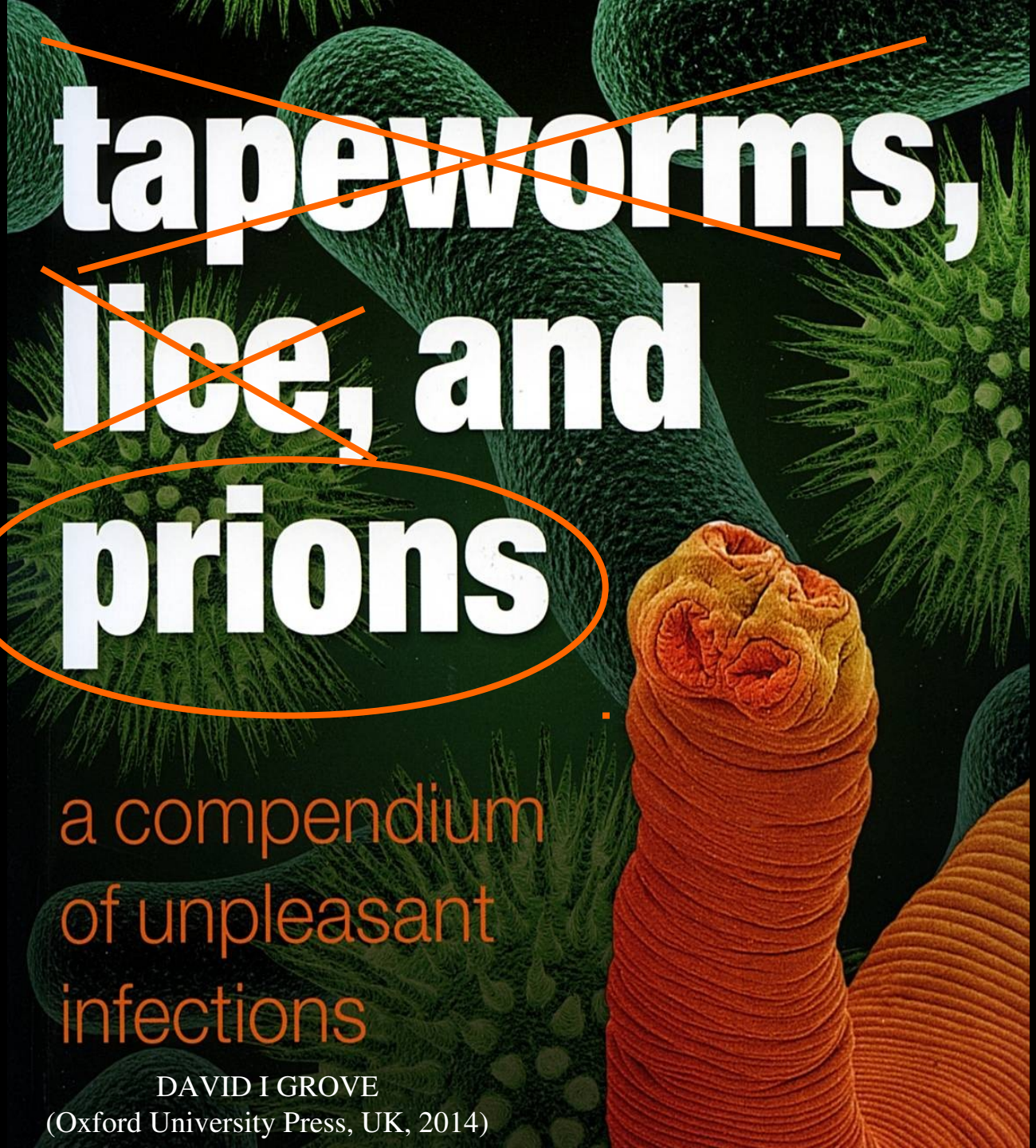
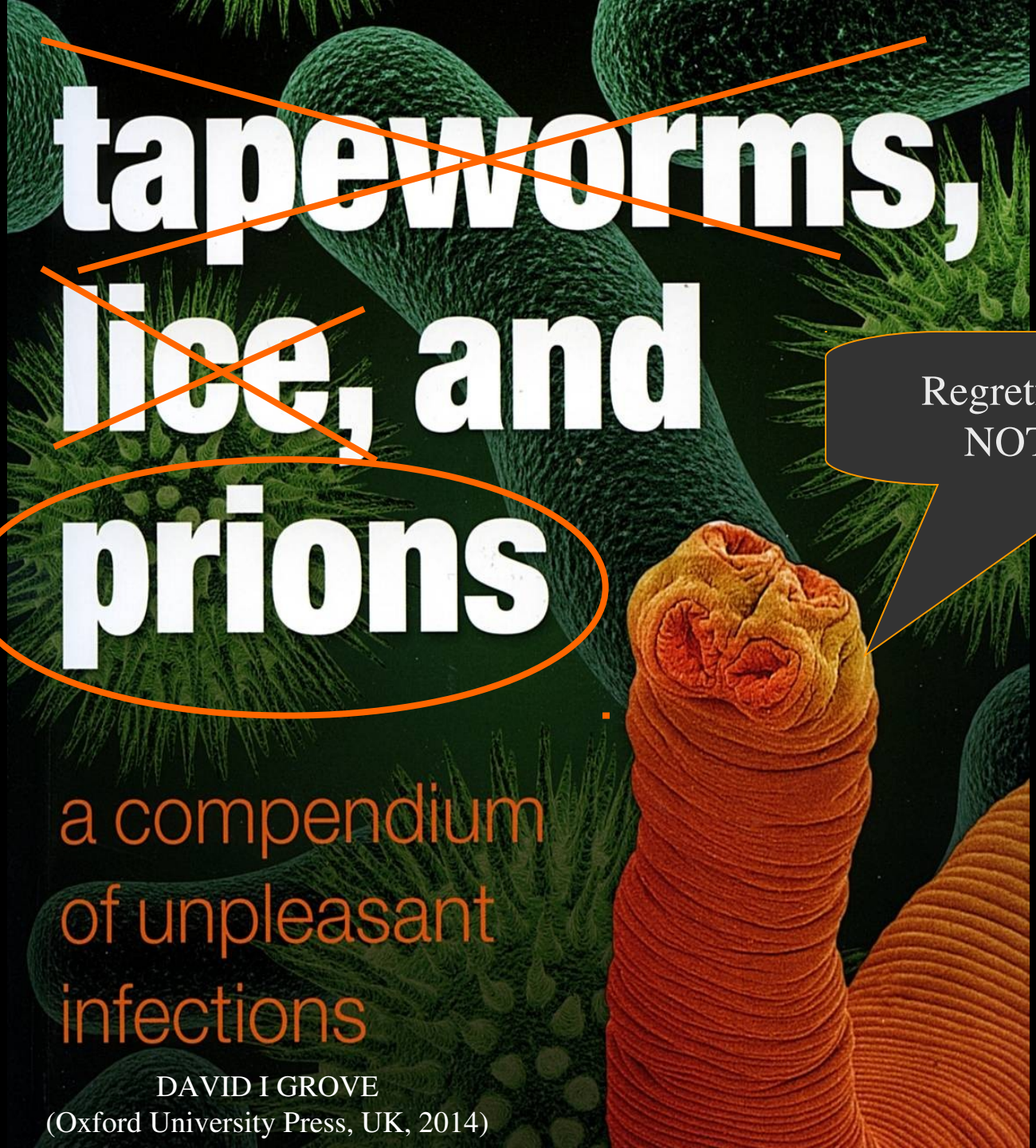


