoes a conformational change to the partially protease-resistant PrP^{Sc}, accumulations in nervous tissue lead to BSE and vCJD. It is hypothesized that PrP^{Sc} can catalyze transformation of PrP^{C} to more PrP^{Sc}.[359]

EPIDEMIOLOGY

Bovine spongiform encephalopathy is thought to have been a low-level disease of cattle for many years. It is presumed to have risen in incidence in 1980 when changes in rendering resulted in reduction in tallow extraction (previously done by the use of solvents) and provided higher fat content in the meat. When these solvents were no longer being used, it allowed cattle protein supplements to become contaminated with a transmissible agent.[95] Since the number of BSE cases in cattle in Great Britain reached a peak of 36,680 in 1992, there was a steady decline to a total of 611 cases in 2003.[102] A total of 778 cases of BSE were reported outside the UK in 2003, including one U.S. case from a cow that was imported from Canada.[396] According to the CDC, a total of 229 cases of vCJD have been identified since 1996, including cases in the UK, France, Italy, Spain, Canada, Ireland, the United States, Portugal, The Netherlands, Japan, and Saudi Arabia.[165] The vast majority (177) of vCJD cases occurred in the UK. Three of the French cases, two of four Irish cases, two of three U.S. cases, the case from Japan, and the case from Canada are believed to have resulted from exposure during time spent in the UK.[395] A total of four cases have been reported in the United States. In addition to the two persons thought to have been exposed through prolonged time in the UK, one case is believed to have been acquired through time in Saudi Arabia, and the source of the most recent case of a man in Texas in 2014 is still under investigation.[166]

The incubation period is variable, according to routes of exposure, with iatrogenic cases (cornea grafts, neurosurgical instruments, and dura mater) less than 2 years, and approximately 15 years after peripheral insertion of pituitary hormones. It is unclear how long the incubation period is for ingested products.[263] With new-variant CJD, it may be only 1 year from inoculation until death, depending on the route of exposure.

TRANSMISSION

Transmission of prions in BSE and vCJD occurs through ingestion of infected ruminant material, which is assumed to be the cause of the UK outbreak in the late 1980s. This practice was banned in 1988 for public health, and more strict measures were put in place in 1989 because of increasing understanding of the disease. In 1996, after continued outbreaks of the disease, recall of all food containing mammalian meat and bone meal (MBM), including animal feed, was put into place.[263]

The only tissues outside the CNS that have been demonstrated to be infectious are the retina, cornea, trigeminal and paraspinal ganglia, distal ileum, and bone marrow.[42] This recovered meat was found in hot dogs, sausages, canned meats, and some luncheon meats. A case report describes five cases of unrelated individuals in Kentucky with vCJD from eating squirrel brains in a cuisine termed Burgoo.[31]

There is also concern about the transmission of vCJD between humans by repeated use of infected surgical instruments and by blood transfusion. Patients have acquired vCJD from nonleukodepleted blood from a then-asymptomatic donor.[356] There is no blood test for products of vCJD. In the UK, patients with known exposure to BSE and vCJD are not allowed to donate blood and tissues, but the risk remains for persons accepting blood from donors with an asymptomatic infection.

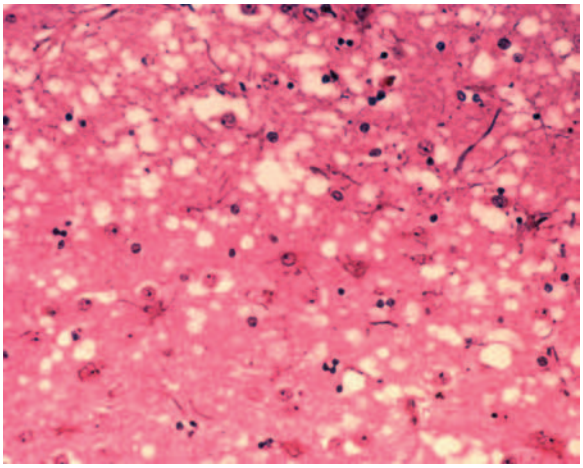

FIGURE 34-47 Micrograph of brain tissue showing the histopathologic changes in the cytoarchitecture found in bovine spongiform encephalopathy (BSE). The vacuoles in the gray matter give the brain of BSE-affected cows a sponge-like appearance in tissue sections. *(From Centers for Disease Control and Prevention Public Health Image Library. Courtesy U.S. Department of Agriculture, Animal and Plant Health Inspection Service, and Dr. Al Jenny.)*

SYMPTOMS AND DIAGNOSIS

The incubation period for BSE is 2 to 8 years. Cattle affected by BSE may display apprehension, incoordination, aggression, hind limb ataxia, tremor, difficulty rising, and hyperesthesia to sound and touch. The animal's condition gradually deteriorates, and it dies in 2 weeks to 6 months.[104] Diagnosis can be made by necroscopic examination of brain tissue (Figure 34-47).

Variant Creutzfeldt-Jakob disease is a progressive neurologic disorder that, unlike traditional CJD, affects a younger population (average age 29 years vs. 65 years) and lasts relatively longer (median 14 months vs. 4.5 months). Early illness is often accompanied by psychiatric features, including depression and schizophrenia-like psychosis.[388] Subsequent neurologic symptoms include ataxia, involuntary movements, lack of coordination, and pain.[93] Brain MRI may show hyperdensity in the pulvinar and dorsomedial thalamus, called the "pulvinar sign."[208] As with BSE, diagnosis can be confirmed only by postmortem histopathologic analysis of the brain, although new CSF tests are forthcoming.

TREATMENT AND PREVENTION

There is no treatment for either BSE or vCJD. Prevention is based on public health measures, which have led to a remarkable decline in cases in Great Britain. These measures may include a ban on ruminant-to-ruminant feeding, active surveillance for early detection of BSE, and a ban on importation of cattle and bovine products from countries known to have BSE. The economic implications of an importation ban have made such a measure controversial, although it is almost universal. There have been attempts to devise a treatment for vCJD and BSE, but little to no progress has been made.[36,337]

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CHAPTER 35

Bites by Venomous Reptiles in Canada, the United States, and Mexico

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The medical impact of venomous reptiles in the "New World" is relatively low compared with that in the eastern hemisphere. Recent estimates suggest approximately 300,000 snakebites per year in North America and Latin America, with approximately 4000 deaths, compared with more than 2 million bites per year in the eastern hemisphere, with approximately 80,000 deaths.[102] Although these estimates are inexact, given major barriers to data gathering in developing regions of the world, they paint a picture of snakebite at a "macro" level in the New World as an annoyance, but as a major health issue on the other side of the planet. However, the bite of a venomous snake or lizard in North America is quite significant to the individual victim and to those tasked with rendering care in the field and hospital. This chapter reviews venomous reptiles of medical importance in Canada, the United States, and Mexico, detailing clinical effects and proper approach to management of their bites. A general discussion of antivenom therapy is included. Venomous snakes are discussed first, followed by venomous lizards.

VENOMOUS SNAKES

SCOPE OF THE PROBLEM

The oft-quoted number of venomous snakebites in the United States is 7000 to 8000 per year. This estimate stems from work originally done in the late 1960s by Dr. Henry Parrish[200] and expanded on by Dr. Findlay Russell.[212] Parrish estimated deaths caused by snakebite in the United States to be about 15 per year.[200] No rigorous, systematic review has ever been done in the United States to determine a precise incidence of venomous snakebite, but compared with much of the developing world, the problem is relatively uncommon. A review of bites by native U.S. venomous snakes reported to the American Association of Poison Control Centers (AAPCC) from 2009 through 2013 revealed 35,751 cases (average, 7150 per year) with 11 total deaths (just over two per year).[24-26,186,187] Given that some unknown percentage of snakebites goes unreported to poison control centers, these numbers are an underestimate but illustrate the scope of the problem in the United States. With snakes being absent in most of Canada, the incidence of venomous snakebite is much lower than in the United States. In Mexico, snakebite has greater medical importance given that it has more venomous snake species than any other nation in the New World.[48] An estimated 3000 snakebites, with as many as 150 deaths, occur in Mexico each year.[93,228]

Table 35-1 lists the species of dangerous venomous reptiles found in Canada, the United States, and Mexico.[4,5,47,49,54,140,221] All the medically important North American venomous snakes belong to the families Viperidae (subfamily Crotalinae, the pit vipers) and Elapidae (subfamily Elapinae, the coral snakes, and subfamily Hydrophiinae, the sea snakes). The taxonomy of reptiles has been quite unsettled in recent years. Although discovery of new species in well-explored parts of the world is now rare, recent taxonomic changes are largely driven by genetic analyses and comparisons that redefine which forms are more closely related and which should be considered separate species.[240] As a result, recent accounts of the number of species of North American venomous snakes may appear inflated compared to references from just a decade ago. This is a result of the rapidly increasing understanding of relationships between familiar forms, not because snakes are rapidly evolving. For example, the "western rattlesnake," *Crotalus viridis*, was for many decades considered to contain 9 or 10 "subspecies," until geneticists demonstrated that the Rocky Mountains genetically isolated the forms east and west of the mountains long ago, with one modern form alone having diverged. The result was three species where there had previously been one. There now seems to be increasing consensus among taxonomists to eliminate subspecies completely, elevating many to full species status.

