

Transmission of BSE to Nonhuman Primates:

a model for human risk assessment

and determination of infectious dose

The macaque model to study human TSEs

Clinical symptoms

vCJD, BSE

Behaviour

- ◆ Increased timidity/aggressiveness
- ◆ Yawning

Motricity

- ◆ Truncal ataxia
- ◆ Incoordination, imbalance
- ◆ Hypermetria
- ◆ Dysesthesia
- ◆ Hindlimb paresis

sCJD

Behaviour

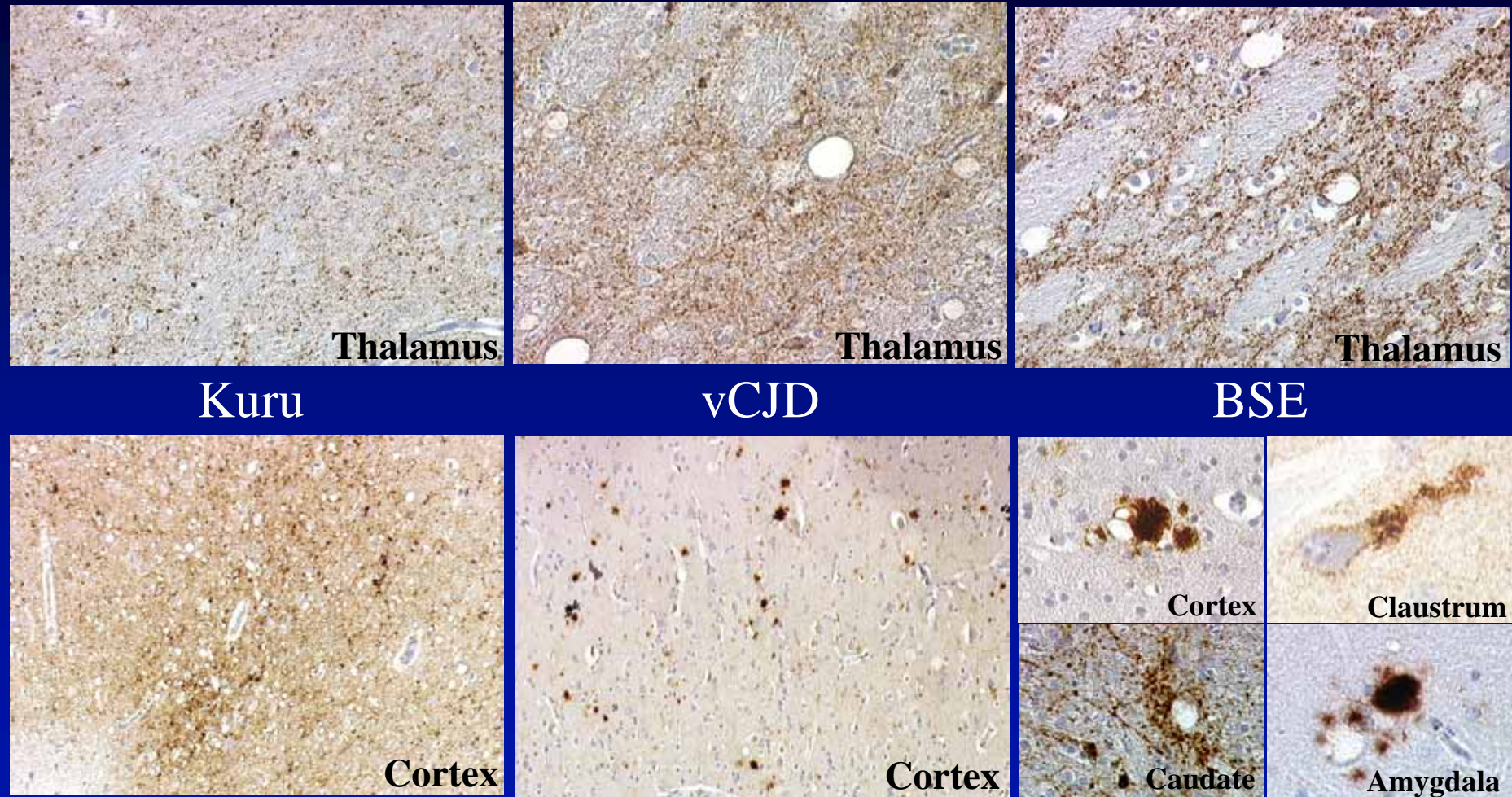
- ◆ Confiding
- ◆ Withdrawal into himself

