


VARIANT CJD
WHERE ARE WE NOW ?

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University of Edinburgh
UK National CJD Research & Surveillance Unit





OUTLINE OF TALK

I INTRODUCTION: PRION DISEASE, BSE & vCJD

II HUMAN-HUMAN SECONDARY TRANSMISSION

III ASPECTS OF INFECTION & TRANSMISSION

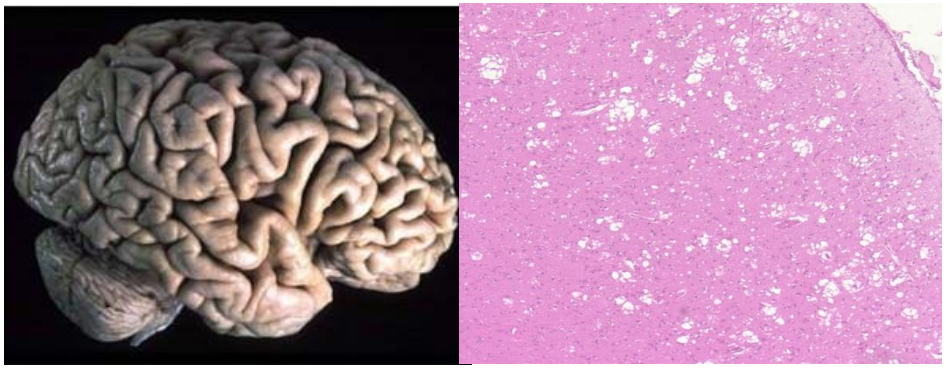
III WHAT HAS HAPPENED & WHY ?

IV CONCLUSION & REMAINING UNCERTAINTIES

I

INTRODUCTION:
PRION DISEASE, BSE & vCJD

PRION DISEASES



AFFECT ANIMALS & HUMANS

PROGRESSIVE, FATAL, BRAIN DISEASES

WHAT ARE PRION DISEASES ?

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DISEASES IN WHICH THE PRION PROTEIN UNDERGOES A POST-TRANSLATIONAL CHANGE IN CONFORMATION

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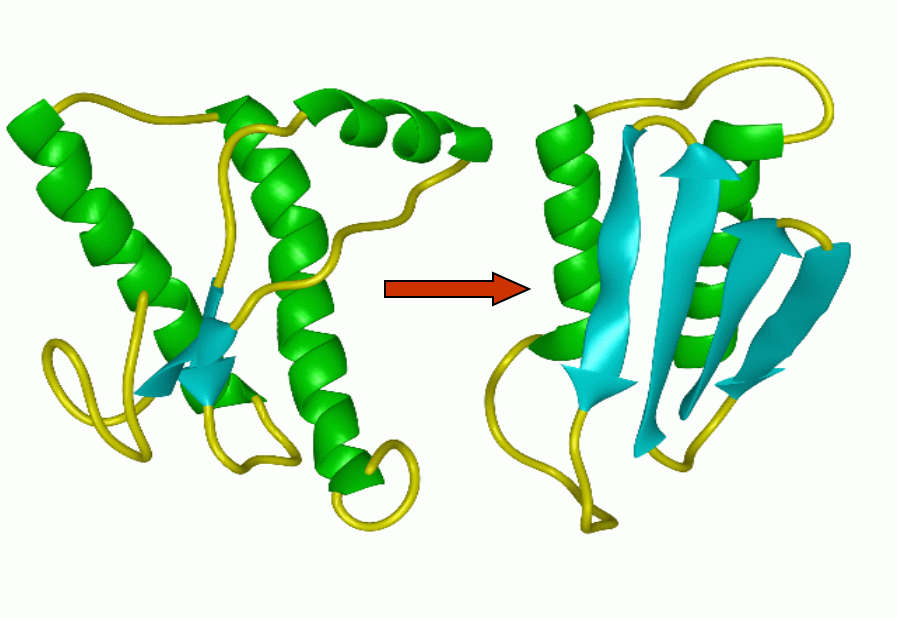
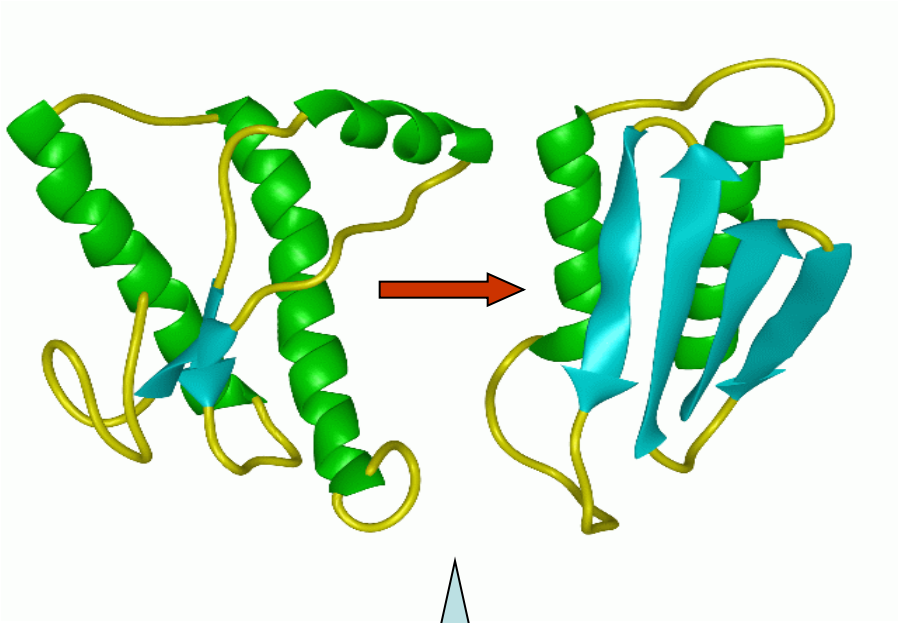
PrP^{C}