Being poikilothermic, snakes rely on environmental heat energy to support such physiologic processes as locomotion, feeding, digestion, and reproduction. Pit vipers are widely dispersed throughout most of the New World south of southern Canada (i.e., south of 55 degrees north latitude).[179] Pit vipers occurring north of Guatemala include the rattlesnakes (genera *Crotalus* and *Sistrurus*); copperheads, cottonmouth water moccasins, and cantils (genus *Agkistrodon*), as well as numerous species unique to Latin America (genera *Atropoides* [jumping pit vipers], *Bothriechis* [palm pit vipers], *Bothrops* [lancehead pit vipers], *Cerrophidion* [montane pit vipers], *Ophryacus* [Mexican pit vipers], and *Porthidium* [hognose pit vipers]). Recalling that taxonomic changes continue to be made, at this time there are three pit viper species (all rattlesnakes) found in Canada, 18 in the United States, and approximately 50 in Mexico.

Rattlesnakes are the most widespread pit vipers, found throughout much of North America (Figures 35-1 to 35-10). At least one species is found in each of the 48 contiguous states of the United States except Maine and Rhode Island. Copperheads (*Agkistrodon contortrix*) are found in the central and southeastern United States and westward into the Big Bend region of Texas (Figure 35-11). Cottonmouth water moccasins (*Agkistrodon piscivorus*) are found in the southeast from Virginia to Florida and extend westward into central Texas (Figure 35-12). In Mexico, copperhead and cottonmouth snakes are replaced by the cantils, *Agkistrodon bilineatus* (Figure 35-13) and *Agkistrodon taylori*.

In terms of elapids, coral snakes (akin to cobras [*Naja* sp.], mambas [*Dendroaspis* sp.], and kraits [*Bungarus* sp.] of the eastern hemisphere) are the only land-dwelling members of this family in North America, with two genera (*Micrurus* and *Micruroides*) on the continent (Figures 35-14 to 35-16). There are no coral snakes indigenous to Canada and only three species in the United States, but 16 species are found in Mexico. In the United States, these colorful reptiles are found in Arizona (Sonoran coral snake, *Micruroides euryxanthus*), the southeastern United States (eastern coral snake, *Micrurus fulvius*), and Texas (Texas coral snake, *Micrurus tener* [formerly *M. fulvius tenere*]). Mexican coral snakes include *Micruroides euryxanthus* and 16 *Micrurus* species.[49,140] One species of sea snake (*Hydrophis platurus,* formerly *Pelamis platurus*) reaches the southwestern coast of North America, occasionally visiting the coast of southern California. Sea snakes are discussed in Chapters 36 and 75.

The largest and most cosmopolitan snake family, Colubridae, consists largely of species that are completely harmless to

Text continued on p. 734

TABLE 35-1 Venomous Reptiles of Canada, the United States, and Mexico

Genus	Species	Common Name	Canada	U.S.	Mexico
Pit Vipers					
Agkistrodon		Cantils, copperheads, water moccasins			
	bilineatus	Common cantil	—	—	+
	contortrix	Copperhead	—	+	+
	piscivorus	Cottonmouth water moccasin	—	+	—
	taylori	Taylor's cantil	—	—	+
Atropoides		Jumping pit vipers			
	mexicanus	Central American jumping pit viper	—	—	+
	nummifer	Mexican jumping pit viper	—	—	+
	occiduus	Guatemalan jumping pit viper	—	—	+
	olmec	Tuxtlan jumping pit viper	—	—	+
Bothriechis		Palm pit vipers			
	aurifer	Yellow-blotched palm pit viper	—	—	+
	bicolor	Guatemalan palm pit viper	—	—	+
	rowleyi	Mexican palm pit viper	—	—	+
	schlegelii	Schlegel's viper	—	—	+
Bothrops		Lanceheads			
	asper	Terciopelo	—	—	+
Cerrophidion		Montane pit vipers			
	barbouri	Barbour's montane pit viper	—	—	+
	godmani	Godman's montane pit viper	—	—	+
	petlalcalensis	Petlalcala montane pit viper	—	—	+
	tzotzilorum	Tzotzil montane pit viper	—	—	+
Crotalus		Rattlesnakes			
	adamanteus	Eastern diamondback rattlesnake	—	+	—
	aquilus	Querétaro dusky rattlesnake	—	—	+
	atrox	Western diamondback rattlesnake	—	+	+
	basiliscus	Mexican west coast rattlesnake	—	—	+
	catalinensis	Santa Catalina rattlesnake	—	—	+
	cerastes	Sidewinder	—	+	+
	enyo	Baja California rattlesnake	—	—	+
	ericsmithi	Guerreran long-tailed rattlesnake	—	—	+
	horridus	Timber/canebrake rattlesnake	+	+	+
	intermedius	Mexican small-headed rattlesnake	—	—	+
	lannomi	Autlán long-tailed rattlesnake	—	—	+
	lepidus	Rock rattlesnake	—	+	+
	mitchelli	Speckled rattlesnake	—	+	+
	molossus	Black-tailed rattlesnake	—	+	+
	oreganus	Western rattlesnake			
	oreganus abyssus	Grand Canyon rattlesnake (formerly *C. viridis abyssus*)	—	+	—
	oreganus caliginus	South Coronado Island rattlesnake (formerly *C. viridis caliginus*)	—	—	+
	oreganus cerberus	Arizona black rattlesnake (formerly *C. viridis cerberus*)	—	+	—
	oreganus concolor	Midget faded rattlesnake (formerly *C. viridis concolor*)	—	+	—
	oreganus helleri	Southern Pacific rattlesnake (formerly *C. viridis helleri*)	—	+	+
	oreganus lutosus	Great Basin rattlesnake (formerly *C. viridis lutosus*)	—	+	—
	oreganus oreganus	Northern Pacific rattlesnake (formerly *C. viridis oreganus*)	+	+	—
	polystictus	Mexican lance-headed rattlesnake	—	—	+
	pricei	Twin-spotted rattlesnake	—	+	+
	pusillus	Tancitaran dusky rattlesnake	—	—	+
	ravus	Mexican pygmy rattlesnake	—	—	+
	ruber	Red diamond rattlesnake	—	+	+
	scutulatus	Mohave rattlesnake	—	+	+
	simus	Middle American rattlesnake	—	—	+
	stejnegeri	Sinaloan long-tailed rattlesnake	—	—	+
	tancitarensis	Tancítaro cross-banded rattlesnake	—	—	+
	tigris	Tiger rattlesnake	—	+	+
	totonacus	Totonacan rattlesnake	—	—	+
	transversus	Cross-banded mountain rattlesnake	—	—	+
	triseriatus	Mexican dusky rattlesnake	—	—	+
	viridis	Prairie rattlesnake	+	+	+
		(formerly *C. viridis abyssus* [Grand Canyon rattlesnake], *C. viridis caliginis* [Coronado Island rattlesnake], *C. viridis cerberus* [Arizona black rattlesnake], *C. viridis concolor* [midget faded rattlesnake], *C. viridis lutosus* [Great Basin rattlesnake], *C. viridis nuntius* [Hopi rattlesnake], *C. viridis viridis* [prairie rattlesnake])			
	willardi	Ridge-nosed rattlesnake	—	+	+

