CENTRAL NERVOUS SYSTEM AND EYE INFECTIONS (KC BLOCH, SECTION EDITOR)

Rabies: Still a Uniformly Fatal Disease? Historical Occurrence, Epidemiological Trends, and Paradigm Shifts

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Abstract Rabies has the highest case fatality of any infectious disease. Pathobiological and clinical insights have questioned the assertion that death is inevitable after onset of acute encephalomyelitis. Relying upon national laboratory-based surveillance, we reviewed records of human rabies acquired in the United States during 1960–2009. Changes in the epidemiology of human rabies were notable, due to improved animal management, safer and more efficacious biologics, and revisions in prevention guidelines. Historically, domestic animals were the most important source of infection. Since the 1990s, more human cases were associated with rabid bats. Prior to 1980, postexposure prophylaxis failures were reported. After development of modern rabies immune globulin and vaccines, none occurred. Of 75 human cases identified, only four patients survived. Rabies remains an extremely high consequence zoonosis, but the disease is not uniformly fatal, per se. Rabies is essentially preventable when primary exposures are averted, or appropriate prophylaxis occurs before illness.

Keywords Rabies · Rabies survivors · Rabies prophylaxis · Virus · Encephalitis · Lyssavirus · Experimental therapy · Biomedical paradigm shifts · Public health · Infectious diseases

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Introduction

Rabies is one of the most feared infectious diseases. Annually, tens of thousands of people die from rabies worldwide. Most deaths occur within Asia and Africa, typically following a rabid dog bite. In the United States, aggressive campaigns to vaccinate dogs against rabies began after World War II. As a result, sustained rabies virus transmission in dogs was eliminated, and the last suspected dog bite-associated human rabies case in the U.S. occurred near the Mexican border in the early 1990s. Clearly, the epidemiology of rabies in the United States changed dramatically over the 20th century, as well as basic knowledge towards its prevention and potential treatment. The objective of this paper is to summarize reported human cases of rabies acquired in the United States from 1960 to 2009 [1–59]. Moreover, considering the extreme case fatality associated with this zoonosis, our primary purpose is to review the epidemiology, rabies postexposure prophylaxis (PEP) failures, clinical presentations, laboratory findings, and outcomes of human rabies cases acquired in the United States over the past 50 years, to provide an insight to the question if rabies should be considered a uniformly lethal disease.

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Methods

We identified human cases of rabies acquired in the United States in the *Morbidity and Mortality Weekly Report* from 1960 to 2009 and records at CDC. Additionally, we conducted literature searches for other cases over this period. Case reports were tabulated.

Exposure histories were characterized as domestic animal bites, non-domestic (wild) animal bites, domestic or wild animal contact without an identified bite, bat related exposures (including bat bites, bat contact without an identified bite, a bat in the house, or other close proximity to a bat), laboratory exposures, transplant exposures, or no identified exposure. Imported human rabies cases from exposures abroad or rabies virus variants found outside the United States were excluded.

The clinical course was separated into three categories: 1) encephalitic form characterized by loss of cognitive functions, usually with agitation; 2) paralytic form, characterized by focal or quadriparesis with initial normal cognitive function; and 3) atypical presentation, characterized by focal pain, cranial nerve palsies, and seizures [60].

All cases were confirmed through laboratory diagnostic testing (performed by CDC and/or a state laboratory) by one of the following: 1) detection of rabies virus antibodies in the serum of an individual with no history of rabies immunization or in CSF, regardless of immunization status; 2) detection of rabies virus antigens by immunofluorescence (FA) or histology/electron microscopy in a skin biopsy of the neck, corneal impressions, or brain tissue; 3) detection of rabies virus RNA by RT-PCR in saliva, skin biopsy, or brain tissues; and 4) rabies virus isolation from saliva, tears, skin biopsy, or brain tissues [60–65].

Results

Human Rabies Cases Acquired in the United States (1960–2009)

From 1960 to 2009, records were reviewed from 75 cases of human rabies (Table 1). These included cases with an identified bite from a rabid or potentially rabid animal (29 cases), cases secondary to laboratory exposures (2 cases), cases due to tissue transplantation (5 cases from 2 separate donors), cases of contact with a sick or wild animal without an identified exposure (6 cases), cases with bat contact but without an identified exposure (14 cases), cases with a history of a bat in the house without identified exposure (2 cases), cases with bats observed out of the home without identified exposure (4 cases), and cases with no known exposures (13 cases).

Cases from known domestic or wild carnivore bites occurred only in the first and second decades (1960–1979).

Patients developed rabies after bat bites in all five decades (1960–2009). Rabies following bat contact, but without a reported bite, occurred in recent decades (1990–2010). Cases without an identified exposure were found over the last four decades. Overall, 24/75 (32 %) were in the pediatric age group (≤ 18 years of age) and 12 of these 24 (50 %) were <10 years of age. The mean age was 29 years (range 2 to 82 years of age). A male gender-bias was apparent in all five decades, while children predominated in the first (1960–1969) decade.

Initial symptoms were listed for 65 of 75 patients (clinical descriptions were not obtained for 10 patients). Many of these 65 patients presented first to emergency care or primary care with non-specific complaints, including focal pain and/or paresthesias (34/65, 52 %), vomiting and headache (13/65, 20 %), sore throat or dysphagia (10/65, 15 %), malaise (5/65, 8 %), and confusion and/or agitation (3/65, 5 %). Most of these 65 patients were discharged home, including 15 who were diagnosed with upper respiratory infections, given antibiotics, and discharged. All 65 patients were hospitalized ultimately, usually within 7 days of their presentation.

Documented Bites Preceding Rabies and Failures of Prophylaxis

Documented bites from carnivores and development of rabies (13 cases) occurred from 1960 to 1979. Animals included dogs (5 cases), a cat (1 case), skunks (4 cases), foxes (2 cases), and a bobcat (1 case). Documented bat bites resulting in rabies (16 cases) occurred over all five decades. Of these 29 subjects who developed rabies following bites, 14 (48 %) did not receive rabies PEP, 12 (41 %) received partial rabies PEP, and 3 (10 %) received the recommended PEP. The partial rabies PEP included duck embryo vaccine (DEV) without rabies immune globulin (RIG). The last patient to develop rabies after PEP was in 1979. Since 1979, DEV was replaced by more effective tissue culture vaccines, and no documented rabies PEP failures have been reported in the United States.

