

Rabies



The Face of Fear

Stephen J Scholand, MD

Rabies Free World

29 June 2017

Bernard

- 8 yo Filipino boy
- Agitation x 1 day
- Fever x 2 days
- Bitten on foot
 - 7 weeks PTA
- Dog died 2 weeks later, no lab analysis
- MD consult - amoxicillin only, no other treatment



- Observe
 - Hyperventilation, ataxic resps
 - Agitation - alternates with calm
 - Hypersalivation - gagging

Bernard

- **Hydrophobia**
 - Painful muscle spasms with drinking
 - Also triggered by sight of water, (liquids), sound or even mention of water



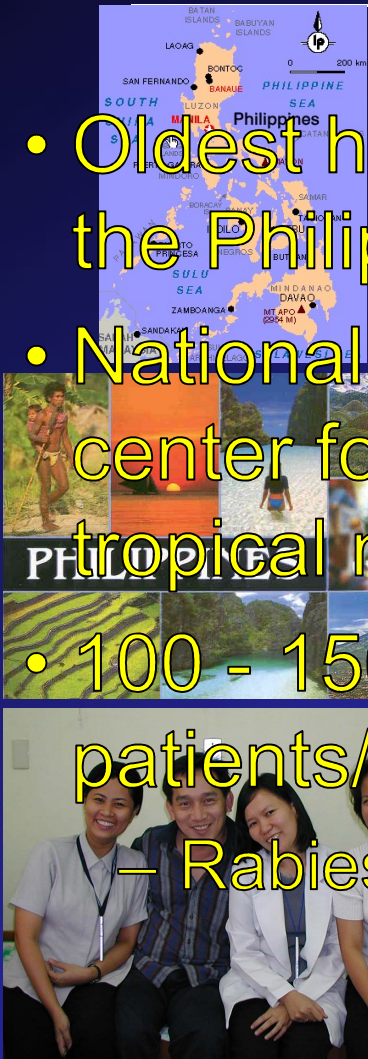
Bernard

- Aerophobia
 - Fan test: Wind is a noxious stimulus



San Lazaro Hospital

- Oldest hospital in the Philippines
- National referral center for ID and tropical medicine
- 100 - 150 rabies patients/yr
– Rabies 'ward'



Organization of Themes

- Introduction to Rabies
 - Rabies is a Neglected Tropical Disease
- Human exposures and disease
 - Large burden of suffering
- Rabies Education and Prevention Efforts
- Conclusions - Rabies Free World?

Rabies

OPD-OUTPATIENT DEPT.

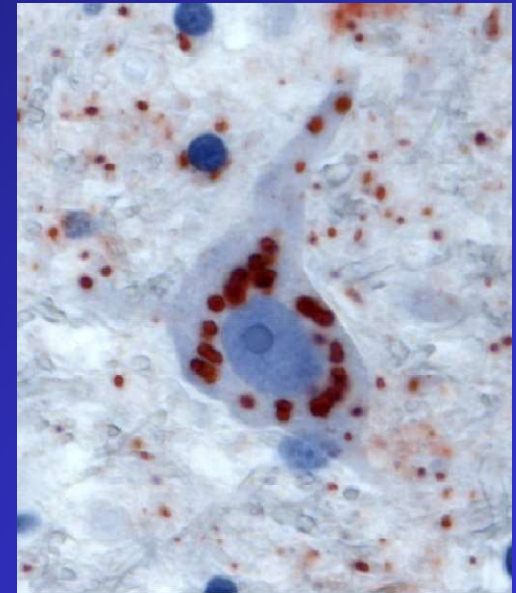
- 11th cause of Infectious Disease death
- 60,000+ deaths/yr¹
- Tens of millions of exposures^{2,3}

- SLH: Large volume about 400 to 500 patients/day
- Nationwide: In 2010 266,200 animal bites reported

WHO. *World Health Organ Tech Rep Ser.* 2013;(982):1-139. 2. Rabies fact sheet. WHO web site. March 2017. <http://www.who.int/mediacentre/factsheets/fs099/en/#>. Accessed May 19, 2017. 3. CDC. *Health Information for International Travel 2016*. New York, NY: Oxford University Press; 2016. <http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/rabies>. Accessed May 19, 2017.