TABLE 35-1 Venomous Reptiles of Canada, the United States, and Mexico—cont'd

Genus	Species	Common Name	Canada	U.S.	Mexico
Ophryacus		Mexican horned pit vipers			
	melanurus	Black-tailed horned pit viper	—	—	+
	undulatus	Mexican horned pit viper	—	—	+
Porthidium		Hognose pit vipers			
	dunni	Dunn's hognose pit viper	—	—	+
	hespere	Colima hognose pit viper	—	—	+
	nasutum	Rainforest hognose pit viper	—	—	+
	yucatanicum	Yucatán hognose pit viper	—	—	+
Sistrurus		Rattlesnakes			
	catenatus	Massasauga	+	+	+
	miliarius	Pygmy rattlesnake	—	+	—
Elapids					
Micruroides	*euryxanthus*	Sonoran (Arizona) coral snake	—	+	+
Micrurus		Coral snakes			
	bernadi	Blotched coral snake	—	—	+
	bogerti	Bogert's coral snake	—	—	+
	browni	Brown's coral snake	—	—	+
	diastema	Variable coral snake	—	—	+
	distans	West Mexican coral snake	—	—	+
	elegans	Elegant coral snake	—	—	+
	ephippifer	Oaxacan coral snake	—	—	+
	fulvius (formerly *M. fulvius fulvius*)	Eastern coral snake, Harlequin coral snake	—	+	—
	laticollaris	Balsan coral snake	—	—	+
	latifasciatus	Long-ringed coral snake	—	—	+
	limbatus	Tuxtlan coral snake	—	—	+
	nebularius	Ixtlán coral snake	—	—	+
	nigrocinctus	Central American coral snake	—	—	+
	pachecogili	Azpotitlán coral snake	—	—	+
	proximans	Nayarit coral snake	—	—	+
	tamaulipensis		—	—	+
	tener (formerly *M. fulvius tenere*)	Texas coral snake	—	+	+
Hydrophis (formerly *Pelamis platurus*)	*platurus*	Pelagic sea snake (see Chapters 36, 74, and 75 for discussion of sea snake bites)	—	+	+
Lizards					
Heloderma		Venomous lizards			
	suspectum	Gila monster	—	+	+
	horridum	Beaded lizard	—	—	+

Data from references 4, 5, 47, 49, 54, 140, 221.
+, Present.

FIGURE 35-1 Eastern diamondback rattlesnake (*Crotalus adamanteus*) is the largest pit viper of the United States and can attain lengths of 2 m (6.5 feet). *(Courtesy Michael Cardwell, Extreme Wildlife Photography.)*

FIGURE 35-2 Western diamondback rattlesnake (*Crotalus atrox*) causes many serious bites in the U.S. Southwest. *(Courtesy Michael Cardwell, Extreme Wildlife Photography.)*

FIGURE 35-3 Mohave rattlesnake (*Crotalus scutulatus*) has two geographic populations in terms of venom composition, one with predominantly neurotoxic effects and one with more local sequelae. *(Courtesy Michael Cardwell, Extreme Wildlife Photography.)*

FIGURE 35-4 Timber rattlesnake (*Crotalus horridus*) is a large, dangerous snake of the eastern United States. *(Courtesy Michael Cardwell, Extreme Wildlife Photography.)*

FIGURE 35-5 Canebrake rattlesnake (*Crotalus horridus*), a form of the timber rattlesnake found in Florida, Georgia, and South Carolina, possesses a more neurotoxic and myotoxic venom than does its more northern variant. *(Courtesy Michael Cardwell and Medtoxin Venom Labs.)*

FIGURE 35-6 Prairie rattlesnake (*Crotalus viridis*) is a widely distributed species of the western United States. *(Courtesy Michael Cardwell, Extreme Wildlife Photography.)*

FIGURE 35-7 Northern Pacific rattlesnake (*Crotalus oreganus oreganus,* formerly *C. viridis oreganus*) is a moderate-sized but very toxic snake of the Pacific Northwest. *(Courtesy Joel Levis, MD.)*

FIGURE 35-8 Southern Pacific rattlesnake (*Crotalus oreganus helleri,* formerly *C. viridis helleri*) replaces *C. oreganus oreganus* in southern California and northwestern Mexico. *(Courtesy Michael Cardwell, Extreme Wildlife Photography.)*

FIGURE 35-9 Tropical rattlesnake (*Crotalus simus,* formerly *C. durissus durissus*) is a large, dangerous species found in southern Mexico. *(Courtesy Michael Cardwell, Extreme Wildlife Photography.)*

FIGURE 35-10 Western pygmy rattlesnake (*Sistrurus miliarius streckeri*) is one of the smaller rattlesnake species of North America. *(Courtesy Michael Cardwell, Extreme Wildlife Photography.)*

FIGURE 35-11 Southern copperhead (*Agkistrodon contortrix contortrix*) has markings that make it almost invisible when lying in leaf litter. *(Courtesy Michael Cardwell and Medtoxin Venom Labs.)*

FIGURE 35-12 Cottonmouth water moccasin (*Agkistrodon piscivorus*) exhibiting its threat display. This snake is found most often around standing-water sources in the southeastern United States. *(Courtesy Sherman Minton, MD.)*

FIGURE 35-13 Cantil (*Agkistrodon bilineatus*) is a close relative of the copperheads (*A. contortrix*) and cottonmouths (*A. piscivorus*) of the United States. This pit viper is found in Mexico and Central America. *(Courtesy Michael Cardwell and William W. Lamar.)*

FIGURE 35-14 Eastern coral snake (*Micrurus fulvius*) has a highly potent venom but is secretive, and bites are uncommon. *(Courtesy Michael Cardwell, Extreme Wildlife Photography, and Medtoxin Venom Labs.)*

FIGURE 35-15 Texas coral snake (*Micrurus tener*, formerly *M. fulvius tenere*), which although dangerous, tends to cause less severe envenomation than does *Micrurus fulvius*. *(Courtesy Michael Cardwell and the Gladys Porter Zoo.)*

humans. However, there are occasional reports, particularly in Africa and Asia, of human envenomation and even death caused by a handful of colubrid species (see Chapter 36). These species possess secretory glands (Duvernoy's glands) and enlarged maxillary teeth (sometimes grooved) in the rear of their mouths (opisthoglyphous). Secretions from these glands vary, depending on the species, and contain proteolytic enzymes and phospholipases.[118] The venoms help to immobilize, kill, and digest prey, and, when injected into humans, may cause envenomation—generally limited to pain, soft tissue swelling, bruising, and blister formation. Such local consequences have been reported in the United States after bites by the western hognose snake (*Heterodon nasicus*)[251] and the wandering garter snake (*Thamnophis elegans vagrans*).[94] Effective envenomation generally requires that these snakes maintain a bite for several minutes to inject sufficient venom into the tissues through their posterior teeth. These bites in the United States do well with conservative treatment alone, but it is important that they be differentiated from bites by pit vipers that may require antivenom therapy. A careful description or digital photograph of the involved snake should be obtained from a safe distance.

Throughout North America, pit vipers are responsible for approximately 98% of venomous snakebites.[226] Coral snakes tend to be secretive in nature and possess a less efficient venom delivery mechanism compared with pit vipers (see Anatomy, next). Bites by coral snakes are infrequent, even in regions where the snakes are relatively common. The 2013 report of the AAPCC Toxic Exposure Surveillance System recorded 73 coral snake bites in the United States that year.[187]

FIGURE 35-16 Sonoran coral snake (*Micruroides euryxanthus*) is also known as the Arizona coral snake. No documented fatality has followed a bite by this species. *(Courtesy Michael Cardwell and Jude McNally.)*

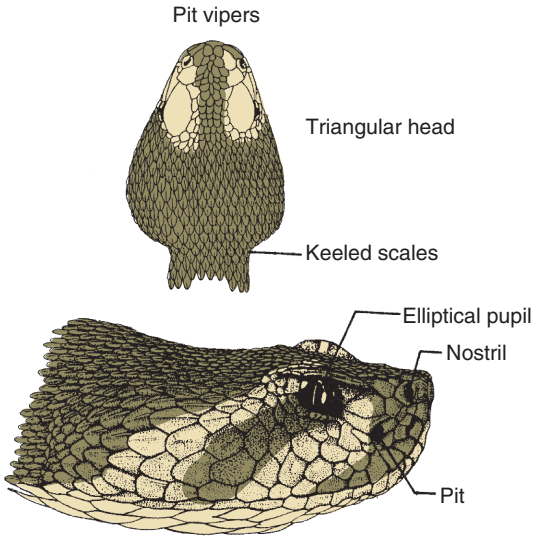

FIGURE 35-17 Pit viper's head. Note the elliptical pupil and the heat-sensing pit for which these reptiles are named. Viewed from above, the head has a distinctly triangular shape. Many nonvenomous snakes also possess triangular heads, and this is not a reliable means of differentiation. *(Courtesy Marlin Sawyer, 1994.)*