Initial Suspicion and Laboratory Findings

For 63 patients, some description was obtained of clinical course after hospitalization. On admission, temperature was reported in 42 patients and 37 (88 %) were febrile. The initial serum white blood cell count (WBC) was reported for 23 patients and mean WBC was 13,880/mm² (range 7,700–20,000/mm²) with 78 % polys (range 65–91 %). The initial CSF findings were reported for 45 patients, and for 39 (87 %) the CSF was abnormal. The WBC was elevated (> 5/mm²) for 34/45 patients with a mean of 98 (range 6–1,000/mm²) and 19 % polys (range 0–67 %). The

Table 1 Human cases of rabies acquired in the United States, 1960–2009

	Year	Age/Sex	State	Exposure Source	Variant Source	Incubation Period	CSF	Initial Symptoms	Comments/References
Bite exposures									
1	1960	9/M	GA	Dog	NR	56 days	NR	NR	Subject was severely bitten on face and back. Patient received anti-rabies serum but vaccinations were discontinued after 7 doses of DEV because dog remained normal during 2 weeks of observation. It is likely that the wrong dog was identified [1].
2	1961	53/F	KY	Fox	NR	52 days	NR	NR	Subject was bitten on leg by fox that was attacking her dog. Subject received 14 doses of DEV but no HRIG [2].
3	1961	76/M	CA	Dog	NR	31 days	NR	NR	Subject was bitten by a dog on the wrist. Subject received 14 doses of DEV but no HRIG [3].
4	1961	74/M	KY	Fox	NR	35 days	NR	Left arm paresthesias	Subject was bitten on left thumb by fox that was attacking her chickens. Initially refused medical care. Began DEV two weeks later (received 14 injections). Never received RIG [4].
5	1962	11/M	ID	Bat	NR	41 days	WBC 6/mm³ (4 polys), protein 72 mg/dL	Fever, sore throat.	Subject was bitten on the face, likely by bat, while sleeping outside. His mother identified five puncture marks. No initial medical care [6].
6	1964	10/M	MN	Skunk	NR	19 days	WBC 130/mm³ (6 polys), glucose 24 mg/dL	Wrist pain, fever	Subject was bitten by a skunk while sleeping outdoors. Received 14 doses of DEV but no HRIG [8].
7	1965	60/M	WV	Dog	NR	6–23 months	NR	Hand pain	Bitten on hand by rabid dog. Received 14 DEV doses but no H RIG and 23 months later developed symptoms. Also exposed to a possibly rabid fox 6 months before developing symptoms [9].
8	1966	10/M	SD	Skunk	NR	24 days	NR	Arm paresthesias	Subject was bitten on his arms, legs, abdomen and neck after a skunk crawled into his sleeping bag. Patient received 21 DEV doses and HRIG. Immunization failure [10].
9	1968	14/M	KS	Dog	NR	Unknown	NR	Vomiting, malaise	Subject delivered newspapers and was frequently bitten by stray dogs. Sought no medical care [11].
10	1969	2/M	CA	Bobcat	NR	17 days	NR	Sore throat, fever	Subject was attacked by rabid bobcat in his backyard. Received 14 DEV doses but no HRIG. During an outburst of "rage" subject bit his mother. Child survived 133 days in hospital and brain biopsy was rabies positive ante mortem but negative post mortem [12].
11	1970	11/M	AZ	Skunk	NR	21 days	WBC 61/mm³ (2 polys)	Left hand paresthesias	A rabid skunk got into child's sleeping bag and bit the child on the left hand. He received 14 DEV doses but no HRIG [13].
12	1970	4/M	SD	Skunk	NR	32 days	WBC 149/mm³ (89 polys), protein 75 mg/dL	Sore throat, fever	A rabid skunk attached to child's arm while playing in back yard. Mother hit the skunk with metal pipe. Child received 14 DEV and HRIG. Immunization failure though received fewer vaccine doses than recommended [13].
13	1970	6/M	OH	Bat	NR	20 days	WBC 125/mm³ (50 polys), protein 178 mg/dL	Neck pain	Subject was bitten on thumb by a rabid big brown bat while asleep in his room. Father had to pull bat off his son's thumb. Received 14 doses of DEV without HRIG. Child survived [14].
14	1971	64/M	NJ	Bat	NR	59 days	NR	Malaise	

Table 1 (continued)