What Every Neuropathologist Needs To Know

Mark Cohen, M.D.
National Prion Disease
Pathology Surveillance Center
University Hospitals
Case Medical Center
Cleveland in Ohio



Regretfully, Dr. Cohen has NOTHING to disclose

Learning objectives

1. List 3 presenting features that suggest diagnoses other than Jakob-Creutzfeldt disease.
2. Explain the value of a positive CSF-tau result in the differential diagnosis of Jakob-Creutzfeldt disease.
3. Compare and contrast protein misfolding cyclic amplification (PMCA) with real-time quaking induced conversion (RT-QuIC).
4. List 5 brain regions that must be examined to adequately characterize human prion disease.

Which clinical features should suggest JCD?

MRI-JCD Consortium Criteria (98% Sensitive, 70% Specific)

1. Dementia
2. At least 2
   - ✓ Myoclonus
   - ✓ Visual or cerebellar disturbance
   - ✓ Pyramidal or extrapyramidal signs
   - ✓ Akinetic mutism
3. And one or more
   - ✓ Periodic EEG discharges
   - ✓ Positive CSF 14–3-3 and duration to death< 2 years
   - ✓ High signal in caudate and putamen or at least two cortical regions (temporal-parietal-occipital, but not frontal, cingulate, insular or hippocampal)
   - ✓ No alternative diagnosis on routine investigations.

Takada LT, Geschwind MD. Prion diseases. Semin Neurol. **33**:348-56, 2013

Which clinical features should **not** suggest JCD?

1. Acute neurological disorders
   - Delerium
   - Seizures/Status epilepticus
2. Other neuroimaging abnormalities
   - Predominant white matter abnormalities
   - Isolated limbic hyperintensities
3. Other CSF abnormalities
   - CSF pleocytosis
   - Elevated CSF IgG index

What is the utility of CSF 14-3-3 in JCD diagnosis?

CSFs with prion disease: 75 of 1000

- Positive 14-3-3 (true positive): 68 of 75
- Negative 14-3-3 (false negative): 7 of 75

CSFs without prion disease: 925 of 1000

- Postive 14-3-3 (false positive): 555 of 925
- Negative 14-3-3 (true negative): 370 of 925

What is the utility of CSF tau in JCD diagnosis?