Rabies: Definition

- Rabies is an acute, progressive encephalomyelitis^{1,2}
- 100% fatality rate
 - the highest of any infectious disease^{1,3}
- One of the oldest described diseases³

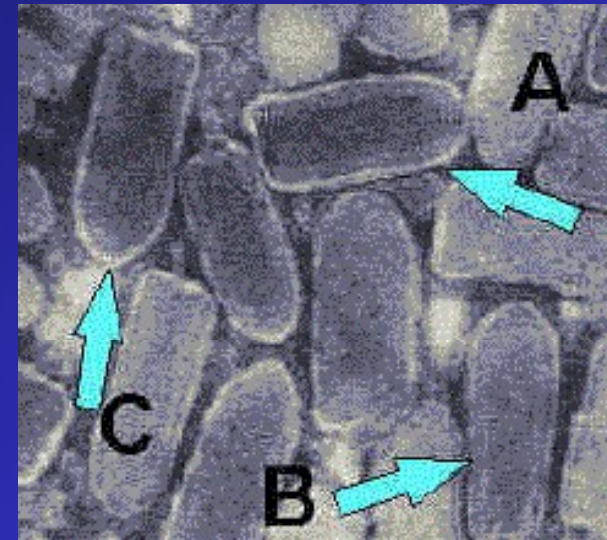


Microscopic
Immunohistochemical
Detection of Rabies Virus
Antigens in the Brain

1. Rupprecht CE, et al. *Curr Opin Virol.* 2011;1(6):662-670. 2. Manning SE, et al. *MMWR Recomm Rep.* 2008;57(RR-3):1-28. 3. Feder HM, et al. *Curr Infect Dis Rep.* 2012;14(4):408-422. 4. Rupprecht CE, et al. *Lancet Infect Dis.* 2002;2(6):327-343. 5. Hampson K, et al. *PLoS Negl Trop Dis.* 2015;9(4):e0003709. 6. Rabies' victims. Global Alliance for Rabies Control website. <https://rabiesalliance.org/rabies/rabies-and-children/>. Accessed May 9, 2016.

Rabies: Definition

- The leading viral zoonosis in terms of global public health significance¹
- 40% of cases in children²
 - Age less than 15



Electron Micrograph
of Rabies Virions

www.cdc.gov/ncidod/dvrd/rabies

Rabies: Global Burden

- Most cases occur in developing countries^{1,2}
- Outside the US, the dog is the most important animal reservoir^{2,3}
- Wildlife are important reservoirs, especially in developed countries, i.e. Europe and North America^{1,2,4}

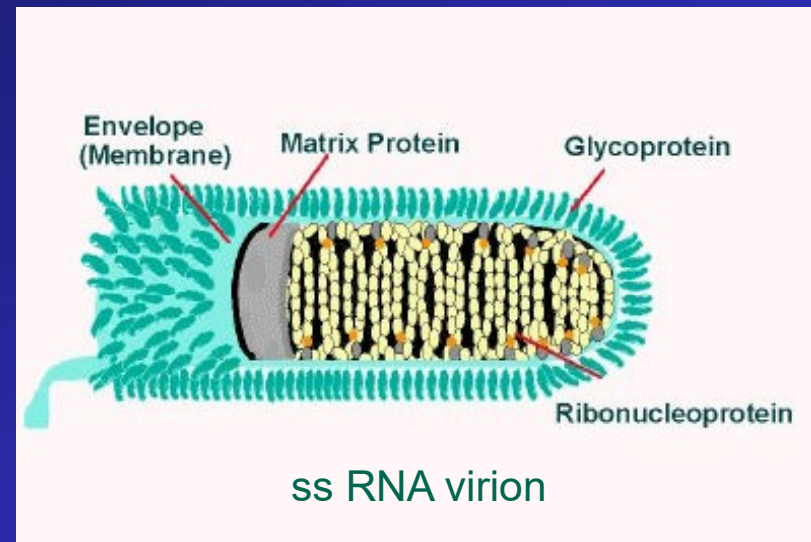


Big Brown Bat - *Eptesicus fuscus*

1. WHO. *World Health Organ Tech Rep Ser.* 2013;(982):1-139. 2. Rabies fact sheet. WHO web site. September 2015. <http://www.who.int/mediacentre/factsheets/fs099/en/#>. Accessed March 2, 2016. 3. CDC. *Health Information for International Travel 2016.* New York, NY: Oxford University Press; 2016. <http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/rabies>. Accessed March 2, 2016. 4. Monroe BP, et al. *J Am Vet Med Assoc.* 2016;248(7):777-788.