	Year	Age/Sex	State	Exposure Source	Variant Source	Incubation Period	CSF	Initial Symptoms	Comments/References
15	1973	26/M	KY	Bat	NR	22 days	Normal	Facial paresthesias	Subject was bitten by a bat on the lip while sitting on his porch. Received 14 doses of DEV without HRIG [15].
16	1975	60/M	MN	Cat	Skunk[a]	53 days	WBC 9/mm³ (0polys), protein 70 mg/dL	Fever, malaise myalgias	Subject was bitten on finger by a stray cat. The cat escaped. Then 21 days later received 14 doses DEV and no RIG [18].
17	1976	55/F	MD	Bat	Bat[a]	25 days	NR	Left hand paresthesias weakness	While outside, subject was bitten on the left finger by a rabid bat. Received 21 doses DEV and HRIG. Immunization failure [19].
18	1979	7/F	TX	Dog	Mexican dog[a]	Unknown	WBC 45/mm³ (15 polys)	Fever, headache, vomiting stiff neck	Subject, who lived close to the Mexican border, was bitten on the leg by a rabid dog. Received 20 doses of DEV and HRIG starting 5 days after exposure. Immunization failure though initiation of prophylaxis was delayed by 5 days [23].
19	1983	5/F	MI	Bat	NR	5 months	WBC 10/mm³	Arm pain, fever	When rabies was suspected, the child's parents reported a probable bat bite. Sought no medical care [28].
20	1990	22/M	TX	Bat	Mexican free-tailed bat	47 days	WBC 1/mm³, protein 51 mg/dL	Right hand weakness	The subject was bitten by a bat on his right index finger while at a tavern. Sought no medical care [30].
21	1991	29/M	AR	Bat	Silver-haired bat	45 days	NR	Sore throat	While the subject was sleeping in an abandoned house a bat landed in his mouth and also he suffered a bat bite of the thumb. Sought no medical care [31].
22	1994	41/M	WV	Bat	Silver-haired bat	94 days	NR	Vomiting, agitation, tremors	The subject shot a bat from his porch and examined the dead bat's mouth [36].
23	2000	47/M	MN	Bat	Silver-haired bat	60 days	WBC increased	Arm pain and paresthesias	Subject awoke with bat on his hand. He was bitten on the hand in the process of killing the bat. Sought no medical care [44].
24	2003	66/M	CA	Bat	Silver-haired bat	5 weeks	NR	Malaise, headache, right arm pain, paresthesias, and weakness	Subject was bitten by a bat on the right index finger while in bed. The bat flew away and was unavailable for testing. Patient washed the wound but did not seek medical care [49].
25	2004	20/M	AR	Bat	Bat	Unknown	NR	Vomiting, difficulty swallowing	The subject was an organ donor to cases #33, #34, #35, and #36. Death was thought secondary to a subarachnoid hemorrhage. After the rabies diagnoses were made it was learned that the subject had been bitten by a bat [50].
26	2004	15/F	WI	Bat	Bat	1 month	WBC 23/mm³ (2 polys), protein 50 mg/dL	Hand paresthesias fatigue	Subject picked up a bat at church then released it outside and was bitten on the finger in the process. Sought no medical care. Survived rabies after drug induced coma and IV ribavirin [51].
27	2006	10/F	IN	Bat	Bat	3 months	WBC 25/mm³,	Right arm pain, paresthesias	Subject was bitten by a bat in her bedroom. Sought no medical care [53].
28	2007	46/M	MN	Bat	NR	1 month	WBC 12/mm³ (2 polys), protein 107 mg/dL	Hand paresthesias	Subject handled a bat and reported a "prick". Sought no medical care [55].
29	2008	55/M	MO	Bat	Bat	6 weeks	WBC 1/mm³		Subject was bitten on the ear by a bat. Sought no medical care [17].

Table 1 (continued)

	Year	Age/Sex	State	Exposure Source	Variant Source	Incubation Period	CSF	Initial Symptoms	Comments/References
								Paresthesias of face and arm	Subject was bitten on the left ear by a bat that flew into the home. Sought no medical care [55].
Laboratory Aerosol Exposures									
30	1972	56/M	TX	Lab aerosol	NR	12 days	WBC 131/mm² (69 polys)	Vomiting, headache	Subject exposed to a rabies aerosol in a laboratory via a leaking blender. He received pre-exposure prophylaxis with an experimental vaccine in 1958. Sought no medical care [16].
31	1977	32/M	NY	Lab aerosol	NR	14 days	NR	Malaise, headache	Subject was exposed to rabies virus aerosol in a laboratory via leaking equipment. He received pre-exposure rabies prophylaxis in 1968 and last rabies booster 6 months before this incident. Survived with severe neurologic sequela [20].
Transplants									
32	1978	37/F	ID	Corneal transplant	Bat^a	30 days	WBC 14/mm² (1 poly), protein 53 mg/dL	Headache, paresthesias	Subject received corneal transplant from patient # 63 [21].
33	2004	53/M	TX	Organ transplant	Bat	20–30 days	WBC 26/mm³	NR	Subject received liver transplant from patient # 24 [50].
34	2004	50/F	TX	Organ transplant	Bat	20–30 days	NR	NR	Subject received kidney transplant from patient # 24 [50].
35	2004	55/F	TX	Artery transplant	Bat	20–30 days	NR	NR	Subject received iliac artery transplant from patient # 24 [50].
36	2004	18/M	TX	Organ transplant	Bat	20–30 days	NR	NR	Subject received kidney transplant from patient # 24 [50].
Contact with sick or wild animals without identified bite									
37	1962	3/M	TX	Dog	NR	Unknown	NR	NR	The subject played with a puppy that died several weeks before the child developed rabies. Sought no medical care [5].
38	1963	52/F	AL	Known dog contact	NR	Unknown	NR	NR	The family's dog died of possible rabies 25 days before the subject become ill. No known bite. Sought no medical care [7].
39	1979	45/M	KY	Unknown	Bat^a	Unknown	WBC 23/mm³ (1 poly), protein 146 mg/dL	Vomiting, dizziness	A hunter killed an ill appearing ground hog about 6 months before he developed symptoms. Sought no medical care [25].
40	1993	82/M	TX	Unknown	Silver-haired bat	Unknown	Normal	Confusion	The subject was exposed to a cow that died of unknown disease. Sought no medical care [32].
41	1994	14/M	TX	Unknown	Texas coyote	Unknown	NR	Sore throat, dyspnea	The subject had a puppy that died of diarrhea. Sought no medical care [34].
42	1994	44/M	CA	Unknown	Silver-haired bat	Unknown	WBC 5/mm³ (0 polys), protein 98 mg/dL	Arm pain	The subject cared for a sick stray kitten. Sought no medical care [35].
Bat contact without an identified bite									
43	1995	27/M	CA	Known bat contact	Mexican free-tailed bat	Unknown	WBC 0/mm³, protein 68 mg/dL	Vomiting, headache	The subject emigrated from Mexico 6 months before illness. He may have brushed a bat off his chest while at home. Sought no medical care [39].
44	1995	74/M	CA	Known bat contact	Mexican free-tailed bat	Unknown	WBC 1000/mm³, protein 174 mg/dL	Arm paresthesias and weakness	The subject lived on a ranch where he would catch bats. No known bites. Sought no medical care [39].