Motricity

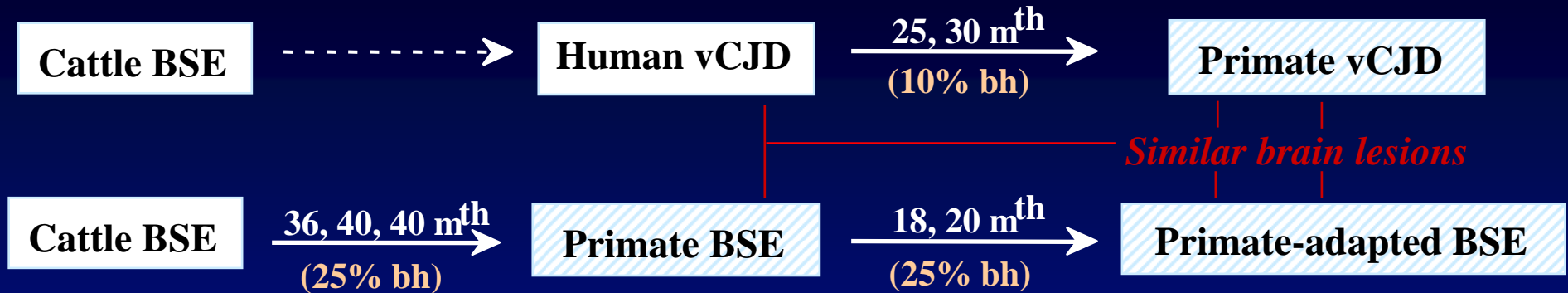
- ◆ Slow movements
- ◆ Priapism
- ◆ Myoclonus

Transmission of vCJD/ BSE and Kuru to *Macaca fascicularis* : Comparative pathology