PrP^{Sc}

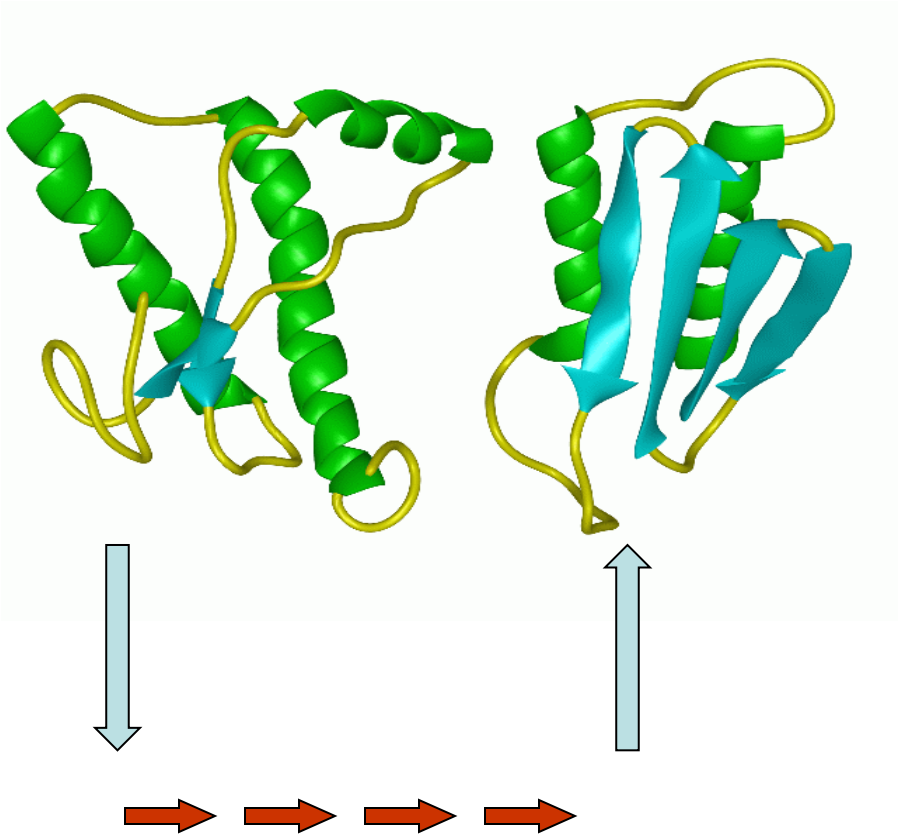
PrP^{C}



PrP^{Sc}

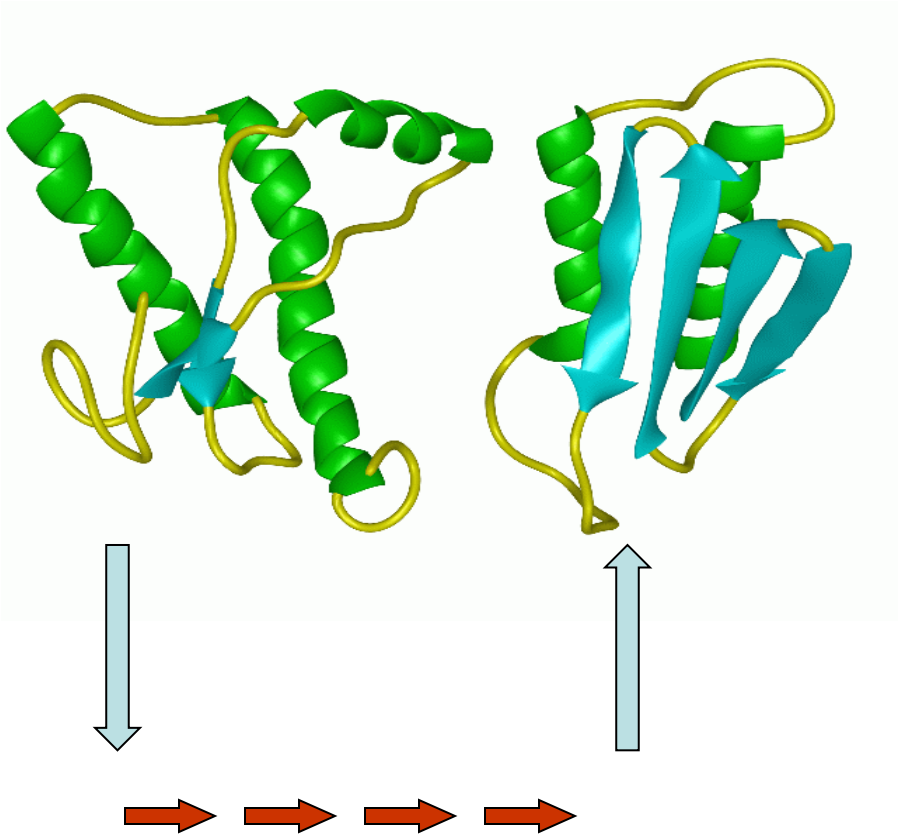
HOW **DOES THE TRANSFORMATION TAKE PLACE ?**