ANATOMY

Pit Vipers

Pit vipers of North America come in a wide range of sizes. Smaller rattlesnakes include the sidewinders (*Crotalus cerastes*), ridge-nosed rattlesnakes (*Crotalus willardi*), and pygmy rattlesnakes (*Sistrurus miliarius*), whose adult lengths are routinely less than 65 cm (25.6 inches). At the other extreme, the eastern diamondback rattlesnake (*Crotalus adamanteus*) can exceed 2 m (6.5 feet).[134]

The term *pit viper* comes from the presence of bilateral, thermal receptor organs (foveal organs or pits) present on the forward portion of the snake's head (Figure 35-17). These structures assist with prey location, aiming strikes (Figure 35-18), and may contribute to the snake's ability to regulate the amount of venom injected during bites[112,221,265] (Figure 35-19). Bilateral venom glands are located in the sides of the head behind the eyes, sandwiched between the muscularis compressor glandulae

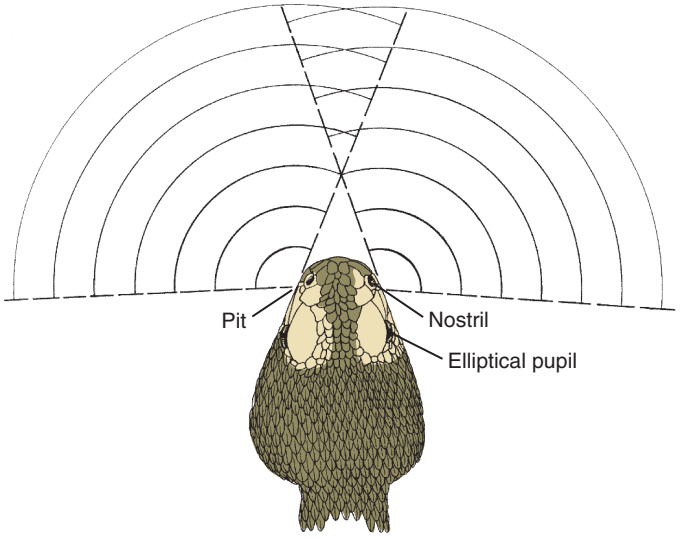

FIGURE 35-18 Paired heat-sensing pits of the pit vipers used to help the snake locate its prey, direct its strike, and probably determine the volume of venom to be expended. *(Courtesy Marlin Sawyer, 1994.)*

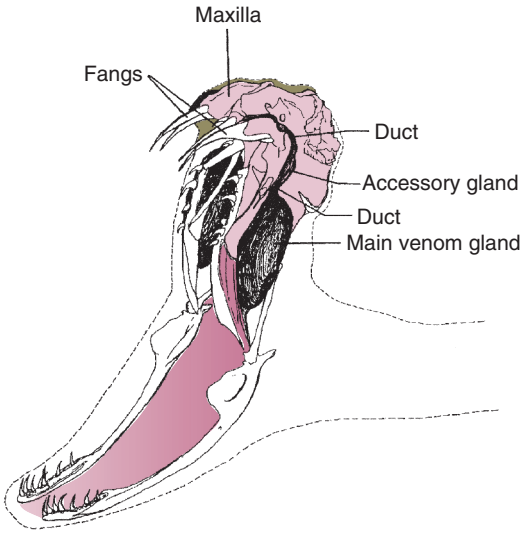

FIGURE 35-19 Venom delivery apparatus of a pit viper. Venom is produced in large venom glands just posterior to the eyes and is passed through a duct system into the hollow, anterior fangs when the snake bites. *(Courtesy Marlin Sawyer, 1994.)*

FIGURE 35-20 Rattlesnake skull. Replacement fangs are behind the primary, functional fangs. The smaller teeth of the palatine, pterygoid, and mandibular bones are used for gripping food. *(Courtesy Michael Cardwell, Extreme Wildlife Photography.)*

dorsolaterally and the muscularis pterygoideus glandulae ventromedially.[264] These glands, which produce and store venom, are connected through ducts to more anterior accessory glands, whose function remains unclear.[253] When the venom glands are compressed by muscular contraction, venom moves forward through ducts and accessory glands into venom sheaths surrounding the proximal portion of the hollow, needle-like fangs with which the snake pierces its target in a stabbing motion. These fangs, anchored in the highly mobile maxillae, are relatively large (up to 20 mm [0.8 inch] in big rattlesnakes[134]). At rest, the snake folds the fangs against the roof of its mouth. During a bite, the maxillae are rotated approximately 90 degrees, erecting the fangs into a position perpendicular to the palate. The snake has voluntary control over its fangs and can open its mouth without raising the fangs or can raise each fang individually at will. The fangs are relatively fragile and fracture or become dull with time and use. Two alveoli are present in each maxilla, and replacement fangs are constantly being produced just posterior to the maxillae. Independently on each side, a new fang periodically migrates forward into the empty alveolus, and the old adjacent fang soon loosens. Loose fangs become embedded in prey animals during swallowing and pass harmlessly through the snake's gut. Bites that happen to occur during this process may receive paired fang punctures on one or both sides, although there is no evidence that venom yield is affected (Figure 35-20). Pit vipers can strike at speeds of up to 2.4 m (8 feet) per second and reach distances of approximately one-half their body length.[260] Table 35-2 lists venom yields for various North American pit vipers.

The fastest pit viper can crawl at a maximum speed of approximately 4.8 km (3 miles) per hour, which approximates an average adult walking pace.[260] Crotaline snakes do not chase people. Accounts suggesting otherwise can be explained by other phenomena. For example, when approached by multiple people, a snake may retreat from one person and inadvertently move toward another. Also, all snakes, including desert species, are intolerant of high temperatures, with body temperatures at or above 35° to 40° C (95° to 104° F) being quickly fatal.[134] If forced to remain in the sun by curious humans, the snake may soon become desperate for the nearest shade, which may be close to a person.

The characteristic forked tongue of the snake is an olfactory tool and possesses none of the offensive "stinging" function ascribed to it in folklore. The snake extends its tongue to detect chemical odors in its environment. The tongue is then retracted and its tips placed into the paired Jacobson's organs, lined with olfactory epithelium, in the roof of its mouth. This sensory system is highly sensitive, allowing the snake to identify potential mates, locate prey, and track down an envenomated food item that has been bitten by the snake and released to die.

Pit vipers have elliptical, or "catlike," pupils (see Figure 35-17), whereas most North American harmless snakes have round pupils. A few, essentially harmless, rear-fanged colubrids in the United States, such as the night snake (*Hypsiglena torquata*) and

TABLE 35-2 Venom Yields of Some Medically Important Snakes of North America

Species	Maximum Venom Yield (mg Dry Weight)
Crotalus adamanteus	848*
Crotalus atrox	1145*
Crotalus cerastes	63*
Crotalus durissus	514 (average)*
Crotalus horridus	229*
Crotalus molossus	540*
Crotalus oreganus helleri (formerly *C. viridis helleri*)	390*
Crotalus oreganos (formerly *C. viridis oreganus*)	289*
Crotalus scutulatus	141*
Crotalus viridis	162*
Sistrurus catenatus	33†
Sistrurus miliarius	18 (average)*
Agkistrodon contortrix	45‡
Agkistrodon piscivorus	150‡
Micruroides euryxanthus	6§
Micrurus fulvius	38§
Micrurus nigrocinctus	20§

*Data from Klauber LM: *Rattlesnakes: Their habits, life histories, and influence on mankind,* ed 2, Berkeley, Calif, 1997, University of California Press.
†Data from Glenn JL, Straight RC: The rattlesnakes and their venom yield and lethal toxicity. In Tu AT, editor: *Rattlesnake venoms: Their actions and treatment,* New York, 1982, Marcel Dekker, pp 3-119.
‡Data from Parrish HM: *Poisonous snakebites in the United States,* New York, 1980, Vantage Press.
§Data from Roze JA: *Coral snakes of the Americas: Biology, identification, and venoms,* Melbourne, Fla, 1996, Krieger.