CSFs with prion disease: 75 of 1000

- Positive tau (true positive): 65 of 75
- Negative tau (false negative): 10 of 75

CSFs without prion disease: 925 of 1000

- Postive tau (false positive): 301 of 925
- Negative tau (true negative): 624 of 925

What is the utility of CSF studies in JCD diagnosis?

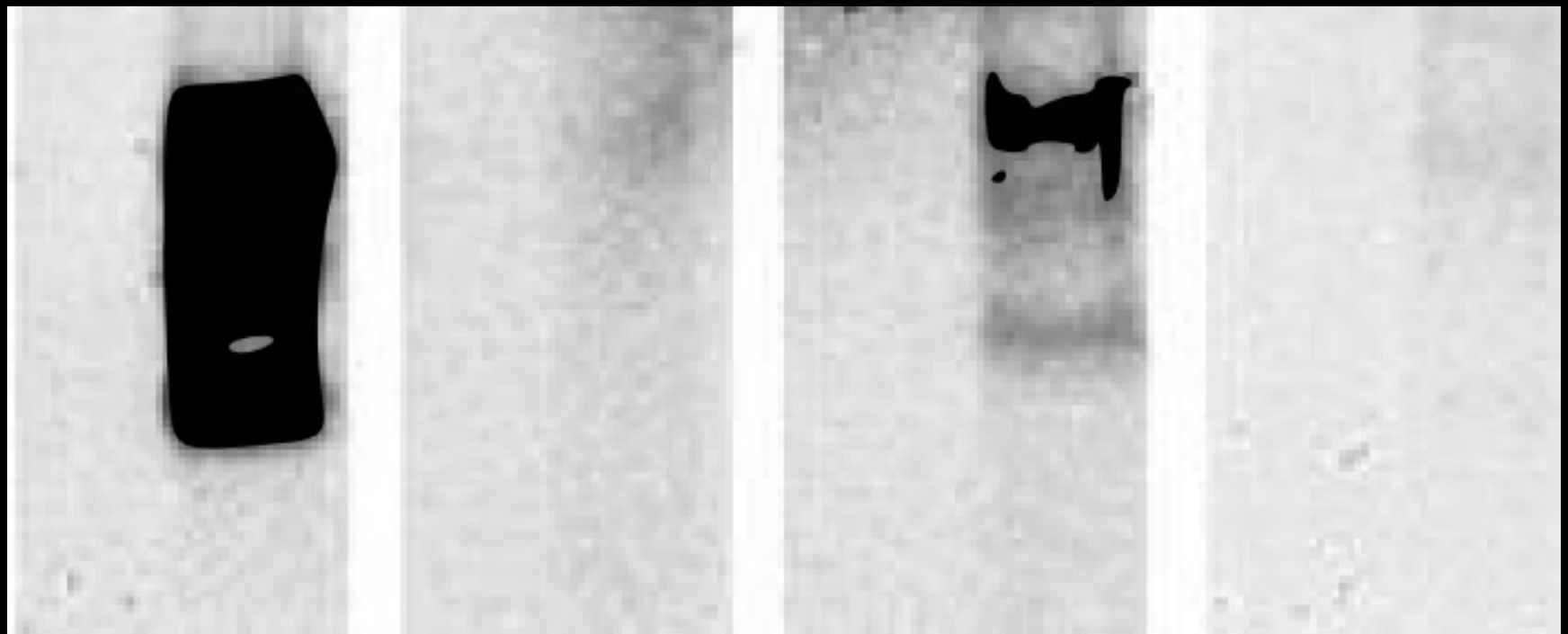
	PPV (%)	NPV(%)	Likelihood Ratio
14-3-3	10	98	1.4
Tau 1150pg/ml	18	99	2.4

- On the basis of positive CSF results alone, the likelihood of prion disease is about 1 in 10 for 14-3-3 and 1 out of 5 for tau
- With an estimated prior of 20%, the likelihood of prion disease is about 1 in 4 for 14-3-3 and 50/50 for tau

Hamlin C, Puoti G, Berri S, et al. A comparison of tau and 14-3-3 protein in the diagnosis of Creutzfeldt-Jakob disease. Neurology. **79**:547-52., 2012