Rabies virus family- Rhabdoviridae

- Genus Lyssavirus
 - Rabies virus
 - European bat lyssavirus types 1 & 2
 - Australian bat lyssavirus
 - Duvenhage virus
 - Aravan virus
 - Khujand virus
 - Irkut virus
 - Bokeloh bat lyssavirus
 - Lagos bat virus*
 - Mokola virus*
 - Shimoni bat virus*

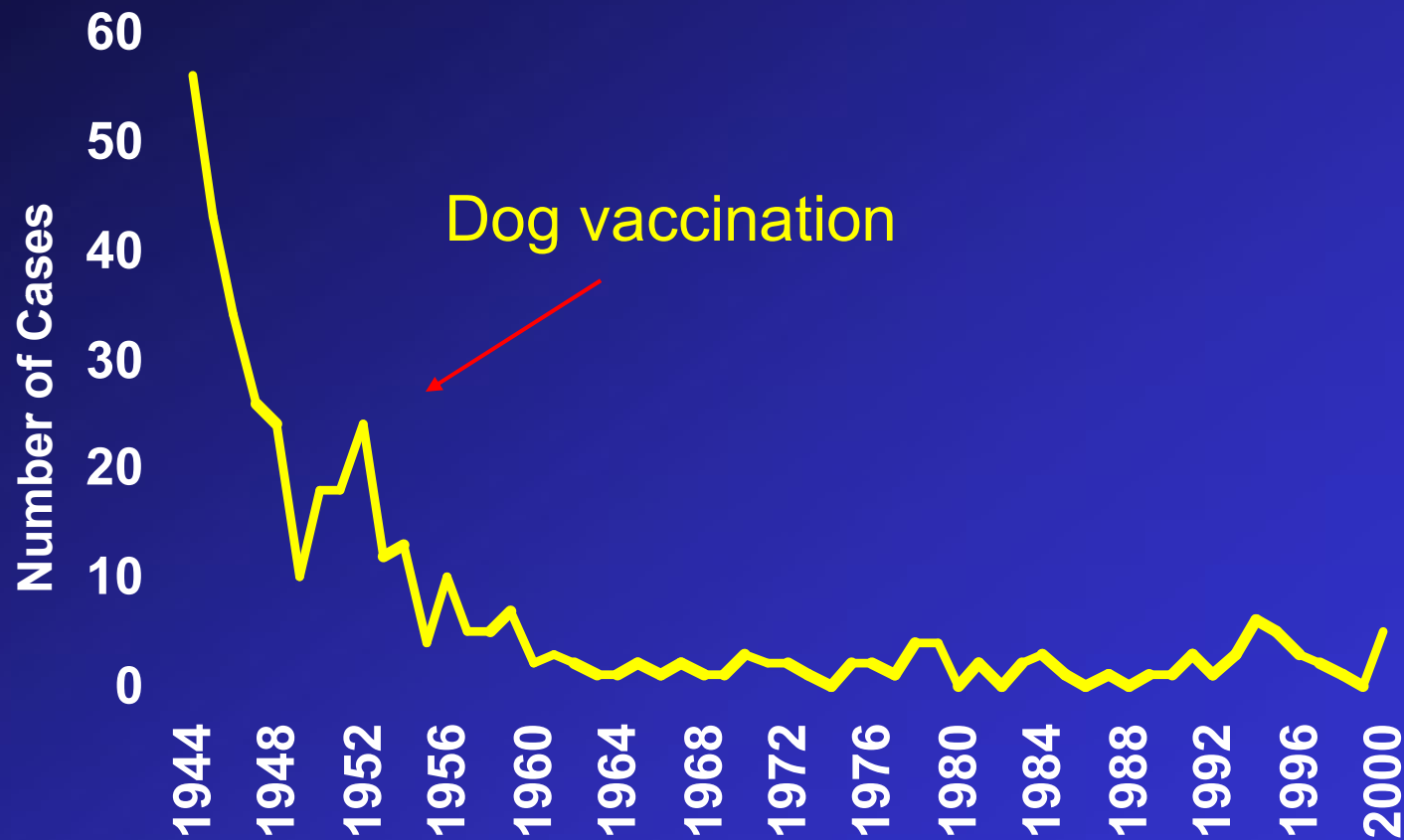


www.cdc.gov/ncidod/dvrd/rabies

- West Caucasian bat virus
- Ikoma virus
- Lleida bat lyssavirus

*Phylogroup II - International Committee on Taxonomy of Viruses (ICTV)

Human rabies cases, USA



CDC Summary of notifiable diseases 1993. *MMWR*. 1994;42(53):67-72, 80 CDC. Summary of notifiable diseases 1998. *MMWR*. 1999;47(53):79, 84 CDC. National Center for Infectious Diseases, Rabies, Epidemiology.