3F4 PrP IHC



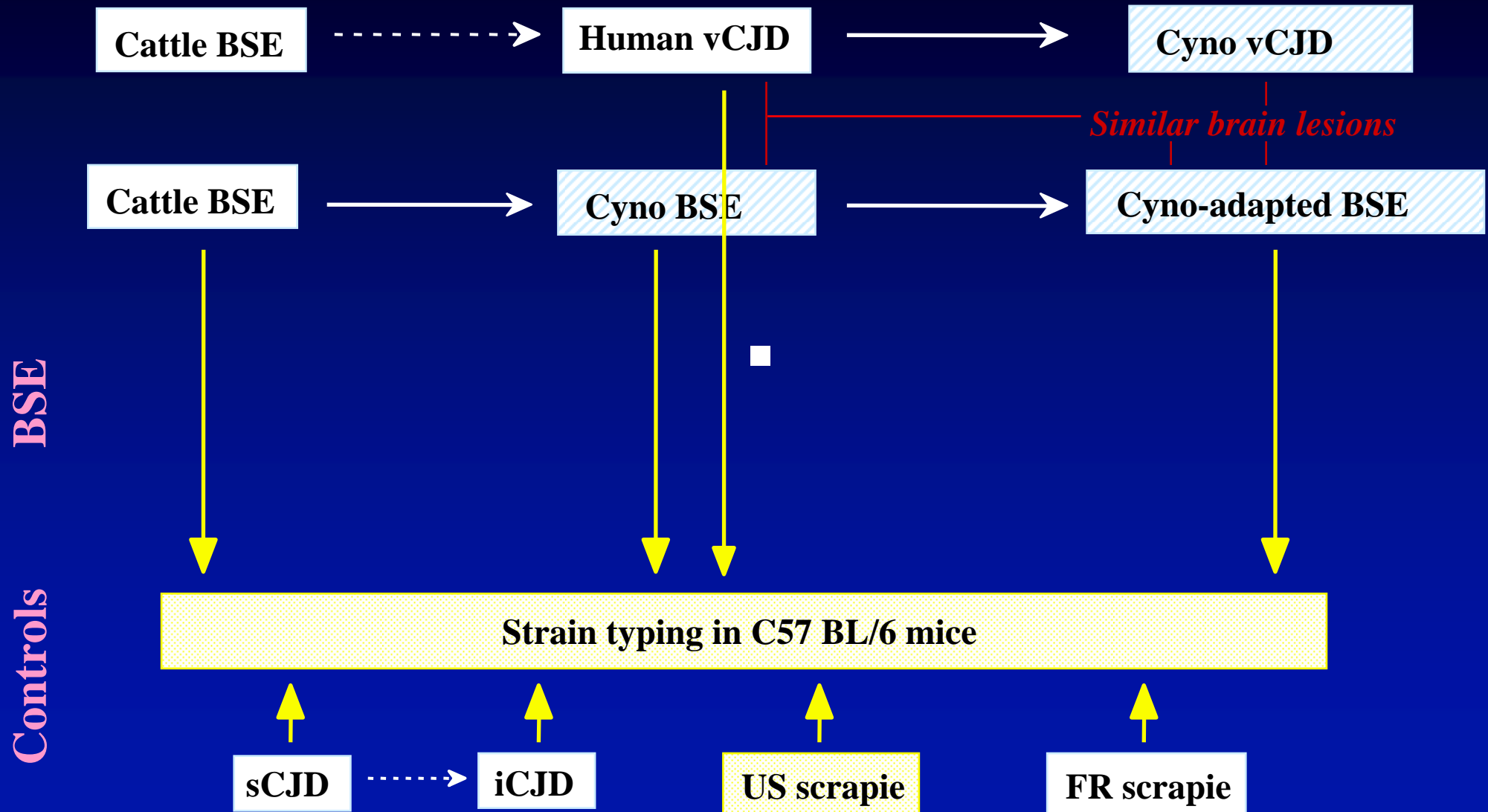
Accidental and experimental transmissions of BSE to primates