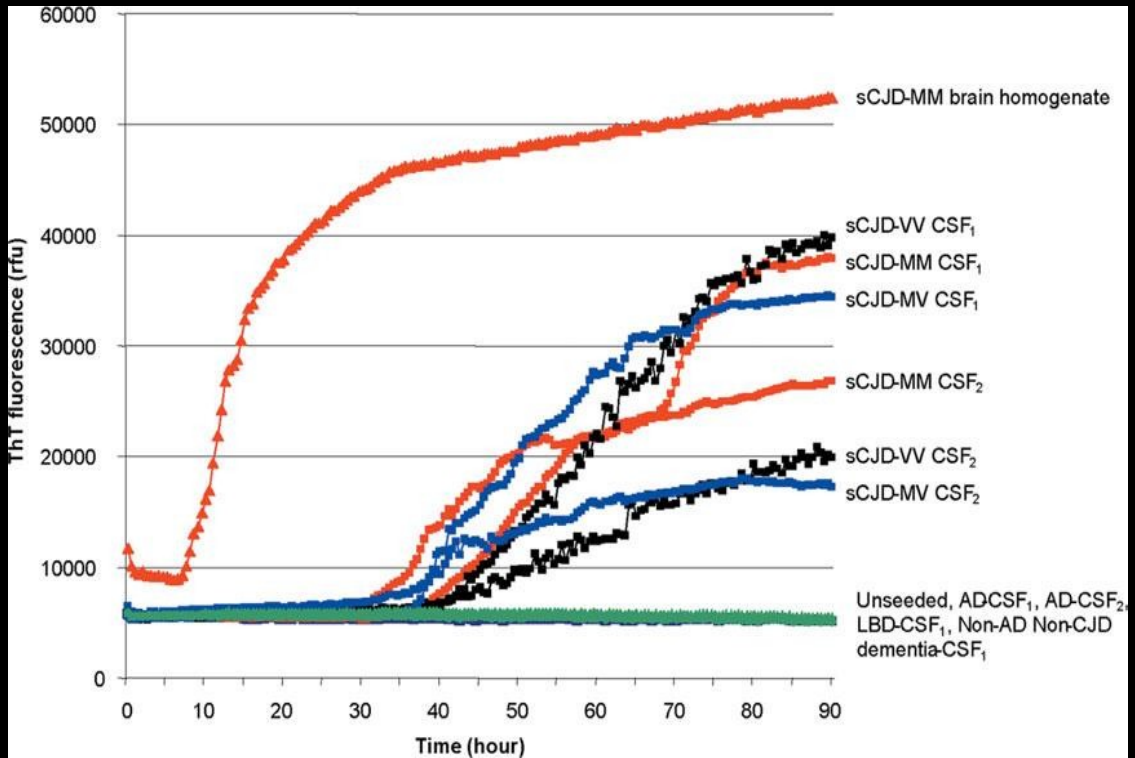
Protein Misfolding Cyclic Amplification (PMCA)

1. Mix normal brain homogenate with inoculum of interest
2. Incubate, sonicate, repeat
3. Run western blot +/- proteinase K



Real Time Quaking Induced Conversion (RT-QuIC)

1. Mix recombinant PrP^C with inoculum of interest (CSF)
2. Add Thioflavin T
3. Incubate, shake, measure fluorescence, repeat



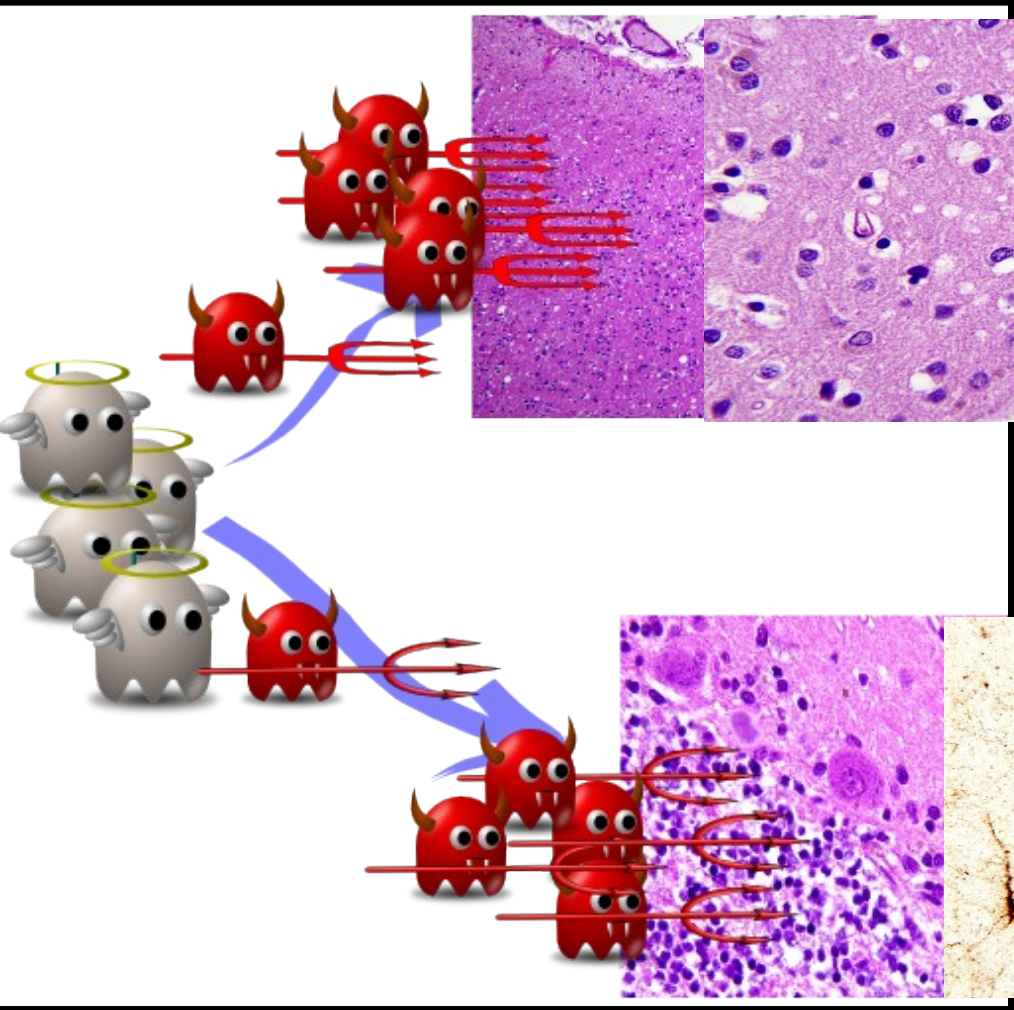
McGuire LI, Peden AH, Orrú CD, et al. Real time quaking-induced conversion analysis of cerebrospinal fluid in sporadic Creutzfeldt-Jakob disease. Ann Neurol. 2012;72: 278-85.