Animal Bites

- Dogs are “self-sufficient”



- 1 in 100 bites is from a rabies-infected animal
- Animal can be shedding virus prior to clinical illness
- Children are often the victims



Courtesy Dr. Elizabeth Miranda

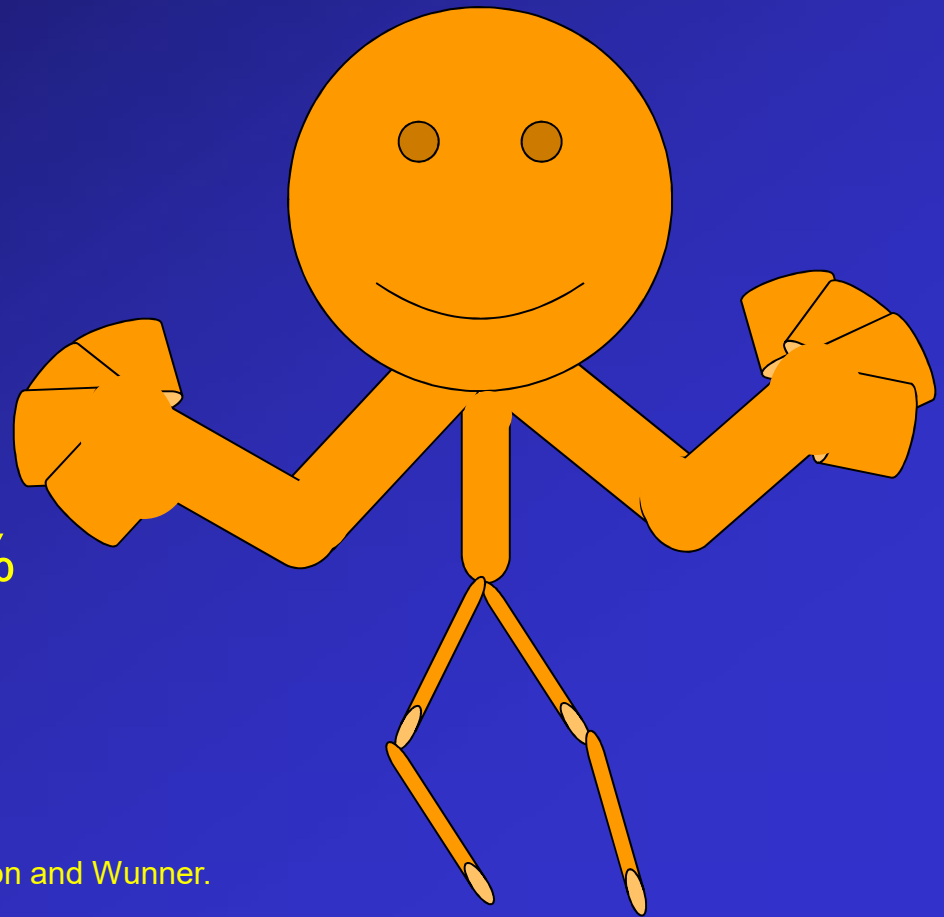
Clinical screening for rabies

- Time and date of bite
- Location: endemic area?
- Location on the body
 - delivery of virus
- Attack provoked or unprovoked?
- Condition of animal
 - acting sick or now dead?



“Rabies Homunculus”

- Other Rabies risks:
 - Bite severity
 - Biting animal
 - Virus variant
- Risk in unvaccinated
 - Head 50 to 80%
 - Finger/Hand 15 to 40%
 - Legs 3 to 10%



Incubation and Prodrome

- Incubation period varies
 - Usually 3 weeks to 3 months
 - Range depends on inoculum, site, other factors
 - 4 days to 19 years (most < 1 yr)
 - Prophylaxis “window”
- Prodrome - when virus enters CNS
 - Nonspecific: fatigue, malaise, anorexia, HA, F/C, ST, N/V/abd pain
 - 50% have pain/paresthesia

Hemachuda et al (1994) “Human rabies: Clinical aspects, Pathogenesis, and Potential therapy,” in *Lyssaviruses*, eds Rupprecht et al, p 121 - 44.