Table 1 (continued)

	Year	Age/Sex	State	Exposure Source	Variant Source	Incubation Period	CSF	Initial Symptoms	Comments/References
45	1997	65/M	MT	Unknown	Silver-haired bat	Unknown	WBC 10/mm³ (5 polys), protein 67 mg/dL	Visual hallucinations	The subject was exposed to animals as a hunter and trapper and he had forced a bat out of his house with a broom. Sought no medical care [41].
46	1997	71 M	TX	Known bat contact	Silver-haired bat	60 days	WBC 7/mm³, protein 67 mg/dL	Facial pain, malaise	While sleeping in a motel, the subject awoke with a bat on his shoulder but was not aware of a bite. Sought no medical care [42].
47	1997	32/M	NJ	Known bat contact	Silver-haired bat	90 days	WBC 1/mm³, protein 51 mg/dL	Shoulder pain.	Using a cloth, the subject captured bat with his hands but he was not aware of a bite or scratch. Sought no medical care [42].
48	2000	49/M	CA	Known bat contact	Mexican free-tailed bat	Unknown	Normal	Arm pain and paresthesias	The subject removed a bat from his house. There was no known bite. Sought no medical care [44].
49	2000	26/M	GA	Unknown	Mexican free-tailed bat	Unknown	Normal	Vomiting, hematemesis	Bats had landed on the subject during his sleep. He did not report a bite. More than 200 Mexican free-tailed bats were living in his attic. Sought no medical care [44].
50	2000	69/M	WI	Known bat contact	Silver-haired bat	Unknown	Normal	Left arm paresthesias, chest discomfort	The subject was hospitalized for a cardiac evaluation. He had removed bat from his house with his bare hands. Sought no medical care [44].
51	2002	13/M	TN	Known bat contact	Bat	60 days	WBC 220/mm³ (88polys), protein 96 mg/dL	Neck pain, headache	The subject had handled a bat but did not report a bite. Sought no medical care [45].
52	2002	28/M	CA	Known bat contact	Bat	8 days	Normal	Vomiting, headache	The subject killed a bat in his house but was not aware of a bite or scratch. Sought no medical care [46].
53	2005	10/M	MS	Known bat contact	Unknown	5 months	WBC 226/mm³, protein 79 mg/dL	Headache, fever, paresthesias	The subject removed a bat from her bedroom. Sought no medical care [52].
54	2006	16/M	TX	Known bat contact	Bat	4–6 weeks	NR	NR	The subject was awakened by direct contact with a bat though no bite was reported. Sought no medical care [52].
55	2009	17/F	TX	Known bat contact	Unknown	1–2 months	WBC 185/mm3, protein 160 mg/dL	Vomiting, headache, paresthesias, fever	The subject visited a bat cave and reported no contact with bats including no bites or scratches. The patient recovered without intensive care [58].
56	2009	55/M	MI	Known bat contact	Silver-haired bat	Unknown	Elevated WBC	Arm paresthesias	The subject claimed to family members that a bat had landed on him during the night. Sought no medical care [59].
A bat in the house without identified contact									
57	1995	4/F	WA	Unknown	Myotis bat	16 days	NR	Neck pain, arm paresthesias, drowsiness	A bat found in child's bedroom and killed by her father. The child denied contact with the bat. The exhumed bat was positive for rabies [37].
58	1995	13/F	CT	Unknown	Silver-haired bat	Unknown	WBC 100/mm³ (48 polys), protein 104 mg/dL	Arm paresthesias, tremors, fatigue	A bat was in the house downstairs while patient was sleeping upstairs. The child had no known contact with the bat. Sought no medical care [38].
Bats in the environment without identified contact									
59	1994	24/F	AL	Unknown	Mexican free-tailed bat	Unknown	NR	Arm paresthesias, fatigue	The subject had no identified contact but she had bats nesting in her fireplace. Sought no medical care [34].
60	1997	64/M	WA	Unknown	Big brown bat	Unknown	WBC 0/mm³, protein 93 mg/dL	Left arm paresthesias and weakness	The subject was hospitalized to rule-out myocardial infarction. He had lived in a heavily wooded rural

Table 1 (continued)

	Year	Age/Sex	State	Exposure Source	Variant Source	Incubation Period	CSF	Initial Symptoms	Comments/References
61	1998	29/M	VA	Unknown	Silver-haired bat	Unknown	WBC 57/mm³, protein 172 mg/dL	Back pain, malaise	area where bats were common though no known exposures were reported [41]. The subject developed rabies while in prison. No known contact but bats were attracted to lights in prison yard [43].
62	2009	43/M	IN	Unknown	Tricolored bat	Unknown	WBC 38/mm³ (0 polys), protein 140 mg/dL	Fever, chest pain, paresthesias	The subject reported to his neighbors that he saw a bat after removing a tarpaulin from a tractor [57].
No known exposures									
63	1978	39/M	OR	Unknown	Bat[a]	Unknown	WBC 8/mm³ (1 poly), protein 63 mg/dL	Back pain	The subject died of presumed Guillain-Barré syndrome. He was later diagnosed with rabies because the person who received his cornea developed rabies. The subject's eye that had been frozen grew rabies. He was a trapper and skinned coyotes [21].
64	1978	50/M	WV	Unknown	NR	Unknown	WBC 70/mm³ (26 polys), protein 104 mg/dL	Shoulder pain	The subject had no known bites. The only identified risk was that he was a hunter [22].
65	1979	24/M	OK	Unknown	Bat[a]	Unknown	WBC 35/mm³ (0 polys), protein 176 mg/dL	Vomiting, headache, fever	The subject worked outdoors as a wood cutter and he had no known exposures [24].
66	1981	27/M	OK	Unknown	Skunk[a]	Unknown	WBC 6/mm³ (0 polys), protein 85 mg/dL	Sore throat, ear pain	The subject had no known exposure. He did have history of camping [27].
67	1984	12/M	PA	Unknown	Bat[a]	Unknown	WBC 149/mm³	Sore throat	The subject had no known exposures [29].
68	1991	55/F	TX	Unknown	Mexican dog	Unknown	NR	Difficulty swallowing, panic disorder	The subject had no known exposures. She was hospitalized for panic disorder which evolved into hydrophobia. An initial neck biopsy was negative for rabies but a later biopsy was positive. Her rabies strain circulated in Mexican dogs [31].
69	1991	27/F	GA	Unknown	Silver-haired bat	Unknown	NR	Sore throat, headache, fever	The subject had no known exposures [31].
70	1993	11/F	NY	Unknown	Bat	Unknown	WBC 23/mm³ (0 polys)	Hand pain	The subject had no known exposures [33].
71	1994	42/F	TN	Unknown	Silver-haired bat	Unknown	NR	Arm paresthesias back pain, vomiting	The subject was initially thought to have zoster then aseptic meningitis. She had no known rabies exposure but kept 18 dogs, 5 cats, and 3 horses at her home [34].
72	1996	42/F	KY	Unknown	Silver-haired bat	Unknown	WBC 5/mm³	Sore throat, shoulder pain	The subject had no identified exposure [40].
73	1996	49/M	MT	Unknown	Silver-haired bat	Unknown	WBC 121/mm³ (1 poly)	Sore throat, headache, fever	Bats seen at the subject's place of work but he had no history of bat contact [40].
74	2002	20/M	IA	Unknown	Silver-haired bat	Unknown	NR	Vomiting, headache, abdominal pain	The subject had no known rabies exposure [47].
75	2003	25/m	VA	Unknown	Raccoon	Unknown	WBC 24/mm³, protein 81 mg/dL	Malaise, fever	The subject had no known rabies exposure but frequently camped outside [48].