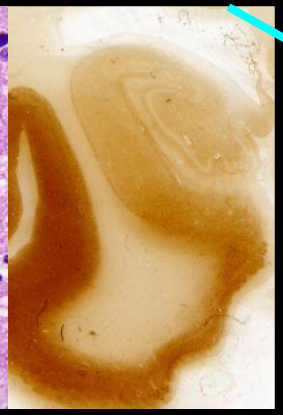
What are prion strains?

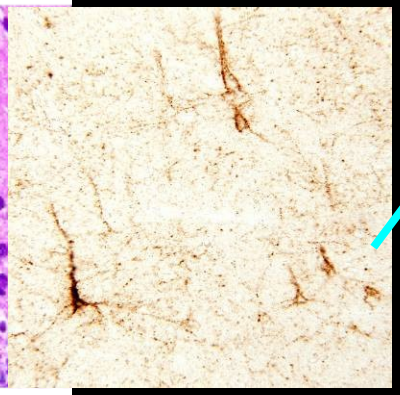
Inoculum source (goats)	Goats innoculated	Goats scratching	Nervous goats
Scratching syndrome	21	21	0
Nervous syndrome	51	4	47

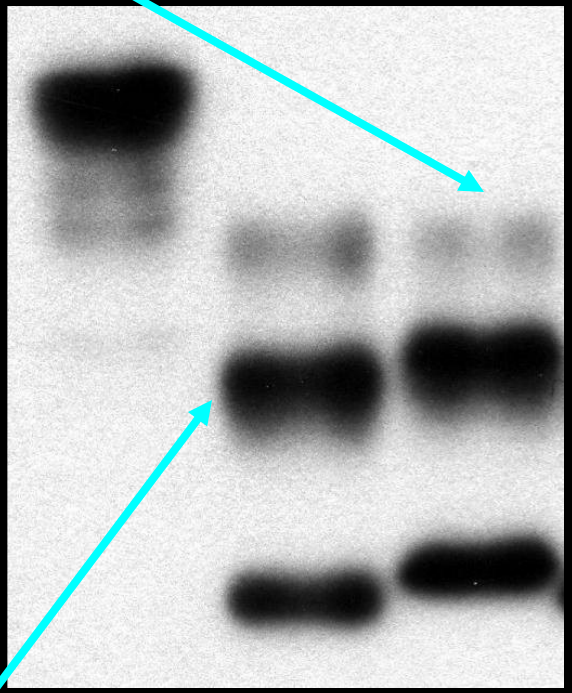
Pattison IH, Millson GC. Scrapie produced experimentally in goats with special reference to the clinical syndrome. J Comp Pathol. **71**:101-9, 1961