Bleck and Rupprecht (2000) “Rabies virus,” in *Principles & Practice of Infectious Diseases*, eds Mandel et al, p 1009-16

Neurological manifestations

- 2 forms: furious and paralytic
- Furious rabies:
 - Hydrophobia
 - Aerophobia
 - Agitation alternating with calm
 - Fever, hyperventilation
 - Autonomic instability:
 - HTN, hyperthermia, tachycardia, hypersalivation, piloerection, pupillary changes
 - Bizarre behavior

Neurologic manifestations

- Paralytic rabies
 - Hyperactivity, agitation is usually absent
 - Varied forms of paralysis
 - The bitten extremity
 - Diffuse and symmetric paralysis
 - Ascending paralysis like Guillain-Barre Syndrome
 - Progression from confusion to coma to death

No effective treatment

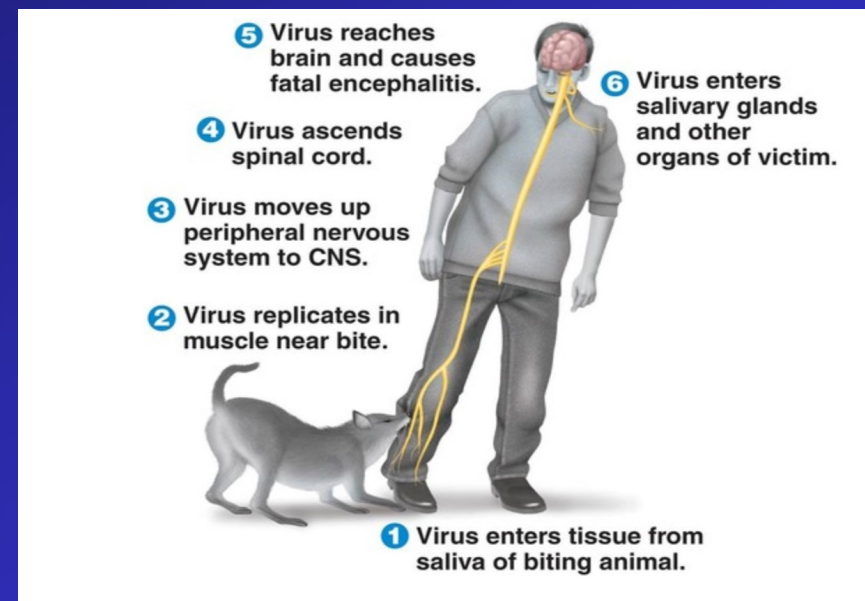
Great grandfather of rabies, Dr. Louis Pasteur

Photo: Gaspard-Félix Tournachon

Rabies Pathogenesis

Virus remains cloaked from the Immune System

- Neurotropic virus
 - Exposure incident
- Virus/Host interaction
 - 3 weeks – 3 months
 - BUT wide range in incubation times
 - ****time for intervention****
- Virus moves to spinal cord, brain



Rabies Post-Exposure

Wound care

10 day dog/cat/ferret
observation if possible

Never Vaccinated

- Rabies Immune globulin infiltrate wound 20iu/kg
- *And* vaccinate with HDCV days 0, 3, 7, 14, 28*
 - * give 5th dose of vaccine if immunosuppressed

Previously vaccinated

- Two booster shots days 0 and 3
- no RIG

Rabies Prevention – Multifaceted Approach

- Education and Awareness
 - Individual level
 - Dog/cat/animal vaccines
 - Exposures
 - Community level
 - World Rabies Day
28 September
- Medical
 - Prophylactic:
Wound Management
 - RIG availability
 - RIG + vaccine
 - Proper follow-up
- Global/Philanthropic
 - Zero deaths 2030