FIGURE 35-21 Although most members of the largely harmless Colubridae snake family have round pupils, some, such as this lyre snake (*Trimorphodon biscutatus*), a mildly venomous, rear-fanged colubrid of the southwestern United States, have elliptical pupils similar to those of pit vipers. *(Courtesy Robert L. Norris, Jr., MD.)*

lyre snake (*Trimorphodon biscutatus*) (Figure 35-21), also possess elliptical pupils but lack facial pits. Although these opisthoglyphous species possess Duvernoy's glands (see earlier discussion), they are innocuous creatures. They are reluctant to bite humans, and their salivary toxins are likely to cause few signs or symptoms, other than slight swelling, bruising, and pain, in the event of a bite. The two harmless North America dwarf boas, the rosy boa (*Lichanura trivirgata*) and the rubber boa (*Charina bottae*), also possess elliptical pupils, but their body form (more cigar shaped and lacking the broad, triangular head of a pit viper) and skin patterns are very different from those of any crotaline.

The caudal rattle of the rattlesnake is composed of loosely interlocked hollow segments of keratin that emit a buzzing sound when the snake rapidly vibrates its tail. This characteristic sound serves as a warning to other animals that might pose a threat. Snakes periodically shed the keratinous corneal layer of their skin, and a new segment is added to the rattle each time this occurs, which can be from one to several times each year, depending on age, health, and feeding success. Newborn rattlesnakes are born with a single button that cannot make noise (Figure 35-22). Not until after their second shed do they possess a second rattle segment that can vibrate against the first to produce a meager sound. As juvenile rattlesnakes grow and shed, they accumulate more segments and are soon able to produce a more audible buzz. Because shedding frequency varies and older distal rattle segments often break off during the snake's life, the number of segments cannot be used reliably to determine age. Although rattlesnakes often sound a warning when closely approached, it is a misconception that they will always do so before striking.

FIGURE 35-22 Newborn western diamondback rattlesnake (*Crotalus atrox*). Note the single "button" of its "rattle." *(Courtesy Michael Cardwell, Extreme Wildlife Photography.)*

A helpful anatomic feature to identify pit vipers in the United States and Canada is the scale pattern on the underside of the tail—the subcaudal scales. If a dead snake can be examined safely (i.e., it can be manipulated with a tool or it has been decapitated; see later), the base of the tail can be easily located by examining its ventral side. The abdomen ends and the tail begins at the level of the cloacal (anal) opening, which lies approximately 95% of the way down the snake's total length from its snout and is covered by an enlarged ventral scale (which is sometimes divided by an angled crease). In U.S. and Canadian pit vipers, the subcaudal scales immediately distal to the anal plate are undivided (i.e., each covers entire width of tail). In most nonvenomous snakes, coral snakes, and in some pit vipers in Latin America (including Mexico), the subcaudal scales are paired (i.e., each covers approximately half the width of tail, separated by zigzag suture) (Figures 35-23 and 35-24). The combination of keeled dorsal scales and undivided subcaudal scales is diagnostic for pit vipers north of Mexico[52] and can be helpful for identifying a dead snake brought in by a bitten victim without close examination of the snake's head, or when the head has been cut off and left at the scene. It should be noted that recently killed pit vipers, and even severed pit viper heads, can retain an autonomic bite reflex for at least 1 hour after death. This reflex can be stimulated by touch, and dead snakes and decapitated heads have caused serious envenomations, including fatalities, in victims who were bitten while handling them.[91,235]

Coral Snakes

Coral snakes are identified primarily by color pattern. In U.S. coral snakes, every other band is yellow (or white in the case of the Arizona coral snake) (Figure 35-25), and the bands completely encircle the snake's body. The contiguity of the red and yellow bands distinguishes U.S. coral snakes from a number of harmless mimics (e.g., several kingsnakes and milksnakes, genus *Lampropeltis*), which generally have red and yellow bands separated by black bands. This can best be remembered by recalling the phrase "red on yellow, kill a fellow; red on black, venom lack" or by considering that the red and yellow lights on a traffic signal are the warning lights. Contiguous red and yellow bands can be used to reliably identify coral snakes only in North America, north of Mexico City. Farther south, bicolor (red and black) coral snake species may be found, and many harmless mimics closely resemble these venomous serpents.[182] One harmless U.S. colubrid, the shovel-nosed snake (*Chionactis* spp.), has contiguous red and yellow dorsal saddles that resemble a coral

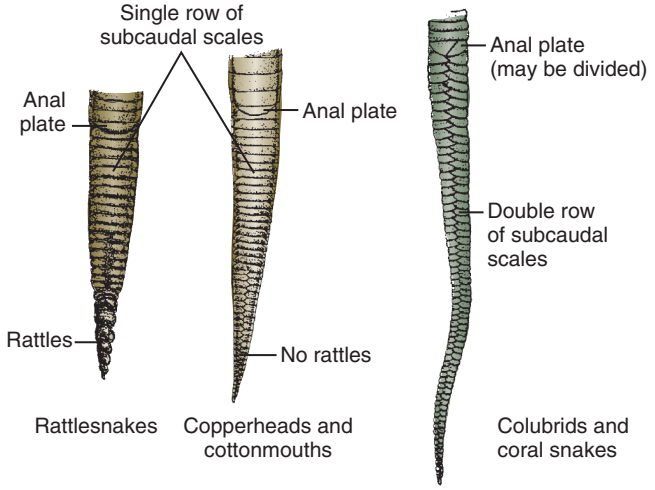

FIGURE 35-23 Subcaudal scale patterns of U.S. snakes. In the United States, pit vipers have a single row of scales on the ventral side of the tail, just distal to the anal plate. Most harmless colubrid snakes have double rows of subcaudal scales, as do coral snakes and some species of Latin American pit vipers. *(Courtesy Marlin Sawyer, 1994.)*

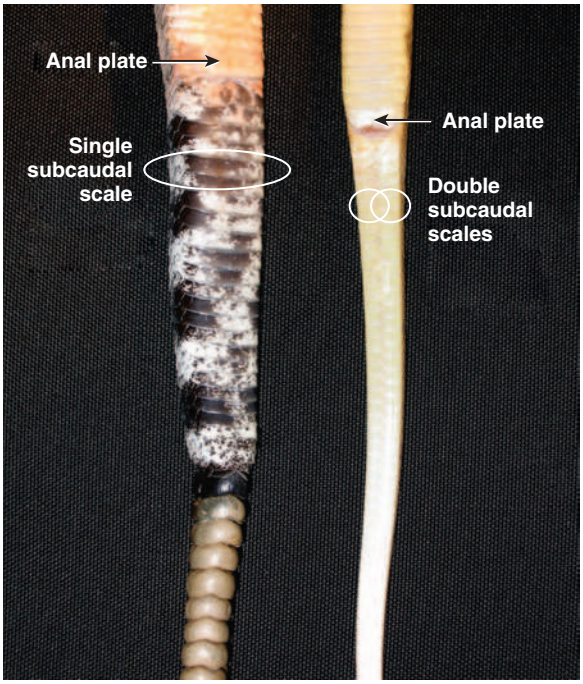

FIGURE 35-24 Comparison of the subcaudal scale pattern of a rattlesnake on the left with a harmless rat snake on the right. *(Courtesy Robert L. Norris, Jr., MD.)*

snake's markings, but the red coloration does not completely encircle its body, and the snake is completely inoffensive. In exceptionally rare cases, coral snakes can be all black (melanistic) or albino.[174]

The coral snake venom apparatus is much less complex than that of pit vipers. The paired venom glands connect through ducts to short, hollow fangs that are fixed in an erect position in the forward portion of the maxillae (Figure 35-26). Given their

FIGURE 35-25 Comparison of the Texas coral snake (*Micrurus tener*) with the harmless Mexican milk snake (*Lampropeltis triangulum annulata*). Coral snake (*bottom*) has contiguous red and yellow bands, whereas red and yellow bands of the milk snake are separated by black. *(Courtesy Charles Alfaro.)*