Human prion strains



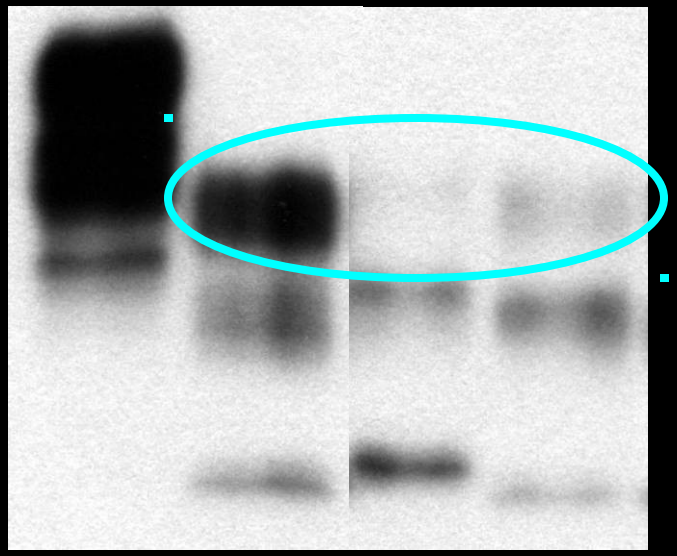


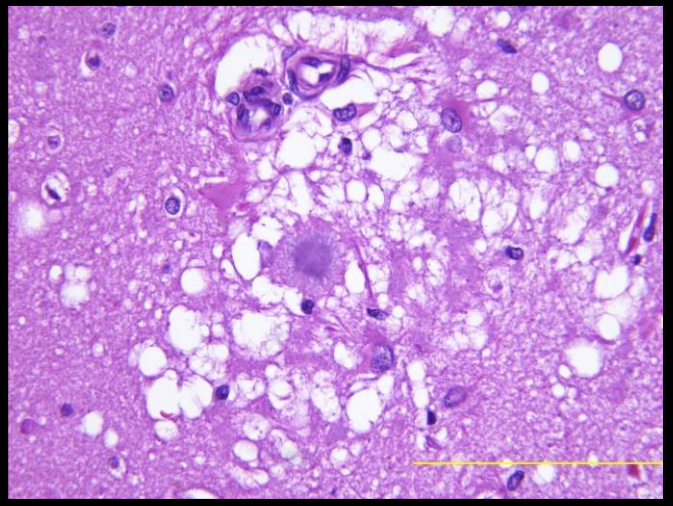




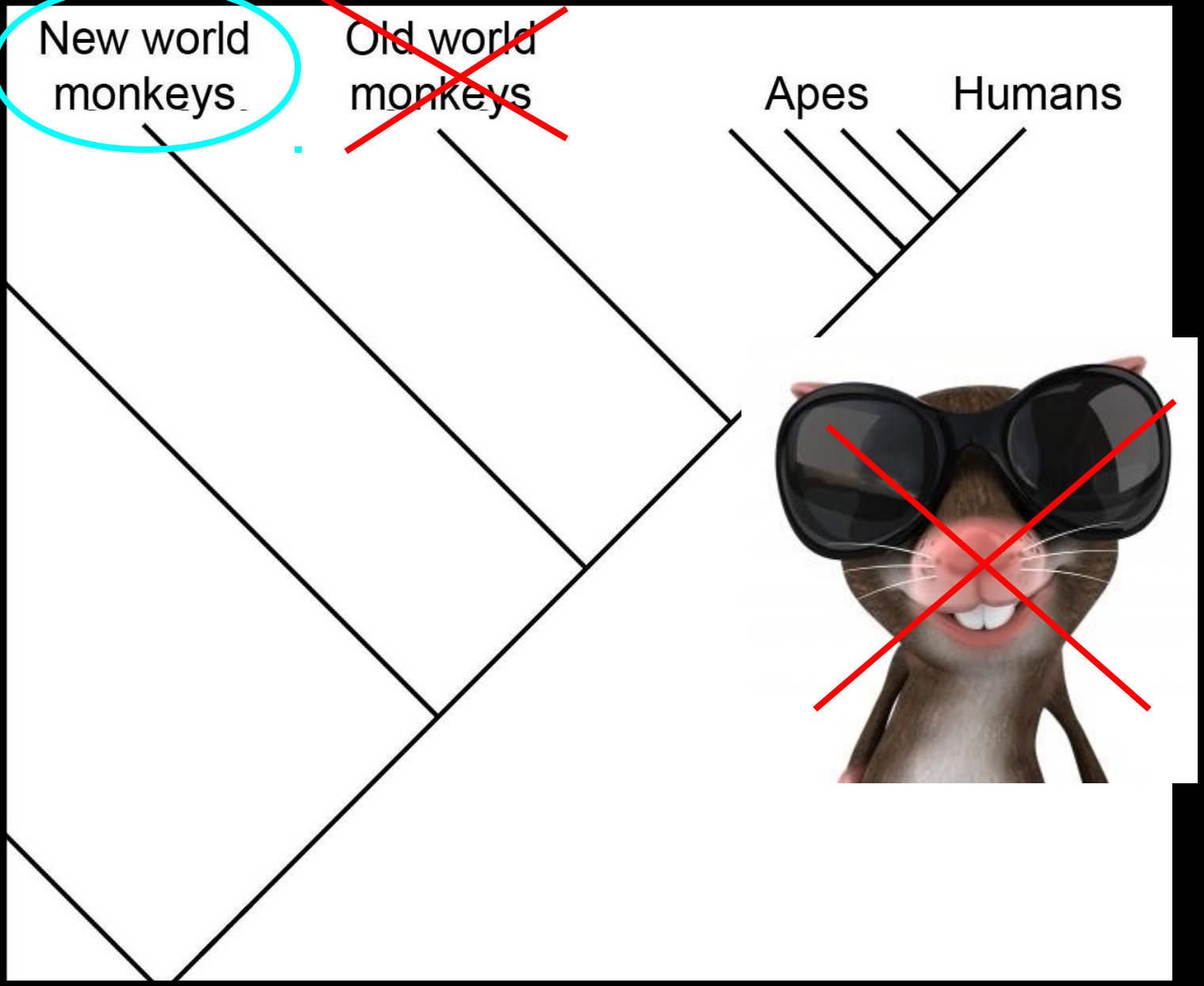
What's going on with variant CJD?