Protecting kids, protecting families



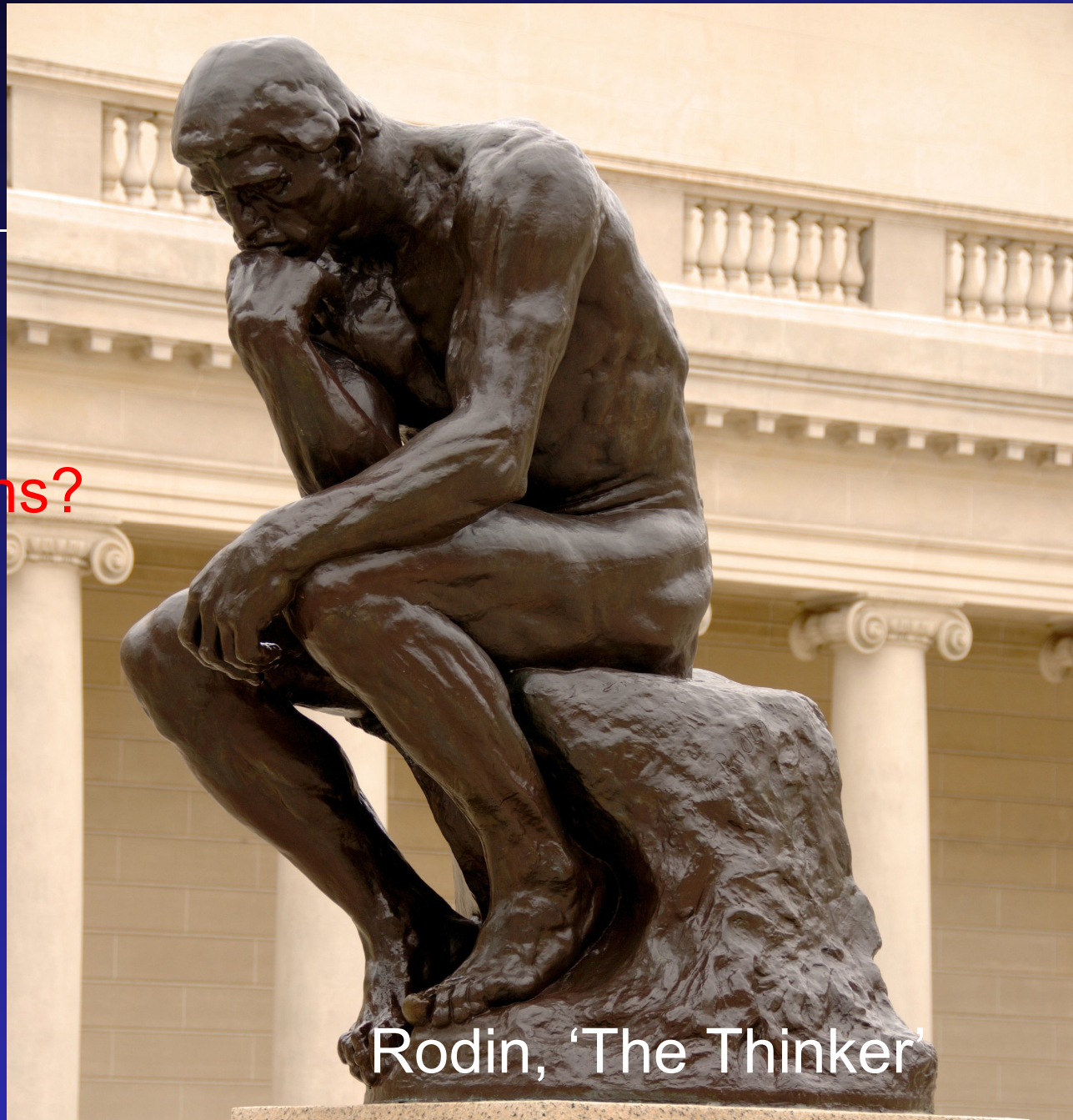
Conclusions

- No one should have to die from rabies!
- Important to prevent:
 - *Starts* with education and investment
 - *Requires* momentum
 - *Ends** with global vaccination



Rabies in the 21st Century

Questions?



Rodin, 'The Thinker'

Back-up slides

Pathogenesis

- Highly neurotropic
- Following inoculation with saliva
- Virus attaches to muscle cell membrane
 - replication -- initial inoculum is important
 - bare particles cross MNJ to nerve cells
 - travel up peripheral nerves at 12-24 mm/d
 - Retrograde axoplasmic flow -- proximity to CNS
 - Ganglia -- more replication
 - Asymptomatic until reaches ganglia...

Pathogenesis

- Once virus reaches the CNS, it travels much faster up the spinal cord
 - 200 - 400 mm/d
- Replication
- Encephalitis develops
- Dissemination along peripheral nerves, especially to the salivary glands
- Virus has remained hidden until too late!