■
How does the BSE agent adapt to Primates

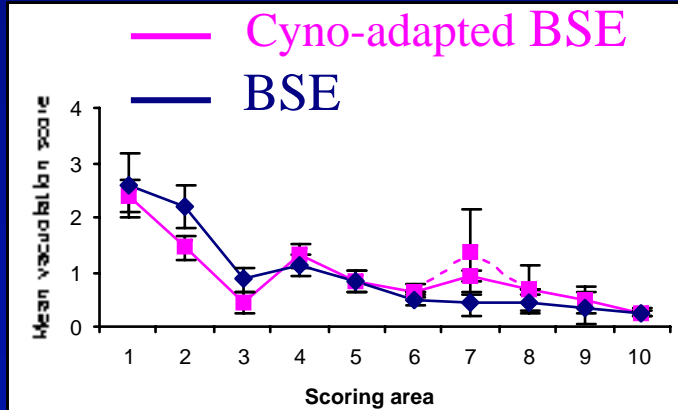
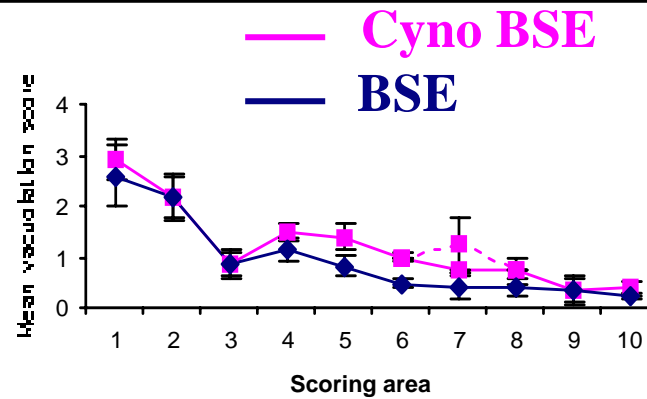
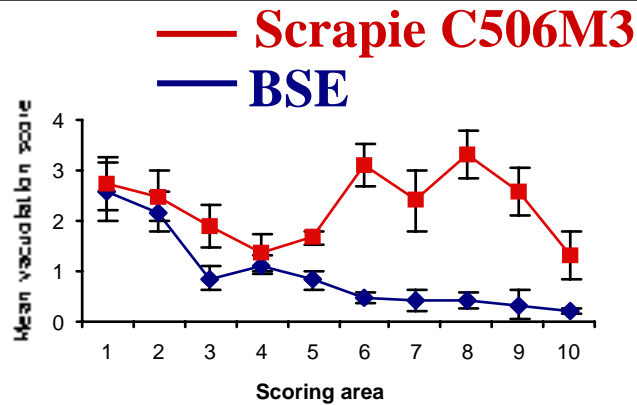
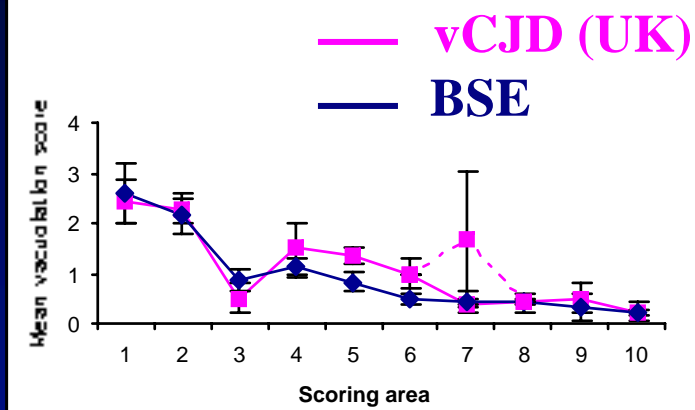
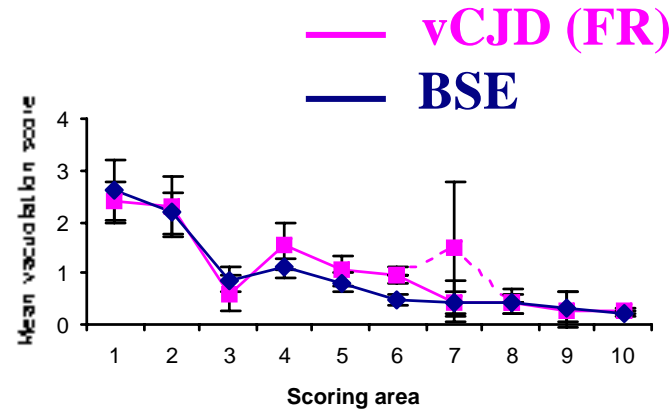
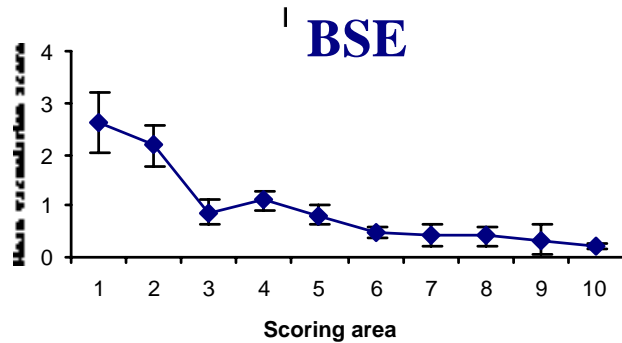
after crossing the species barrier ?