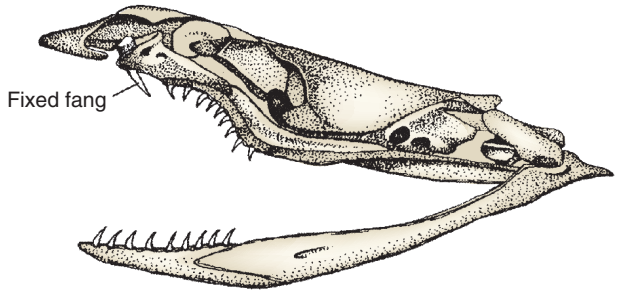

FIGURE 35-26 Coral snake's skull. Note the slightly enlarged anterior maxillary fang that is fixed in its upright position. *(Courtesy Marlin Sawyer, 1994.)*

smaller fangs, these snakes are not capable of striking out with the stabbing motion of a pit viper, although they can bite quickly and effectively into any exposed skin. In the vast majority of bites by coral snakes, the victim was handling the creature when bitten; in some cases, this occurred when the victim misidentified the snake as a harmless kingsnake.[203]

VENOMS

Pit Vipers

Snake venoms are extraordinarily variable and complex chemical cocktails of approximately 100 distinct molecular moieties. Some of the better-characterized and more interesting of these include the phospholipase A_2 (PLA_2) toxins, metalloproteinases, and thrombin-like enzymes.[68,128] PLA_2 toxins are a particularly variable family, including myotoxins, anticoagulants, phospholipid hydrolases, and presynaptic neurotoxins, and are among the most toxic of pit viper venom components. Some increase the lethality of the snake's venom 10- to almost 100-fold.[86] The first of these, crotoxin, was isolated in 1938 from the South American rattlesnake (*Crotalus durissus terrificus*).[1] PLA_2 neurotoxins noncompetitively bind to presynaptic calcium channels, inhibiting acetylcholine release and thereby blocking neurotransmission at the neuromuscular junction, inactivating the muscle. This can cause paralysis of the muscles of respiration, for example, and lead to respiratory difficulty. Additionally, some PLA_2 enzymes damage muscle cell membranes, allowing calcium influx and release of creatine and creatine kinase (CK), which can progress to diffuse myonecrosis and rhabdomyolysis.[130] Metalloproteinases, the enzymes that cause much of the locally destructive effects of pit viper envenomation, activate tumor necrosis factor-α and stimulate endogenous human metalloproteinases, intensifying inflammation. Certain metalloproteinases, the hemorrhagins, cause leakage of red blood cells (RBCs) out of the vasculature, leading to ecchymosis (characteristic of more severe pit viper bites) and fluid shifts.[101,256] High venom toxicity is generally associated with PLA_2 neurotoxins, which are typically (but not always) inversely related in proportionate concentrations to the tissue-damaging metalloproteinases.[163] Thrombin-like enzymes cause consumptive coagulopathy but do not directly activate coagulation factors or form a complex with antithrombin III (and so are not affected by heparin). Disintegrins bind to proteins on blood platelets, blocking their combination with fibrinogen necessary to form clots.[44] Bradykinins cause hypotension, vomiting, and pain. Hyaluronidase decreases the viscosity of connective tissues, allowing venom to spread. Lysolecithin, a byproduct of the enzymatic action of PLA_2, damages mast cell membranes and results in histamine release.[57]

Pit viper venom has both predatory (i.e., food gathering) and defensive functions. Research shows venom evolution and composition to be closely correlated with diet.[166,168,169] The kinematics and venom expulsion during defensive bites differ from predatory bites. Human bites by wild snakes are invariably defensive. Except for occasional bites by long-term captives acclimated to being fed in a cage by a person, snakes do not mistake humans for prey. Thus, caution must be exercised in interpreting studies of predatory bites to explain snakebites to humans. Nonetheless,

understanding the predatory function of venom helps to provide insight into the potential effects in bitten people.

In predatory strikes, the prey animal is usually released after a brief bite, but the venom soon immobilizes the prey and facilitates its retrieval by altering its scent. In species with proteolytic venoms, the venom also accelerates digestion.[56,110,115] Whereas individual snakes regularly feed themselves using predatory strikes, defensive strikes meant to deter potential predators are rare events and therefore seldom practiced. Studies show that the amount of venom injected defensively is often greater and more variable than in predatory bites. Factors such as duration of fang contact and time elapsed since last meal influence the amount of venom released defensively.[110,115] In one comparison, the northern Pacific rattlesnake (*Crotalus oreganus,* formerly *C. viridis oreganus*) expended almost four times more venom when biting a hand model (defensive) than when biting a mouse (predatory).[110,115] The most significant factor influencing potential venom delivery is the size of the snake.[115] A direct relationship between snake length and mass of venom expended has been demonstrated in both predatory and defensive bites.[111,115]

A popular belief is that juvenile rattlesnakes are more dangerous than adults because their venom is more toxic and they are unable to control the volume released. Ontogenic changes in venoms are believed to be correlated with many species' dietary shift from predominantly lizards and frogs as juveniles to mammals as adults.[166,168,169,183] PLA_2 neurotoxicity decreases and metalloproteinase activity increases with age, probably accounting for some decrease in overall toxicity.[166,183] At the same time, proteolytic activity increases with age, possibly to aid digestion of larger prey eaten by older, larger snakes.[111,166,183] Coagulopathic effects can differ between juvenile and adult western diamondback rattlesnakes (*Crotalus atrox*), partly because of the greater amounts of thrombin-like enzymes in younger snakes.[183,208] In murine median lethal dose (LD_{50}) studies, the venom of some juvenile rattlesnakes has proved to be slightly more toxic than that of adults of the same species.[168,169] However, larger rattlesnakes are capable of delivering much greater amounts of venom in a bite. Juvenile prairie rattlesnakes (*Crotalus viridis,* formerly *C. viridis viridis*) have been shown in one small study to possess venom that is two to three times more toxic in mice than that of adults.[79] Large adult snakes, however, deliver an average of 17 times (range, ~10 times to >100 times) more venom than do juveniles.[85,87] The ability to control venom expenditure has been demonstrated in juvenile rattlesnakes. In a series of first exposures to different-sized prey, "naive" juvenile rattlesnakes injected similar quantities of venom into all size classes. However, in the second series of exposures, "experienced" snakes injected significantly more venom into larger prey.[113] The clinical relevance of this is uncertain.

Clinical studies showing that envenomations by large rattlesnakes are generally more severe than those by smaller snakes corroborate and complement these findings in the laboratory and the field.[125] Juvenile pit vipers can, however, deliver a very serious, even life-threatening envenomation.

Venom characteristics may vary with geographic origin of the snake.[89] For example, certain populations of the Mohave rattlesnake (less correctly spelled "Mojave"[165]) (*Crotalus scutulatus*) cause human neurotoxicity with severe envenomation while causing minimal local tissue destruction and no hemorrhagic effects.[61,126] Neurotoxic findings may include respiratory difficulty, generalized weakness, and cranial nerve palsies.[61] The venoms of these snakes possess a presynaptic neurotoxin, originally designated "Mojave toxin"[10] (this spelling persists), and are classified as venom A populations. Venom B populations lack Mojave toxin, and their bites result in consequences more typical of most rattlesnake envenomations: soft tissue swelling, necrosis, and coagulopathy. Venom A populations are found in California, western and southeastern Arizona, Nevada, Utah, New Mexico, and Texas. Venom B populations are found in south-central Arizona. A zone of intergradation between venom A and venom B populations occurs in Arizona, along a U-shaped area extending south from near Prescott, through Wickenburg, and west of Phoenix, then turning northeastward around Tucson and extending to the state boundary in Greenlee County.[104,258] Envenomations manifesting both venom A and venom B effects (i.e., neurotoxicity plus coagulopathy and swelling) occur in this intergradation zone and have also been observed in inland southern California.[41] Recent studies have disclosed further details of the variability of Mohave rattlesnake venom in southeastern Arizona, with venom dominated by metalloproteinase just north of Tucson, grading to the southeast into Mojave toxin plus myotoxin without metalloproteinase, and then Mojave toxin without myotoxin or metalloproteinase in the southeastern corner of the state.[170]

Venom from most populations of Mohave rattlesnakes (venom A) has consistently produced greater lethality than other North American snake venoms when compared in laboratory mouse studies.[87] As a result, Mohave rattlesnakes are often described in field guides and other lay references as one of the most dangerous or deadly North American snakes,[76,165,232] despite being responsible for only occasional fatalities among the dozens of people they bite in California and Arizona each year.[106,108]