Clinical course of human rabies - Jeanna Giese

- Day 1 - fatigue, L hand paresthesias
- Day 3 - diplopia, 'unsteady'
- Day 4 - N/V, blurred vision, L leg weakness
 - Ataxia, CN 6 palsy
 - Normal MRI, brain angiogram
- Day 5 - Fever 38.8, slurred speech, nystagmus, L arm tremors
- Day 6 - transferred to MCW
 - Fever 38.2, semiobtunded - answers questions, scanning speech, bilateral CN 6, dysarthria, myoclonus, L arm tremor, ataxia
 - Normal MRI, angiogram
 - Hypersalivation -- intubation
- Day 7 - confirmed rabies virus specific antibody in CSF and serum

RABIES SUSPECTED

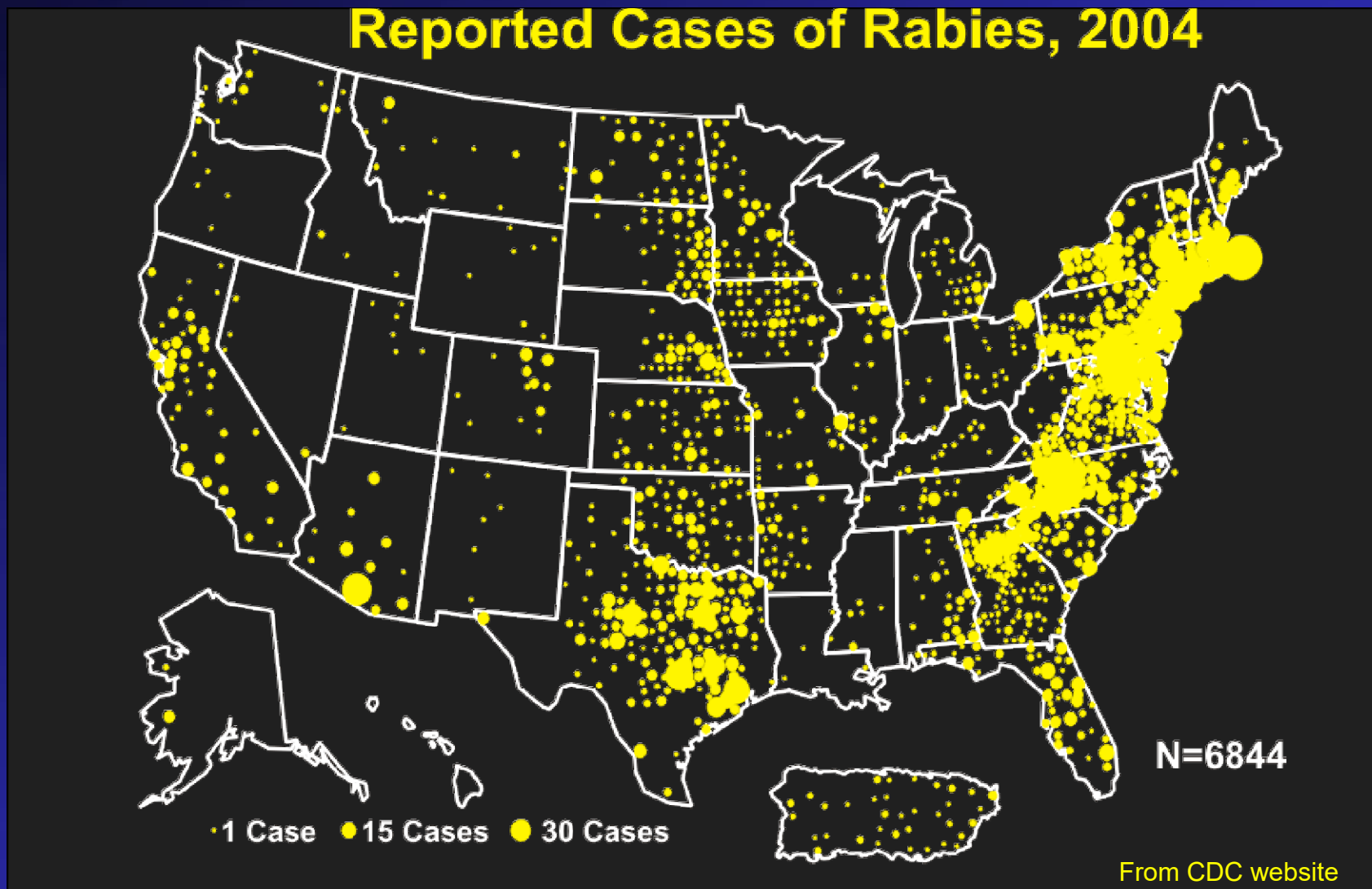
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Bat in the house

- Eastern small footed bat (*Myotis leibii*)
 - Hit with tennis racket
- Animal not analyzed



Animal rabies in the U.S.