Accidental and experimental transmissions of CJD, BSE and scrapie



Adaptation of the BSE agent to Primates

Lesion profiles



C. Lasmézas et al. PNAS 2001

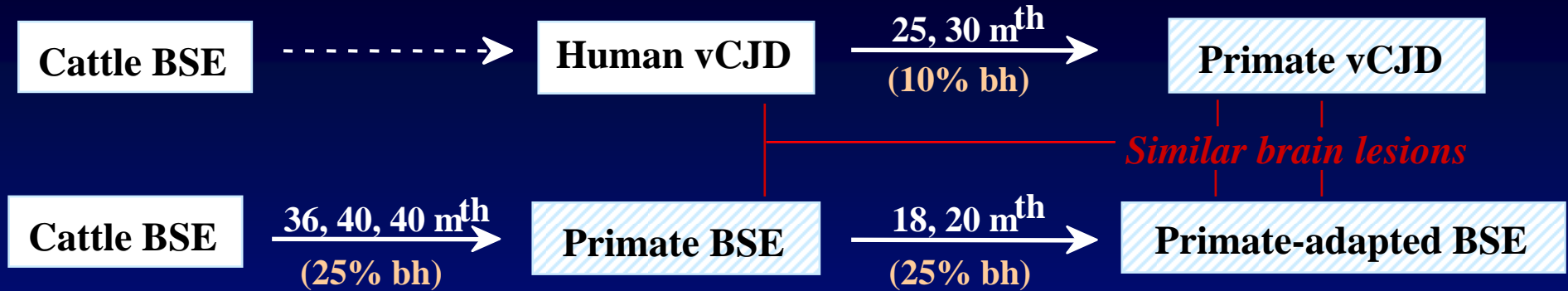
Relative efficiency of inoculation routes

	139A / CW mouse		263K / hamster		ME7 / SM mouse	
Inoculation route	Titres*	i.c. IU / peripheral IU	Titres*	i.c. IU / peripheral IU	Titres*	i.c. IU / peripheral IU
Intracerebral	8,5	1	9,8	1	8,1	1
Intravenous	7,6	9	■		6,7	25
Intraperitoneal	5,9	430	5,2	40 000	6,8	20
Sub-cutaneous	4,1	24 500				
Intragastric	3,5	100 000				
Scarification					6,3	60

* Titres are expressed in log 10 LD50/g of brain

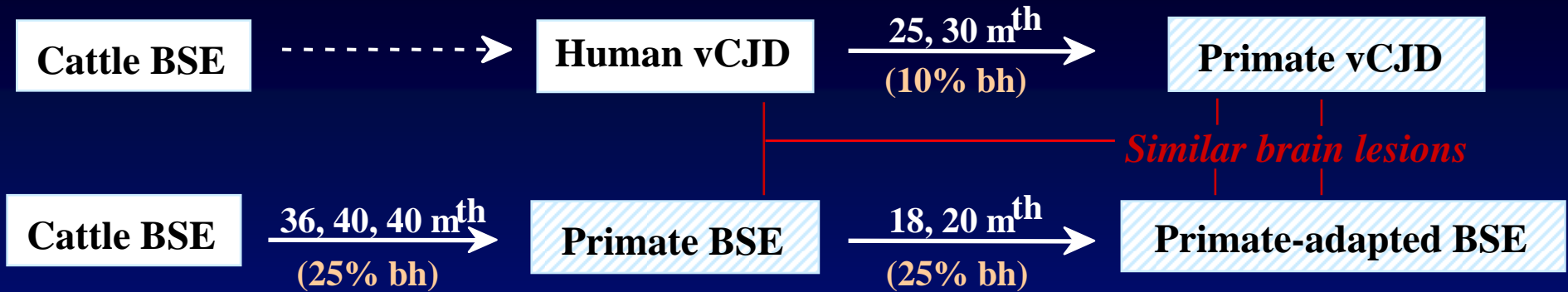
R.H. Kimberlin, 1977, 88, 89; D.M. Taylor, 1996

Efficiency of secondary transmissions in Primates



Intravenous route ?