Toxins with structures and physiologic effects similar to those of Mojave toxin have been isolated from venoms of other species of rattlesnakes, including southern Pacific rattlesnakes (*Crotalus oreganus helleri,* formerly *C. viridis helleri*), prairie rattlesnakes (*C. viridis,* formerly *C. viridis viridis*), midget faded rattlesnakes (*C. concolor,* formerly *C. viridis concolor*), tropical rattlesnakes (*Crotalus durissus*), timber rattlesnakes (*Crotalus horridus*), and tiger rattlesnakes (*Crotalus tigris*).[81,88,90,114,252] Geographic differences occur in the venoms of other snakes as well. Timber rattlesnakes (*C. horridus*; sometimes referred to as canebrake rattlesnakes) from Florida, Georgia, and South Carolina possess more "canebrake toxin," a neurotoxic and myotoxic component, than do specimens from Alabama, Mississippi, Tennessee, and North Carolina.[90] Differences in concentration of this toxin correlate with varying clinical effects seen after bites by this species from different geographic regions.[53]

Neurotoxicity has been clinically associated with severe myotoxicity in many cases.[37,53,65,126] Severe rhabdomyolysis and myoglobinuric renal failure have been reported after Mohave rattlesnake envenomation and are thought to be related to Mojave toxin.[126] The association between neurotoxicity and myotoxicity has been confirmed in laboratory animals.[11] *C. horridus* specimens possessing significant amounts of the neurotoxin (canebrake toxin) produce a rise in serum CK levels as a biochemical signature of significant envenomation. The increased CK level appears to parallel severity of envenomation by these snakes.[53] Autopsy findings have demonstrated that myonecrosis in this setting is systemic and not limited to the bite site. Concomitant rises in MB fractions of CK can occur in the absence of any clinical evidence of cardiac damage. In one such case, troponin-T level was normal despite abnormal total CK and CK-MB levels. Lesser CK elevations (usually <500 units/L) may be seen with other rattlesnake bites, such as that of the eastern diamondback (*C. adamanteus*). In these cases, the elevations appear to more closely parallel local effects.[53]

Mojave toxin is thought to inhibit acetylcholine release at the presynaptic terminal of the neuromuscular junction.[61] Some may consider myokymia, or muscle fasciculations, as a manifestation of neurotoxicity, although this phenomenon occurs through a different mechanism than does Mojave toxin–induced neurotoxicity. Myokymia is believed to be caused by interaction of certain venom components with calcium or calcium-binding sites on the nerve membrane.[61] Myokymia has been reported to occur after envenomation by certain species of rattlesnakes, most notably the southern Pacific rattlesnake, *C. oreganus helleri* (formerly *C. viridis helleri*).[20,248]

The variability of southern Pacific rattlesnake venom has clinical implications. Envenomations by specimens possessing Mojave toxin respond well to treatment with the current U.S. pit viper antivenom, Crotalidae Polyvalent Immune Fab (Ovine) (CroFab), likely because the antivenom was developed using *C. scutulatus* venom A, which contains Mojave toxin. In contrast, certain clinical manifestations, such as myokymia, are much less responsive to CroFab, possibly because of non-neutralized or partially neutralized components in southern Pacific rattlesnake venom. These envenomations often require more antivenom than do those by Mojave toxin–possessing specimens. Novel venom components,

such as hellerase or yet-to-be characterized small, basic, neurotoxic peptides, may explain this phenomenon.[219]

Many modern medicines are derived from reptile venoms. These are being investigated and used for treatment of heart disease, stroke, cancer, diabetes, hypertension, pain, and other conditions. Some of the most promising of these venom-derived pharmaceuticals come from the disintegrins.[44]

Coral Snakes

Coral snake venoms are less complex than are pit viper venoms and have received less research attention. *Micrurus* and *Micruroides* venoms have minimal proteolytic activity but contain the spreading enzyme hyaluronidase and some PLA_2.[218] The primary lethal component is a low-molecular-weight, postsynaptic neurotoxin that blocks acetylcholine binding sites at the neuromuscular junction.[55,241] In addition, the venom contains at least one myotoxic component that may clinically produce a rise in serum CK level.[100]

What coral snake venom lacks in complexity, it makes up in potency. Among U.S. snakes, *Micrurus* and *Micruroides* venom potency, as determined by LD_{50} values in mice, is surpassed only by that of the Mohave rattlesnake (*C. scutulatus*).[214] It is indeed fortunate that these reptiles are shy and inoffensive and possess a less effective venom delivery device than do pit vipers.

CLINICAL PRESENTATION

Pit Vipers

The clinical presentation of pit viper envenomation is variable and depends on the circumstances of the bite. Important factors include the species, size, and health of the snake; age and health of the victim; circumstances that led to the bite; number of bites and their anatomic locations; and quality of the care rendered to the victim, both in the field and at the hospital. Most bites occur to the extremities, but whether upper- or lower-extremity bites are more common is a point of conjecture.[197,200] Lower-extremity bites tend to be more frequently accidental than upper-extremity bites, which often occur after the victim intentionally interacts with the snake (e.g., tormenting the animal, trying to catch it, handling a captive specimen). Less often, bites occur to the head, neck, or trunk. Most bites occur around dawn or dusk and during warmer months, when snakes and people are more active outdoors.[197,200] A young, intoxicated male bitten on the hand while intentionally interacting with a snake is a common clinical scenario in the United States. The ultimate effects of bites by different species can range from temporary, localized pain and swelling to permanent disability or death, but the clinical course may be difficult to predict shortly after a bite.

About 75% to 80% of pit viper bites result in envenomation. Approximately one in every four to five bites is "dry," meaning no venom has been injected.[201,214] The precise mechanisms behind "dry bites" are unclear. The snake may elect to save its venom for its next meal rather than waste it on a large human. Alternatively, the feedback mechanism may "short-circuit" between the heat-sensing pit organs and the venom delivery apparatus, so that when faced with a huge, heat-radiating mass (a human), the system fails and no venom is expelled. Other possible causes of dry bites include glancing blows that fail to penetrate the skin and an exhausted venom supply. Approximately 35% of bites result in mild, 25% in moderate, and 10% to 15% in severe envenomations.[201]

The clinical findings found in crotaline envenomation can be divided into local and systemic signs and symptoms (Table 35-3). After most pit viper bites, severe burning pain at the site begins within minutes. Soft tissue swelling then progresses outward to a variable distance from the bite site. Over hours, a bitten extremity can swell all the way to the trunk. Bites to the face or neck may result in rapid, severe swelling that can compromise the airway.[210] Blood may persistently ooze from fang marks, marking the presence of anticoagulant substances in the venom. Ecchymosis is common, both locally and at more remote sites, as the vasculature becomes leaky and RBCs escape into soft tissues (Figure 35-27). Over hours to days, the patient may develop hemorrhagic or serum-filled vesicles and bullae at the bite site and more proximally, especially if there is a delay in obtaining care (Figure 35-28). Fang marks are usually evident as small puncture wounds, but the precise bite pattern can be misleading.[188] Most nonvenomous snakebites result in multiple rows of tiny puncture wounds (from the maxillary, palatine, pterygoid, and mandibular teeth) that usually cease bleeding quickly. Pit vipers also possess palatine, pterygoid, and mandibular teeth, which can result in more than the classic paired puncture marks from the maxillary fangs. Also, a snake may make contact with only a single fang. For this reason, associated signs and symptoms should carry more significance than the bite pattern in determining whether a bite was inflicted by a pit viper or another snake. Some rattlesnake bites result in minimal or no local pain or swelling despite serious envenomation. For example, serious bites by specimens of Mohave rattlesnakes (*C. scutulatus*) coming from regions where their venom contains substantial quantities of Mojave toxin (venom A) may result in few if any local findings (e.g., pain, swelling, ecchymosis). Such a presentation could result in early underestimation of the severity of envenomation by the treating physician.[260]

Systemic findings after pit viper bites are extremely variable; any organ system can be affected. Nausea with or without vomiting is common and may occur early in serious bites. The victim

TABLE 35-3 Signs and Symptoms Following Rattlesnake Bites

Sign or Symptom	Frequency*
Fang marks	100/100
Swelling and edema	74/100
Pain	65/100
Ecchymosis	51/100
Vesiculations	40/100
Change in pulse rate	60/100
Weakness	72/100
Sweating and/or chill	64/100
Numbness or tingling of tongue and mouth or scalp or feet	63/100
Faintness or dizziness	57/100
Nausea, vomiting, or both	48/100
Blood pressure changes	46/100
Change in body temperature	31/100
Swelling regional lymph nodes	40/100
Fasciculations	41/100
Increased blood-clotting time	39/100
Spherical red blood cells	18/100
Tingling or numbness of affected part	42/100
Necrosis	27/100
Respiratory rate changes	40/100
Decreased hemoglobin	37/100
Abnormal electrocardiogram	26/100
Cyanosis	16/100
Hematemesis, hematuria, or melena	15/100
Glycosuria	20/100
Proteinuria	16/100
Unconsciousness	12/100
Thirst	34/100
Increased salivation	20/100
Swollen eyelids	2/100
Retinal hemorrhage	2/100
Blurring of vision	12/100
Convulsions	1/100
Muscle contractions	6/100
Increased blood platelets	4/25
Decreased blood platelets	42/100

From Russell FE: *Snake venom poisoning*, New York, 1983, Scholium International, p 281, with permission.
*Number of times symptom or sign is reported as observed per total number of patients.