PrP^{C}



PrP^{Sc}

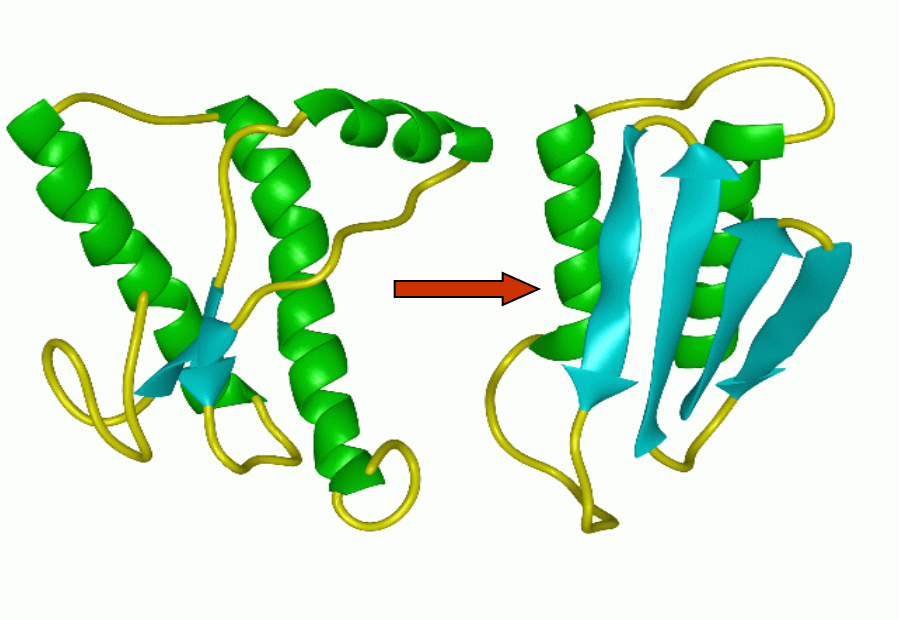
PrP^{C}



PrP^{Sc}

WHAT IS THE SIGNIFICANCE OF THESE INTERMEDIATE FORMS ?

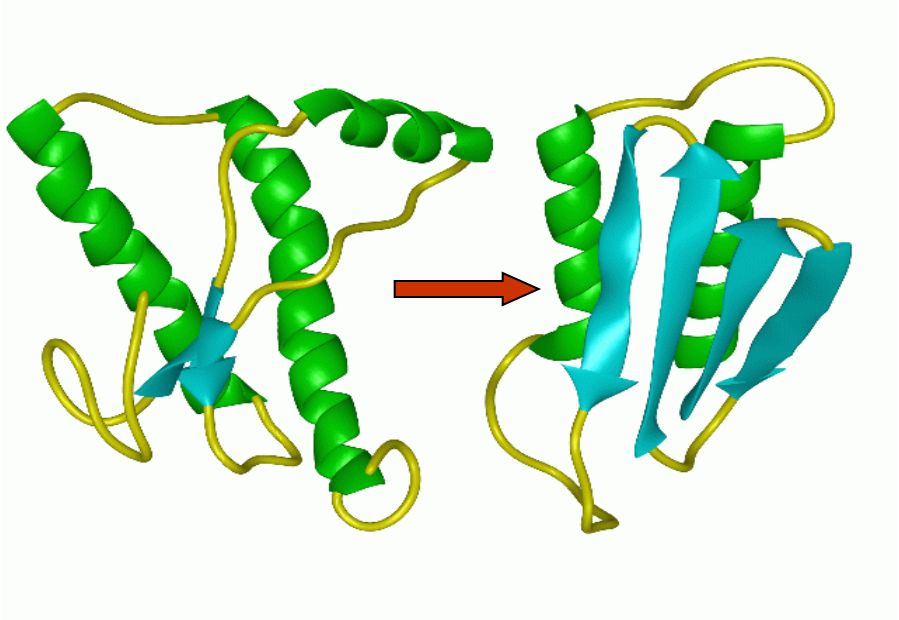
PrP^{C}



PrP^{Sc}

WHAT IS THE SIGNIFICANCE OF PrP^{Sc} ?