CSF cerebrospinal fluid, white blood cell count and abnormal glucose and/or protein results given; DEV duck embryo vaccine; HRIG human rabies immunoglobulin; NR not reported; WBC white blood cells; [a] rabies variant determined from archived pathological tissue

CSF protein was elevated (> for 40 mg/dL) for 27/32 subjects, with a mean of 99 (range 50–178 mg/dL). One patient had a low CSF glucose (24 mg/dL) but simultaneous serum glucose was not reported.

Initial diagnosis at the time of hospitalization included encephalitis of unknown etiology, meningitis, stroke, weakness, transverse myelitis, Guillain-Barré syndrome, subarachnoid hemorrhage, myocardial infarction, vomiting/dehydration, abdominal obstruction, glossitis/pharyngitis, and tetanus. Over the course of hospitalization, patients evolved clinically (63 patients) into what fit best as encephalitic rabies (46 patients), paralytic rabies (9 cases), or atypical rabies (8 cases). Rabies was not suspected during the hospitalization for 17 of these patients. Hence, encephalitic/paralytic/atypical rabies was not considered until postmortem.

Seven of 46 patients with encephalitic rabies were combative and required sedation or restraints. In addition, a 2-year-old boy (patient #10) "in a sudden outburst of rage" bit his mother. His mother received rabies PEP and remained well. This was the only official report of any of the 75 subjects with rabies biting another human. Most of the 46 subjects with encephalitic rabies were described as disoriented, agitated, and/or lethargic.

Clinical manifestations of nine patients fit best into the category of paralytic rabies. They were initially thought to have strokes, transverse myelitis, myelitis, or Guillain-Barré syndrome.

Eight patients had so-called atypical clinical manifestations of rabies. These included focal neuropathies, cranial nerve palsies, and an initially clear sensorium that evolved into seizures.

Rabies Diagnostic Confirmation

Rabies was confirmed by documenting rabies virus antigens or isolates in corneal impressions, saliva, neck skin biopsy, or brain biopsy. Multiple tests were usually conducted for each of the 75 patients. The diagnosis was attempted antemortem in 43 patients, with supportive results in 37 (86 %) (Table 2). The sensitivity of antemortem testing by decade was: 2/3 in 1960–1969; 7/8 in 1970–1979; 2/2 in 1980–1989; 11/14 in 1990–1999; and 15/16 in 2000–2009. Detection using corneal impressions occurred in 7/12 (58 %) samples; virus isolation and/or PCR from saliva in 19/30 (63 %); nuchal skin biopsies in 14/27 (52 %); and brain biopsies in 2/4 (50 %). Four patients survived and in each case rabies was confirmed by antibody testing only.

Postmortem evaluation of brain tissue included detection of antigens or amplicons in 36/38 (95 %); microscopic neuronal intracytoplasmic inclusions or virions detected by electron microscopy 23/28 (82 %); and isolation in 13/15 (87 %). In addition, positive postmortem findings occurred in 2/3 saliva samples, 1/2 corneal impressions, and 2/4 nuchal skin biopsies.

Rabies Virus Variants

Monoclonal antibody typing or molecular sequencing was used for determining the rabies virus variant for 51/75 (68 %) patients. Forty-five were associated with bats, two with skunks, two with dogs, one with a raccoon, and one with a coyote rabies virus variant. Two were likely laboratory strains (subjects #30 and #31), and 22 were not determined because testing was not available or no viral isolate was recovered for testing. Bat viruses were the majority (45/51, 88 %) of the identified variants. Clinically, bat contacts were involved with 35/75 (47 %) patients. Of these 35, 29 had viral characterization and all were bat rabies virus variants. In addition, 5 patients with transplant-related rabies were bat-associated.

Bat bites preceding rabies (16 patients) occurred at least once in all five decades of study. Bat contact without a known bite preceded rabies (14 patients) in only the last two decades.

Thirteen patients had undefined exposures. These occurred in the last four decades. The rabies virus variant was identified in 12 of these 13 patients and included bat rabies viruses in nine, and one each with skunk, dog and a raccoon variant.

Survivors

Case 1 (Patient #13). A 6-year-old boy was bitten by a bat on his left thumb in October, 1970. The bat remained attached until the father removed it. The bat was diagnosed rabid. The child was given 14 doses of DEV, but no RIG. Two days after completing DEV, the patient developed neck pain, fever, vomiting and was hospitalized. Rabies was initially not suspected until the child developed a left-sided weakness followed by unresponsiveness. Rabies virus antibodies were detected in the serum and CSF. Serum neutralization titers peaked at 1:63,000 whereas most people demonstrated titers of 1:32 (and rarely above 1:600) after DEV immunization. This antibody response was considered indicative of clinical rabies and not a post-vaccine effect. No inclusions (Negri bodies) were found in a brain biopsy and no rabies virus was isolated from viral culture of brain tissue. The child was intubated and comatose for 10 days, was extubated and gradually returned to normalcy over the next 3 months.