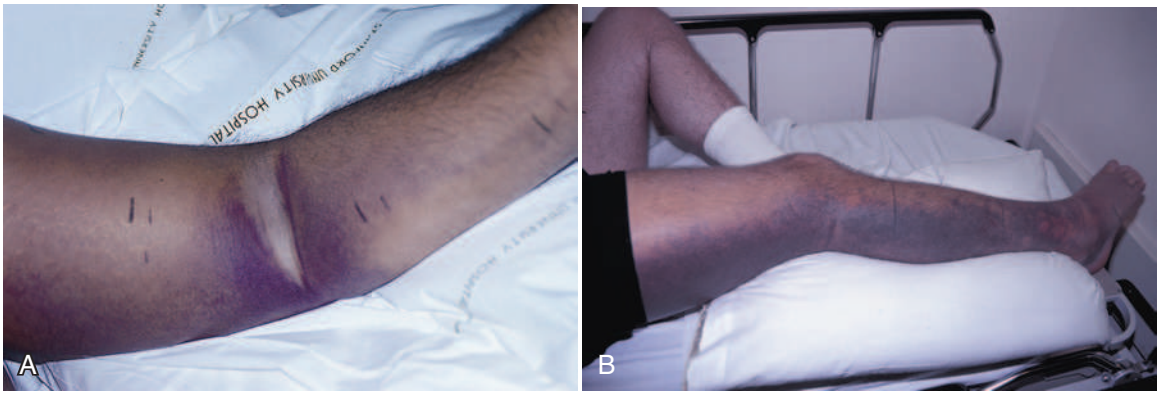

FIGURE 35-27 Rattlesnake envenomation can lead to varying degrees of ecchymosis over time. **A,** Mottled rock rattlesnake (*Crotalus lepidus lepidus*) bite in a young man at 24 hours. Note the exudation of red cells into the soft tissues remote from the bite site. The man was bitten on his left thumb. **B,** Northern Pacific rattlesnake (*Crotalus oreganus oreganus*) bite to the left pretibial region resulted in extensive ecchymosis of the right lower extremity and extended into his flank (seen here 1 week after the bite). *(Courtesy Robert L. Norris, Jr., MD.)*

may complain of an overall sense of weakness. An odd sense of taste, such as a rubbery, minty, or metallic taste, may be present.[214] The victim may complain of numbness of the mouth or tongue. Vital signs may be abnormal, with respiratory and heart rates increased. The victim may experience respiratory distress as a result of neurotoxic components of the venom, especially after bites by venom A–producing Mohave rattlesnakes (*C. scutulatus*). Another important cause of respiratory distress is pulmonary edema from pulmonary artery congestion and translocation of intravascular fluid into alveoli. This can be compounded by myocardial depressant factors in some venoms.[214] The victim's blood pressure may be elevated; however, hypotension, which may progress to frank shock, is more common in severe cases. In the first several hours, hypotension is usually caused by blood pooling in the pulmonary and splanchnic beds. Later, as swelling progresses and fluid exudes into soft tissues, intravascular volume can become significantly depleted. A rare cause of early shock is nonallergic (and possibly allergic) anaphylaxis to the venom itself (see Allergy to Reptile Venom, later).[27,42,71,193]

Musculoskeletal and neurologic abnormalities may be present. As mentioned previously, some rattlesnake venoms possess one or more components that can cause local or systemic myokymia as a sign of significant envenomation. These repetitive, fine muscle contractions may persist for many hours and are variably responsive to antivenom administration.[164,243] Myokymia involving the shoulders, chest wall, or torso has been associated with respiratory insufficiency and the need for endotracheal intubation.[243] Other findings of neurologic dysfunction can include paresthesias, numbness, and frank motor weakness, especially after bites by some Mohave rattlesnakes (*C. scutulatus*) and eastern diamondback rattlesnakes (*C. adamanteus*).

Although uncommon, hemorrhage can occur at multiple anatomic locations because of the complex procoagulant, anticoagulant, and metalloproteinase components of some venoms.[214] Bleeding can occur in the gingival membranes, renal system (microscopic or frank hematuria), gastrointestinal tract (occultly heme-positive stool, frank blood per rectum, or hematemesis), pulmonary tree (hemoptysis) or central nervous system (CNS).

Laboratory evaluation of a victim of pit viper bite may reveal significant abnormalities. The white blood cell (WBC) count may be elevated, reflecting neutrophilic leukocytosis. Hematocrit may be elevated from hemoconcentration or may be depressed secondary to bleeding or hemolysis. Platelet count can drop precipitously as a result of consumptive coagulopathy, sequestration at the bite site, or direct venom effects.[255] Serum chemistries may be abnormal. Blood glucose level may be elevated. Muscle damage can result in elevated serum potassium and CK levels. Renal dysfunction may result from hypotension, myoglobin and hemoglobin deposition, and direct venom effects.[58] Hepatic dysfunction with elevations of serum transaminases may be seen.[173] Coagulation studies may reveal significant abnormalities. Prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT) can be elevated. Fibrinogen levels may be depressed, along with elevation of fibrin degradation products and D-dimer levels.[14] In resource-constrained environments, a 20-minute whole-blood clotting test can be used to diagnose coagulopathy. A few milliliters of blood are drawn and placed in a clean, dry, new glass test tube and allowed to sit, undisturbed, for 20 minutes. After this time, the tube is tipped once to 45 degrees. If the blood is still liquid, coagulopathy is present.[244] Major abnormalities may be seen in serum coagulation studies in the absence of any clinically significant bleeding (i.e., no evidence of bleeding or nothing more serious than gingival oozing or microscopic hematuria).[28] This is particularly relevant for determining when to use blood products in treating these patients (see Hospital Care, later). Recurrent coagulopathic parameters (e.g., thrombocytopenia, hypofibrinogenemia) may persist or recur for as long as 2 weeks after envenomation, particularly after rattlesnake bites (see Indications for Antivenom, later).[12,61,63]

If the initial blood work is normal, laboratory studies (particularly complete blood count and coagulation tests) should be repeated hourly until it is clear that the patient is stable. Once antivenom, when indicated, has been given, laboratory values should continue to be followed, but any identified coagulation abnormalities may take a few hours to reverse fully once envenomation has been controlled. Coagulation derangements that continue to worsen despite antivenom administration indicate that further antivenom is needed.

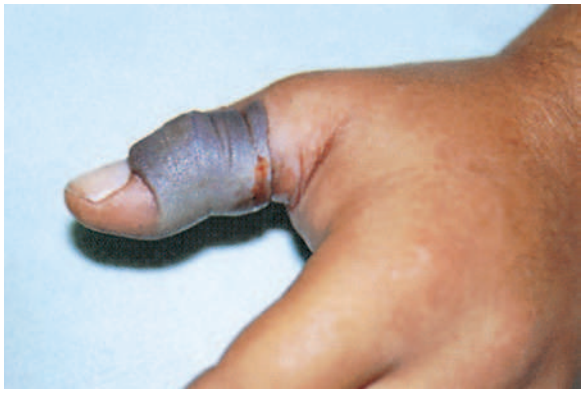

FIGURE 35-28 Hemorrhagic bleb at the site of a western diamondback rattlesnake (*Crotalus atrox*) bite at 24 hours. *(Courtesy Robert L. Norris, Jr., MD.)*