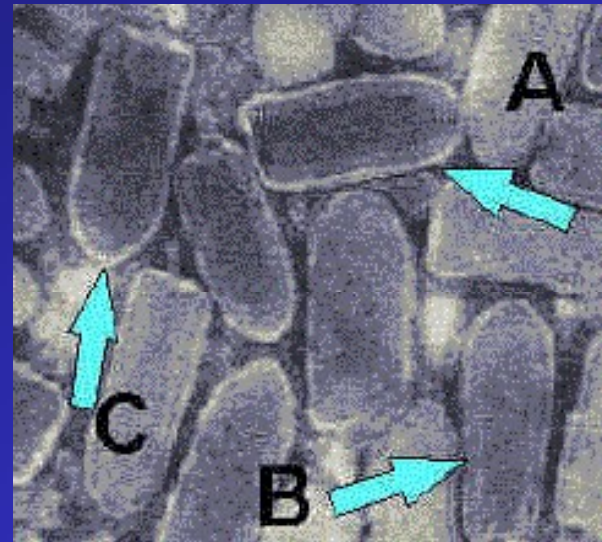
Starfish Palliative Treatment

- **Haloperidol Preferred**
 - 5mg IM/SC q 1 hr x 3 or until calm
 - Then, Haloperidol regularly q 4 - 6
- **Plus Diphenhydramine 50 mg IM q 4 - 6**
- **Alternative**
 - Diazepam 20 mg IM q 2 hrs
- **Plus Diphenhydramine 50 mg IM q 4 - 6**
- **3rd alternative:**
 - Chlorpromazine 100 IM
 - Levomepromazine 100 IM/SC

Marsden, S, "Palliative Care in the developing World" in *International Assoc. Hospice and Pall. Care*, 2004

Rabies virus

- Bullet shaped virus
- Different virus variants
 - Specific to species and geographical area
 - Examples:
 - Philippine dog strain
 - Silver haired bat strain
 - Identify with PCR, monoclonal Ab



www.cdc.gov/ncidod/dvrd/rabies

Case 1 Sheila Marie

- 7 yo girl
- Bitten on R arm
 - 9 weeks PTA
- Dog died 1 week later
- “Quack-quack” doctor
- Observe
 - Hydrophobia
 - Aerophobia
 - CP with swallowing



Case 3 Jerome

- 7 yo boy
- Injury to R cheek
 - 6 weeks PTA
- Dog was killed
- “Witch doctor”
- Observe
 - Physical restraints
 - Face covered
 - Marked agitation



Case 3 Jerome

- Hypersalivation
- Aversion to water
- Agitation, alternating with periods of calm
- “Animal facies”



What should we know about rabies?

- **Epidemiology**
 - Geography, Travel
 - Animal exposures
 - Bat history
- **Clinical**
 - What are the risks? Asking questions
- **Prevention: 1-2-3**
 - 1) wound management
 - 2) RIG –Rabies Immune Globulin
 - 3) vaccine

Rabies Pre-exposure

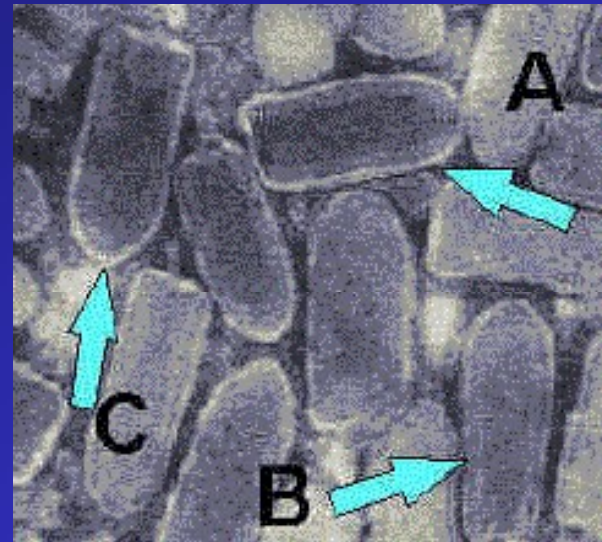
Vaccine

- Vets, animal handlers, lab workers, health care workers
- Travelers > 1 month to a rabies endemic area
- HDCV days 0, 7, 21 or 28



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www.cdc.gov/ncidod/dvrd/rabies

Experimental treatment - Milwaukee protocol

- Dr. Willoughby et al.
NEJM
 - ?Actually worked
 - ?Rare host polymorphism
 - ?Virus variant - clinical rabies thought 100% fatal