Efficiency of secondary transmissions in Primates

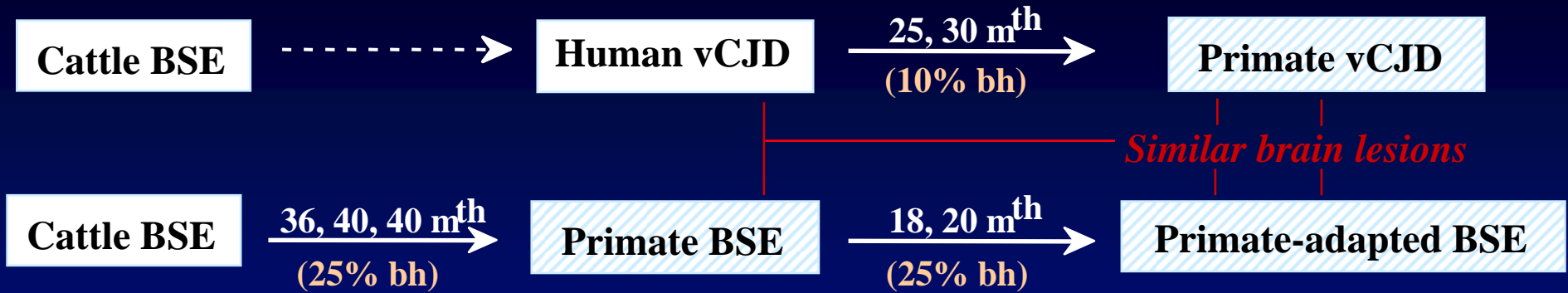


Brain amount

40 mg	■	IC	→	20, 21 m th
4 mg				36 m th
0.4 mg				33 m th
40 mg		IV	→	25 m th
4 mg				38 m th
0.4 mg				33 m th

Herzog et al., Lancet, 2004

Efficiency of secondary transmissions in Primates



	<i>Brain amount</i>		
	40 mg	IC	20, 21 m th
	4 mg		36 m th
	0.4 mg		33 m th
	40 mg	IV	25 m th
	4 mg		38 m th
	0.4 mg		33 m th
5 g		Oral	?
5 g		Oral	47, 51 m th

Herzog et al., Lancet, 2004

BSE and vCJD: risk for human health

- *Upper limit of the number of CJD cases (500?), infections (11 000?)*

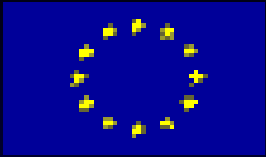
-> Number of contaminated cattle tissue having entered the human food chain in different countries

-> Exposure through sources other than cattle ?

-> Susceptibility of humans to oral infection by the BSE agent



Species barrier ?



Partners

**Swedish Institute for Infectious
Disease Control (SIIDC)**

**Deutsches Primatenzentrum (DPZ)*
Paul-Ehrlich-Institut (PEI)**

**Commissariat à l'Énergie
Atomique (CEA)**

**Istituto Superiore
di Sanità (ISS)**



* co-ordinator

BSE infection and observation of cynomolgus monkeys

Material ^a	Dose	Route of infection and observation period				
		Oral				i.c.
		1 yr	3 yr	5 yr	10 yr	10 yr
BCB	15 g	2 ^b	2	2	6 (PEI)	
	5 g				6 (PEI)	
	500 mg				6 (CEA)	
	50 mg				6 (DPZ)	6 (DPZ)
	5 mg		■		6 (DPZ)	6 (PEI)
	500 µg					6 (CEA)
	50 µg					6 (ISS)
	5 µg					6 (ISS)
NCB	15 g				6 (SIIDC)	6 (SIIDC)
				Total	42	36