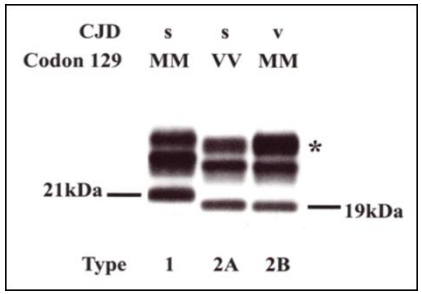
PrP^{C}



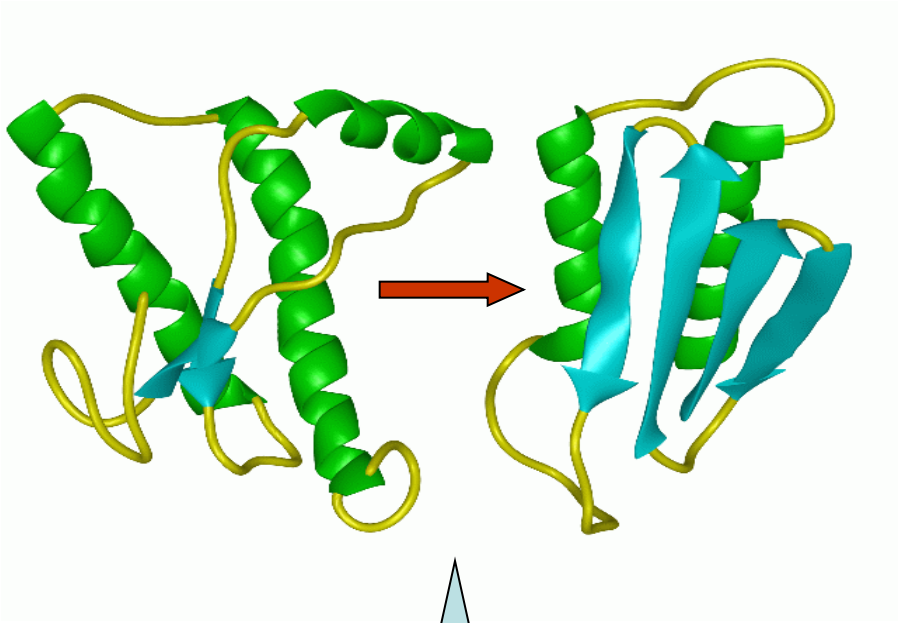
PrP^{Sc}

BIOCHEMICAL TREATMENT

DETECTION IS TYPICALLY OF PrP^{RES}



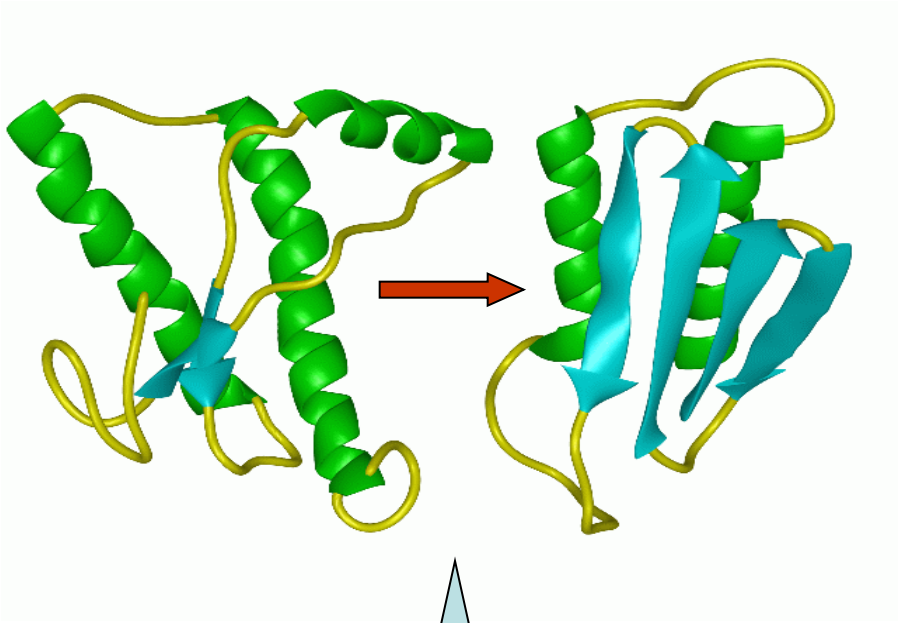
PrP^{C}



PrP^{Sc}

WHY **DOES THE TRANSFORMATION TAKE PLACE ?**

PrP^{C}

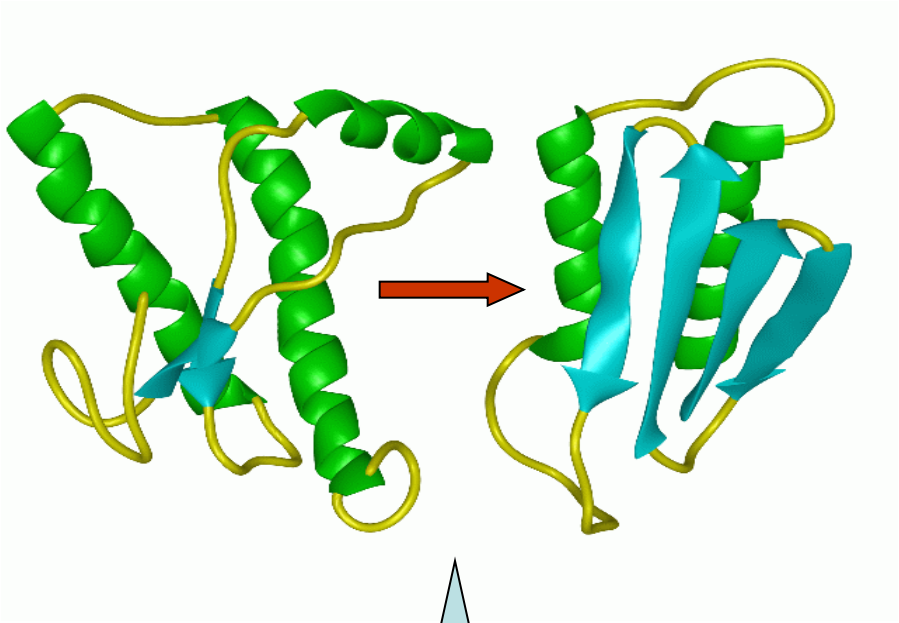


PrP^{Sc}

WHY **DOES THE TRANSFORMATION TAKE PLACE ?**