- 229 cases
  - <6 cases/year since 2005
  - 3 US cases (2004/6/14)
  - 3 transfusion-associated cases (UK)
- 16/32,000 (1:2000) UK appendices positive for PrP^{Sc}
- A blood test has been developed, but not widely tested





Is chronic wasting disease transmissible to humans?



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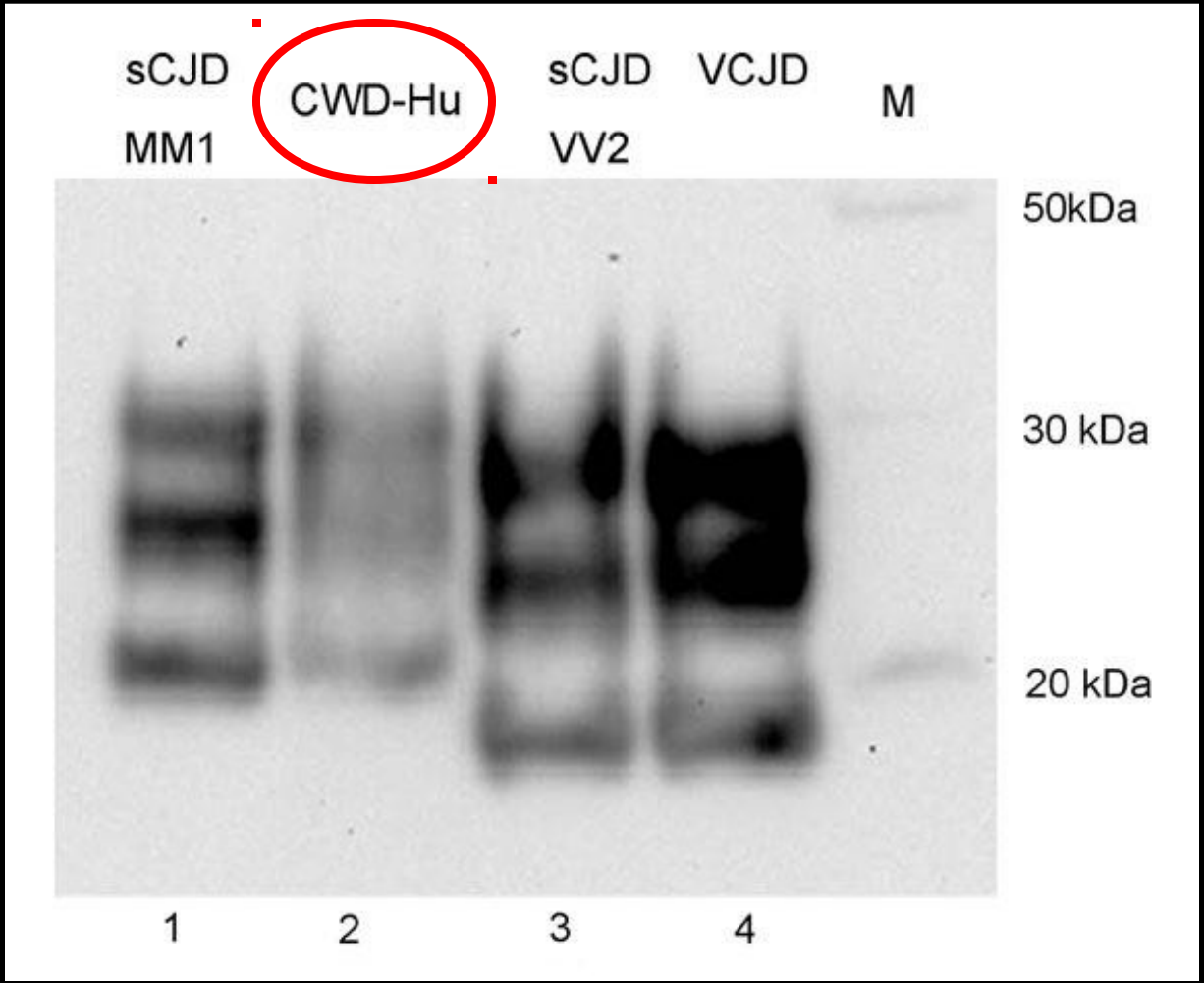


Barria MA, Balachandran A, Morita M, et al. Molecular barriers to zoonotic transmission of prions. Emerg Infect Dis. **20**:88-97, 2014

Five ways that you can help with prion surveillance

Don't fix all of the brain tissue

Don't overfix the remainder of the brain tissue (send as soon as possible)