Case 2 (Patient #31). In March, 1977, a 32-year-old laboratory technician was exposed to a rabies virus aerosol. Two weeks later, he developed malaise, headaches, fever, lethargy, and was hospitalized. During the next 3 days, he became

Table 2 Antemortem diagnostic test results for 43 patients with human rabies acquired in the United States, 1960–2009

Case	Detection of Antigen			Saliva Virus Isolation	Saliva RNA Detection	Detection of Antibody			
	Cutaneous Nerve	Cornea	Brain			Serum (IFA)	Serum (RFFIT)	CSF (IFA)	CSF (RFFIT)
6	–[a]	–	–	Negative	–	–	–	–	–
9	–	–	–	–	–	Positive	Positive	–	–
10	–	Negative	Positive	Negative	–	Positive	Positive	Positive	–
11	–	Negative	–	Negative	–	–	–	–	–
13	–	–	Negative	Negative	–	–	Positive	Positive	–
15	–	Positive	–	Positive	–	–	–	–	–
17	Positive	Positive	–	–	–	–	Positive	–	–
18	–	Inconclusive	–	–	–	–	Positive	–	Negative
19	Negative	–	–	Negative	–	–	Positive	–	Positive
20	Negative	–	–	Negative	–	Negative[b]		Negative[b]	
22	Positive	–	Positive	Negative	Positive	–	Positive	–	–
23	Positive	–	–	–	Positive	–	–	–	–
24	–	–	–	–	Positive	Negative	Positive	Negative	Negative
26	Negative	–	–	Negative	Negative	Positive	Positive	–	Positive
27	Positive	–	–	–	Positive	Positive	Positive	Positive	Positive
28	Negative	–	–	–	Negative	Positive	Positive	Positive	Positive
29	Positive	–	–	–	Positive	Negative	Positive	Negative	Negative
31	Negative	Negative	–	–	–	–	Positive	Positive	–
39	Negative	Positive	–	Negative	–	Negative[b]		Negative[b]	
40	–	–	–	–	–	–	Negative	–	–
41	Positive	–	–	Positive	Positive	Negative[b]		Negative[b]	
43	Negative	Inconclusive	–	–	–	Positive	–	Negative	Negative
46	–	–	–	–	–	–	Negative	–	–
47	Positive	–	–	–	Positive	–	Negative	–	Negative
48	Positive	Positive	–	–	Positive	–	–	–	–
50	–	–	–	–	–	–	Negative	–	–
51	Negative	–	–	–	Positive	Positive	–	Positive	–
52	Negative	Positive	–	–	Positive	Positive	Positive	–	–
53	–	–	–	–	–	Positive	Positive	Positive	Positive
54	Positive	–	–	–	Positive	Negative	–	Negative	–
55	Negative	–	–	–	Negative	Positive	Positive	Positive	Positive
56	Negative	–	–	–	Negative	Positive	Positive	Positive	Positive
57	Positive	–	–	Positive	Positive	–	–	–	–
58	–	Positive	–	Negative	Positive	–	Positive	–	–
61	Positive	–	–	–	Positive	Positive	Positive	Positive	Positive
62	Negative	–	–	–	Positive	Positive	Positive	Negative	Negative
65	–	–	–	–	–	–	Positive	–	Negative
67	Positive	–	–	–	Positive	–	Negative	–	Negative
68	Positive	–	–	Positive	Positive	Negative[b]		Negative[b]	
71	–	Positive	–	–	–	–	–	–	–
72	–	–	–	–	–	–	Positive	–	–
73	Negative	–	–	–	Positive	–	Positive	–	–
74	Positive	–	Inconclusive	–	–	Positive	Positive	Negative	Negative

[a] Sample not collected, testing not performed, or results not reported, [b] Testing modality not reported

IFA Indirect Fluorescent Antibody; *RFFIT* Rapid Fluorescent Focus Inhibition Test

comatose and was intubated. He had received pre-exposure rabies vaccination during 1968, followed by yearly boosters. His last rabies vaccine booster was November, 1976. Two weeks after this booster his rabies virus serum neutralization titer was 1:32. Upon illness, rabies virus antibodies were detected in his serum (1:64,000) and CSF (1:16,225), supportive of an acute rabies virus infection. No rabies virus antigens were detected in corneal impressions or a nuchal skin biopsy. The patient survived, but with severe neurologic sequelae.

Case 3 (Patient #26). In September, 2004 a 15-year-old girl was bitten on the left index finger while handling a bat. The wound was washed, but no medical care was sought. One month later, she developed fatigue and left hand paresthesia. Over the next 3 days, she experienced vomiting, 6th cranial nerve palsies, fever, lethargy, and was hospitalized. Rabies virus antibodies were found in her CSF, increasing from 1:32 to 1:2,048. No rabies virus antigens were detected in a nuchal skin biopsy. Specific treatment included induction of coma, ketamine, midazolam, ribavirin, and amantadine (later termed the 'Milwaukee protocol'). No rabies vaccine or immunoglobulin was administered. After 4 weeks of induced coma, her medications were tapered and after intensive rehabilitative therapy over the next year she made a complete recovery.

Case 4 (Patient #55). In February, 2009, a 17-year-old female presented to the emergency department with a 2 week history of headache, fever, vomiting, and paresthesias. A lumbar puncture revealed lymphocytic meningitis (WBC of 163/mm^3, 97 % lymphocytes). She was hospitalized, 3 days later felt better, no isolates were obtained from routine cultures, and she was discharged. A week later she returned with headache, vomiting and left-sided weakness. A repeat lumbar puncture showed lymphocytic meningitis (WBC of 185/mm^3, 95 % lymphocytes) and her CSF pressure was increased. She reported a history of contact with flying bats after entering a cave in Texas 2 months before illness onset but had never received rabies prophylaxis. Rabies virus antibodies were found in her serum (1:8,192) and CSF (1:32), indicative of an acute rabies virus infection. Neither viral antigens nor amplicons were detected in submitted samples. One dose of rabies vaccine and 1,500 IU of HRIG were administered following detection of rabies virus antibodies but additional doses were held due to concerns for possible adverse events from immune stimulation. She was treated supportively without intensive care and was discharged a week later. She returned the next week with worsening headache. A third lumbar puncture was performed, which relieved the headache. After this last visit she was lost to follow-up.

Case 5 (Reference #100). In May 2011, an 8-year-old girl in California presented to a local emergency department with a

1-week history of progressive sore throat, difficulty swallowing, and weakness. After developing flaccid paralysis and encephalitis, diagnostic laboratory testing detected of rabies virus–specific antibodies in serum and CSF. Despite extensive testing, no likely alternative diagnosis was identified. The patient recovered after receiving advanced supportive care, including treatment with therapeutic coma. The patient had no history of rabies vaccination and received no rabies biologics during the course of her treatment. Scratches from at least two free-roaming, unvaccinated cats at the patient's school were identified as a possible source of infection.