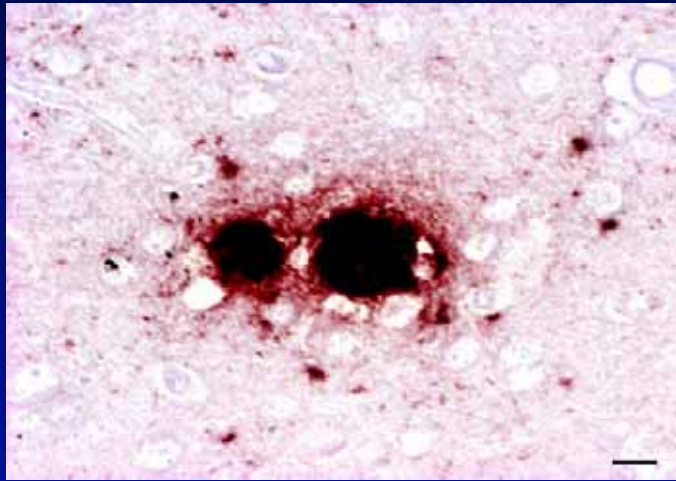
^a BCB: BSE cattle brain; NCB: normal cattle brain

^b number of animals

Animals developing TSE will be autopsied. After an observation period of 10 years the remaining animals will also be sacrificed and examined comprehensively.

Evaluation of the BSE infectious dose for Primates

Preliminary oral infection experiment :



Occipital cortex, BSE macaque
PrP mAb SAF32 (J. Grassi)

**Two adult cynomolgus macaques fed with
5 g BSE cattle brain**

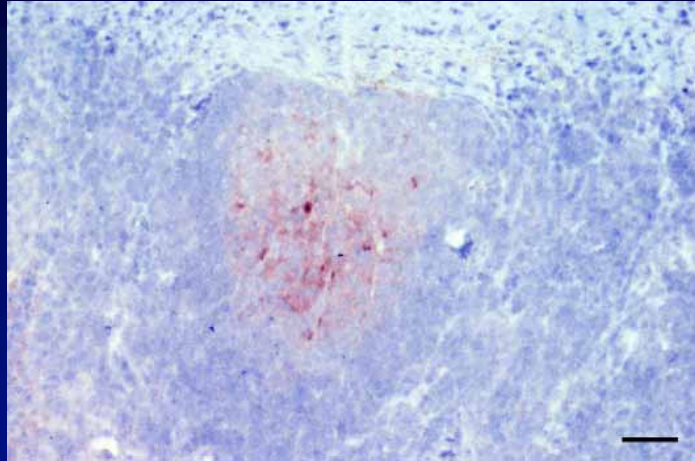


**1/2 : clinical disease at 5 years post-challenge
(sacrifice at 63 months)**

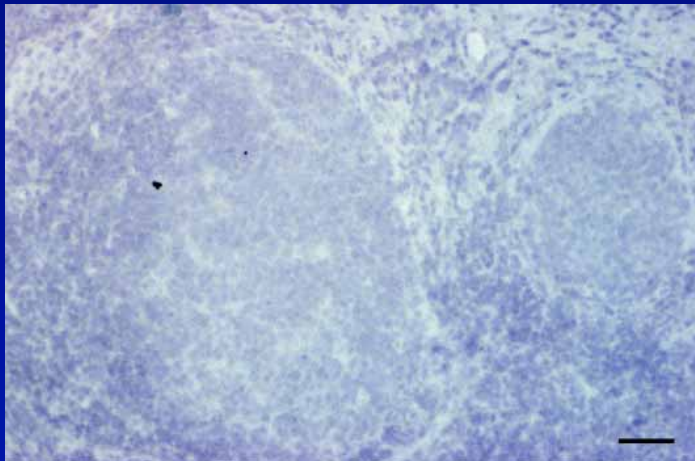
1/2 : healthy at 80 months post-challenge

*Larger experiment using lower doses and a higher number of animals is underway
in a EU consortium*

PrPres detection in tonsils of cynomolgus macaques orally challenged with BSE



**Positive macaque`
(63 months post-oral challenge)**



**Healthy macaque
(72 months post-oral challenge)**

PrP mAb SAF32 (J. Grassi)