Send (at least):

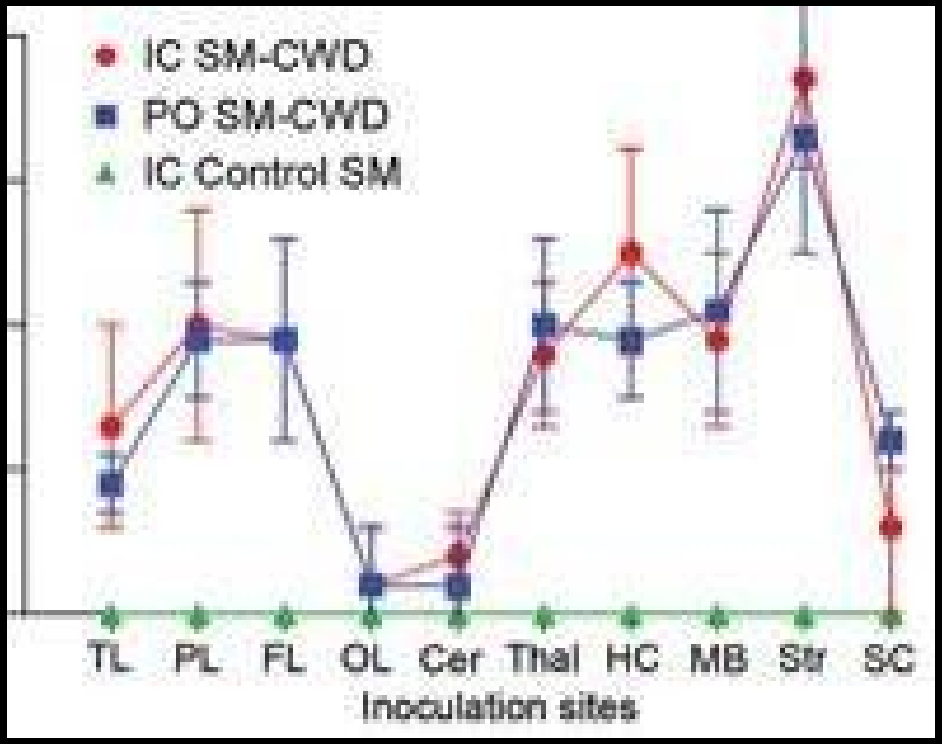
- Frontal & occipital cortex
- Hippocampus
- Striatum
- Thalamus
- Cerebellum

Visit our website:

www.cjdsurveillance.com

Call us at 216-368-0587

- Ask for Katie



Race B, et al. Chronic wasting disease agents in nonhuman primates. Emerg Infect Dis. 20:833-7, 2014.

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Supplemental Slides

Is it CJD or JCD?

Dr. Creutzfeldt..told me that his case did not bear any resemblance to those cases described by Jakob..

Cases reported by Jakob..fit our present concept..

Jakob suggested a possible infectious nature..testing this hypothesis by the inoculation of CJD brain material into the rabbit..

Elias E. Manuelidis, M.D.

AANP Presidential Address

St. Louis, 1983

When I was writing my first paper on the transmission of Jakob-Creutzfeldt disease..I wanted to rename the disease "Gibbs disease."

I didn't think this would be acceptable..so I decided to reverse the names, because..my initials are CJ.

(Clarence) Joe Gibbs

Quoted by Stanley B. Prusiner, M.D.

In **Madness and Memory: The Discovery of Prions--A New Biological Principle of Disease**, Yale University Press, 2014

How common is sporadic JCD?

EuroCJD

<1/10^6/yr: 12 countries

1-1.2/10^6/yr

Australia, Canada, UK

1.2-1.4/10^6/yr

6 countries

1.4-1.6/10^6/yr

4 countries

http://www.eurocjd.ed.ac.uk/surveillancedata3.htm

Health professions

Cases	JCD	Neg
Total	8321	2968
HPs	202 (2.4%)	83 (2.8%)

Alcalde-Cabero E, Almazan-Isla J, Brandel JP, et al. Health professions and risk of sporadic Creutzfeldt-Jakob disease, 1965 to 2010. Euro Surveill. 2012

Which tissues are potentially infectious, and what can be done to eliminate infectivity?

Infectivity

A. High
   - Brain, dura, pituitary, retina, spinal cord & ganglia

B. Lower
   - CSF, nerves & muscles, lymphoreticular tissues, GI tract, blood (vJCD), saliva/urine/feces (CWD), milk (Scrapie)

C. Not detectable
   - Bone & tendon, gingival tissue, trachea, sweat/tears/mucus/bile/ semen

Decontamination

- Surfaces
  - 2N NaOH or 20,000 ppm NaOCL (bleach) for 1 hour
- Instruments
  - Above, plus autoclave
- Tissue
  1. Fix well
  2. Immerse cassettes in 98% formic acid for 1 hour
  3. Fix again for at least 48 hr