Discussion

"Rabies" comes from a Latin term, meaning rage or fury, and is one of the oldest recorded infectious diseases. Rabies virus is a highly neurotropic RNA virus in the family *Rhabdoviridae* and genus *Lyssavirus*, and the only lyssavirus detected in the New World [60, 64]. To date, more than a dozen putative lyssavirus species/genotypes have been recorded. All lyssaviruses result in an acute, progressive encephalitis, and most have been documented as human pathogens. After a bite or mucous membrane exposure, virions infect peripheral nerves, uncoat, and travel via retrograde axoplasmic transport to the spinal cord and brain at a rate of 50 to 100 mm/day [64]. After replication in the central nervous system, viral spread occurs throughout the body, including the salivary glands, cornea, the skin of the neck, and other innervated areas. Incubation period is usually 4 to 6 weeks, but periods of longer than a year have been reported. Incubation periods of 2 weeks or less have been observed in patients with severe bites to the head and face [66, 67].

Death is an expected, but not uniform, outcome, occurring on average 2 weeks after onset of symptoms [68]. Manifestations of the acute neurological phase are grouped into three forms: encephalitic ("furious rabies"), paralytic ("dumb rabies") or atypical rabies. A severe encephalitic form matches the stereotypical image of the "mad" dog and is uncommon in humans [69]. Humans with encephalitic rabies may show agitation, altered mental state, hydrophobia, dysphagia, hyper salivation, and signs of autonomic dysfunction. In the paralytic form patients exhibit muscle weakness that rapidly deteriorates into flaccid paralysis. Early signs and symptoms for both presentations are nonspecific, including fever, malaise, focal or generalized weakness, difficulty swallowing, headache, and pain or paresthesias in the area of the wound [60, 69].

Dogs are the most important global reservoirs from a public health perspective. Important wild carnivores include foxes, skunks, raccoons, mongooses and jackals. Infected

Chiroptera have been documented on all inhabited continents, including insectivorous, frugivorous, and vampire bats (Latin America) [70].

Rabies Epidemiology

During 1950–1959, 99 cases of human rabies were acquired in the United States. Most were the result of a bite from a rabid domestic animal. In the 1950s and 1960s intense public health efforts to vaccinate dogs made canine rabies uncommon, and cases in humans plummeted [71, 72]. Over the last five decades, rabies cases in humans evolved from an infection acquired via exposure to rabid domestic or wild carnivores (usually in children) to an infection acquired from bats (children and adults, in equal proportion).

Bats were first reported rabid in the United States during the 1950s [73]. The importance of bat rabies was better appreciated after the development of monoclonal antibody typing techniques that allowed identification of the likely reservoir source of infection. Domestic or wild carnivores rarely are found infected with bat rabies viruses [73]. The last human rabies cases involving documented bites from a domestic animal occurred in 1975–1979, identified as rabies virus variants associated with skunks and dogs. Of 19 cases involving bat exposures without a documented bite (1990–2009), 17 were bat-associated variants, and 2 did not have a rabies virus variant identified.

Rabies Diagnosis

Human rabies is a rare disease in the United States. Not surprisingly, rabies is often not considered during early course of illness. Furthermore, initial signs are often non-specific, including focal pain and/or paresthesias, headache, vomiting, sore throat and/or dysphagia. Even after hospitalization, rabies may not be considered. For two patients (one who died of presumed Guillain-Barré syndrome, and the other of presumed subarachnoid hemorrhage) rabies was only considered when recipients of their tissues developed rabies. Presumably, other cases of human rabies have occurred in the United States and were not identified.

Specific laboratory diagnosis requires demonstration of rabies virus antigens, isolates, detection of rabies virus nucleic acids, or the presence of rabies virus antibodies in the serum of unvaccinated individuals, or CSF, irrespective of vaccination status. Postmortem examination of the brain reaches 100 % sensitivity. During the last 50 years, antemortem detection of rabies virus was attempted in less than half of patients reported with rabies. Saliva samples were useful in 13/16 (81 %), corneal impressions in 9/13 (69 %), and nuchal skin biopsies in 14/25 (56 %) (Fig. 1). Over this period, methods for detecting rabies virus infection have improved. Tissue culture for the isolation of virus has
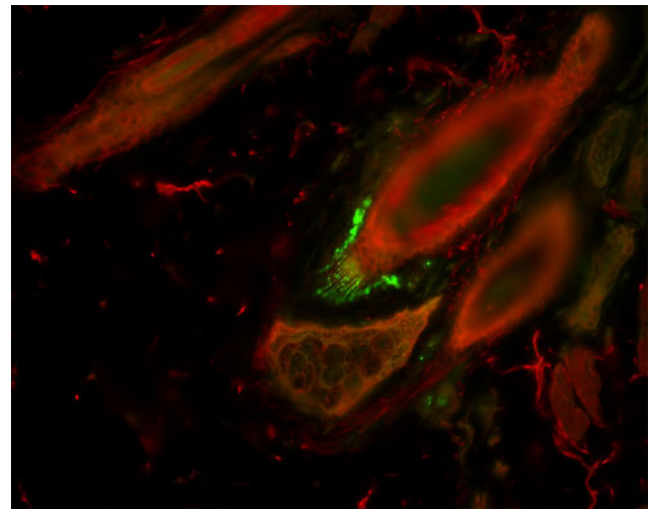

Fig. 1 Microscopic image of a cryostat section of a human skin biopsy showing fluorescent rabies virus inclusions in a hair follicle (photograph courtesy of Michael Niezgoda)

replaced laboratory animals, RT-PCR with sequencing augments antigen testing, and electron microscopy can identify virions during pathogen detection. Testing of antemortem nuchal biopsies was ≥98 % sensitive, and three successive saliva specimens were 100 % sensitive in one study using a heminested RT-PCR assay [74].

Bat-Associated Rabies (1990–2010)

Over the last two decades (1990–2010), 45 human cases of rabies were acquired in the United States. Of these, 42 (89 %) were rabies virus variants associated with bats. Ten were due to bat bites, 14 had bat contact, 6 had bats in their homes or neighborhoods, 4 followed transplants from a donor with a bat bite, and 6 had no documented exposures. In addition, patient #32 had contact with a sick cow and patient #35 had contact with a sick kitten.