	BSE bovine brain inoculum								
	100 g	10 g	5 g	1 g	100 mg	10 mg	1 mg	0.1 mg	0.01 mg
Primate (oral route)*			1/2 (50%)						
Cattle (oral route)*	10/10 (100%)	7/9 (78%)		7/10 (70%)	3/15 (20%)	1/15 (7%)	1/15 (7%)		
Rlll mice (ic+ip route)*						17/18 (94%)	15/17 (88%)	1/14 (7%)	
PrP ^{sc} biochemical detection						+	+	+	-

The comparison is made on the basis of calibration of the bovine inoculum used in our study with primates against a bovine brain inoculum with a similar PrP^{sc} concentration that was inoculated into mice and cattle.³ *Data are number of animals positive/number of animals surviving at the time of clinical onset of disease in the first positive animal (%). The accuracy of bioassays is generally judged to be about plus or minus 1 log. ic+ip=intracerebral and intraperitoneal.

Table 1: Comparison of transmission rates in primates and cattle infected orally with similar BSE brain inocula

Cattle : oral LD50 between 100 mg (20%) and 1 g (70%)

Non human primates : provisional oral LD50 : 5 g

Cattle central nervous system : 700 g

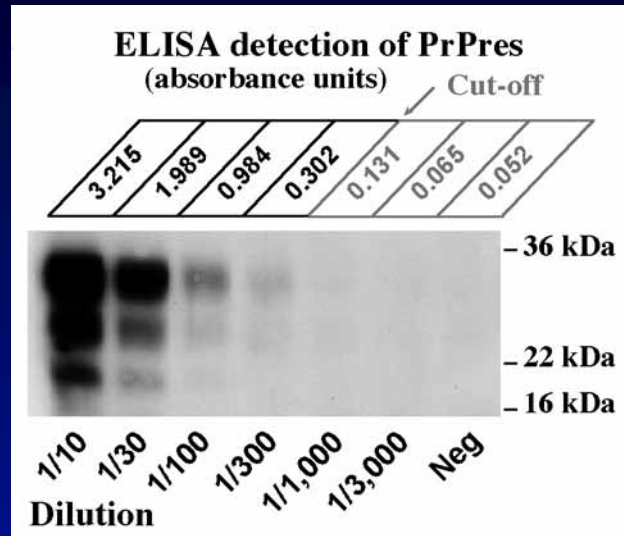
- Can infect 490 (70% of 700 cattle infected with 1 g) to 1400 bovines (20% of 7000 cattle infected with 100 mg).
- Can infect 70 primates (50% of 140 primates infected with 5 g).

Hence, the order of magnitude of the species barrier between cattle and primates is 7 to 20.

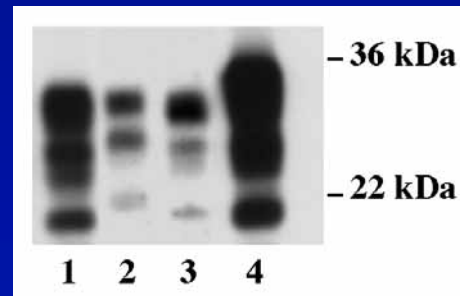
PrPres detection by rapid biochemical tests (BioRad)

Screening test

Confirmatory test



PrPres detection in the cattle BSE inoculum



1 : vCJD patient

2 : sCJD patient

**3 : cynomolgus macaque
infected orally with BSE**

4 : cattle BSE inoculum

Risk of oral infection with BSE agent in Primates

Preliminary assessment of the efficiency of current measures to protect the human food chain :

Limit of sensitivity of abattoir testing : 1/300

Amount of brain necessary to infect a primate:

Clinical BSE case : 5 g ■

Test negative cow : 1.5 kg

If primate LD50 is 10x lower :

Clinical BSE case : 0.5 g

Test negative cow : 150 g

Hence, proper removal of specified risk material and testing seem adequate to protect the human food chain.

Lasmézas et al. Lancet, 2005