In 1995, a 4-year-old child in Washington and a 13-year-old child from Connecticut died of rabies [37, 38]. The 4-year-old had a bat in her room and the 13-year-old had a bat downstairs while she slept upstairs. Neither had identified bat contact. Before 1995, rabies PEP was recommended for a bat exposure only when a bite or non-bite exposure had occurred. Following these cases, CDC updated recommendations to include consideration of PEP "in situations in which a bat is physically present and the persons(s) cannot exclude the possibility of a bite" unless prompt testing of the bat has ruled out rabies. Thus, a bat in the house with a child or a sleeping family member could result in PEP. Unfortunately, a bat in the house is a common scenario. In 2009, De Serres et al. reviewed the risks of house bat exposures without identified contact and concluded that more than

one million people would need PEP at a cost of over a billion dollars to prevent a case of rabies [73]. Current Advisory Committee on Immunization Practices (ACIP) guidelines for human rabies prevention state: "situations that might qualify as exposures include finding a bat in the same room as a person who might be unaware that a bite or direct contact has occurred" [61]. Thus, simply finding a bat in the house does not require PEP, but a bat found in the same room as a person should be investigated thoroughly.

Rabies Postexposure Prophylaxis

Rabies is preventable with proper administration of modern rabies PEP, combining active and passive immunization [61, 62, 75–77]. Two rabies vaccines are commercially available in the United States: the human diploid cell culture vaccine (HDCV) and the purified chick embryo vaccine (PCEV). These vaccines are highly effective and safe, rarely causing serious adverse events [61, 62]. The older vaccine DEV was used during the 1960–70s, a period when at least 27 people developed rabies. Eleven of these received vaccinations with DEV alone, but no RIG, while five patients received vaccination with DEV plus RIG. Since introduction of modern cell culture rabies vaccines and RIG during the 1980s, no failures of rabies PEP have been reported in the United States. Rabies PEP is composed of one dose of RIG and four or five doses of HDCV or PCEC vaccine. A 4-dose vaccine regimen is recommended by the ACIP [76•].

Indications for PEP have changed little over the last five decades in the United States. Rabies PEP is recommended for bite exposures from suspect rabid animals or non-bite exposures involving contamination of an open wound, scratch, or mucous membrane with saliva or nervous tissue from a potentially rabid animal [61]. Evaluation is indicated for direct bat contact, since a person may not recognize the risk and lesions could be minimal [78]. Changes in recommendations for rabies PEP in the last two decades include: 1) rabies PEP may not be needed for a provoked bite by a well-appearing stray dog in some areas of the United States which are free of rabies in carnivores, 2) rabies PEP should be considered if a bat is found in the room of a sleeping person or a person who cannot report contact [76•].

Historically, rabies vaccines derived from nerve tissue (NTV) caused severe swelling and was administered subcutaneously in the abdomen. These NTV were associated with rare but serious neuroparalytic reactions and were less potent than modern cell culture vaccines. While NTV have been discontinued gradually over the past 50 years they are still used in some developing countries [61, 63, 65]. Patient # 10, who failed PEP with DEV plus RIG, bit his mother. His mother was given PEP with DEV and NTV plus RIG and survived. Likely, the NTV was selected because her son failed PEP with DEV.

Unfortunately, after even the remotest of rabies virus exposures (e.g. washing saliva from any pet) some medical providers may advocate rabies PEP. A clear understanding of rabies virus pathogenesis, current PEP guidelines, and basic rabies epidemiology can be used to reassure patients and avoid unnecessary PEP.

Survivors of Rabies

Historically, rabies was recognized as a fatal infection in humans. Without medical intervention, exposed persons develop severe encephalopathy, paresis, and death, usually within 7–14 days. With intensive care, the longest fatal case (patient #10) survived 133 days prior to succumbing to infection. Besides patients in the United States, several other patients have survived rabies [79]. Of these survivors, most received some form of rabies vaccination before developing symptoms. Two patients survived rabies and did not receive any PEP prior to onset of symptoms (patients #25 and #53). The first reported survivor without rabies vaccination was treated with induction of coma and anti-viral drugs, while her immune response developed [80]. Initially, she had motor abnormalities which resolved over a year through physical rehabilitation [81]. Unfortunately, attempts to apply this protocol to scores of other rabid patients have failed (http://www.chw.org/display/PPF/DocID/33223/router.asp). Patient #53 survived without intensive care or antiviral agents and is the first reported case of presumptive abortive human rabies.

Conclusions

Rabies remains a high consequence zoonosis, requiring a thorough medical evaluation after animal bite, predicated in part by the species, circumstances, severity, and epizootiology in question. Human cases of rabies are rare in developed countries, such as the United States, despite the presence of enzootic rabies perpetuation among wildlife [82•]. Application of modern prevention and control strategies can limit the extreme mortality associated with this encephalitis [83•]. For example, from 1960 to 1984, human rabies cases acquired in the United States secondary to exposures to carnivores, such as dogs, decreased, while cases associated with wildlife, such as bats, increased, from 1985 to the present time. Moreover, bites by stray dogs prior to the 1970s required the consideration of rabies PEP, while today the United States is free of canine rabies virus transmission, and bites from dogs unavailable for risk assessment (in areas that free of rabies in carnivores) may not require PEP. In contrast, bat exposures need thorough investigation to determine the need for rabies PEP, especially if the bat is not available for diagnostic testing. Rabies PEP in the naïve

patient should always entail immediate wound care, RIG infiltration, and administration of rabies vaccine. Following such established guidelines in the United States since 1980, no PEP failures have occurred, despite thousands of human exposures to rabid animals annually. The lapse of medical education about rabies and the ease of global travel present a challenge for developed and developing countries alike [84•, 85, 86]. Despite case reports of a few survivors, rabies is still considered incurable, with no proven treatment [87•, 88•]. However, although controversial, this disease should be viewed as a continuum and basic research and applied clinical insights into viral pathogenesis, animal model development, and experimental therapy may provide the primary evidence necessary for new anti-viral drugs and improved intensive care and management of the rabid patient [89–99, 100•]. Prevention of exposures and proper PEP are key elements to avoid or prevent rabies infection.

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