SPONTANEOUSLY

PrP^{C}



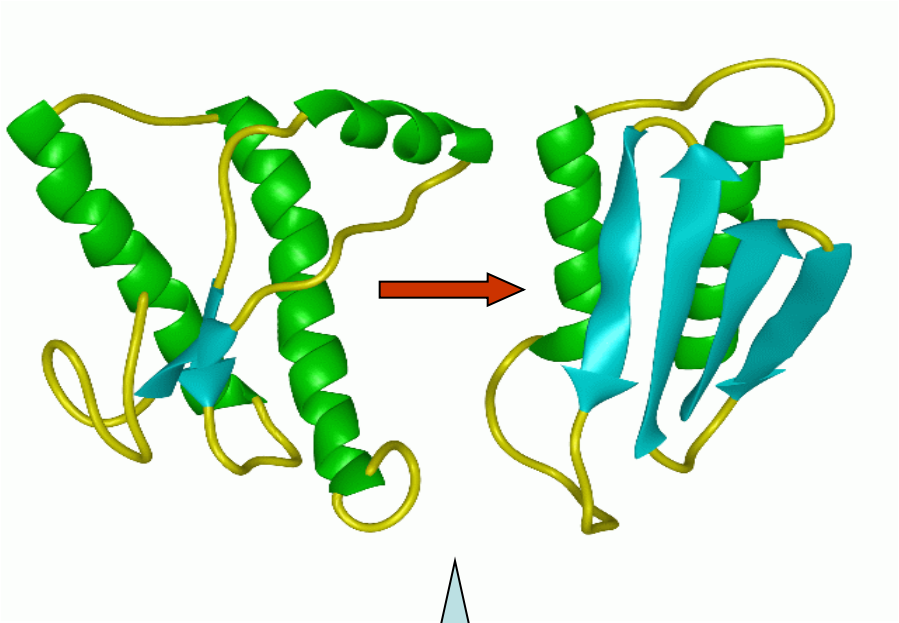
PrP^{Sc}

WHY **DOES THE TRANSFORMATION TAKE PLACE ?**

SPONTANEOUSLY

GENETIC MUTATION

PrP^{C}



PrP^{Sc}

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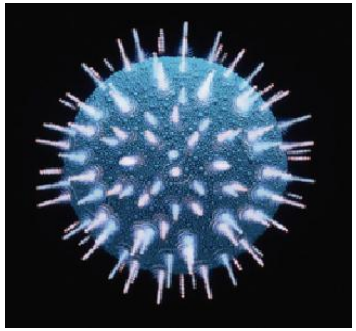
GENETIC MUTATION

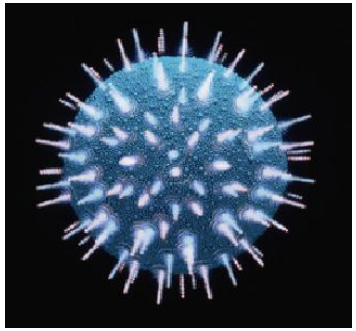
INFECTION

INFECTION REQUIRES AN INFECTIVE AGENT

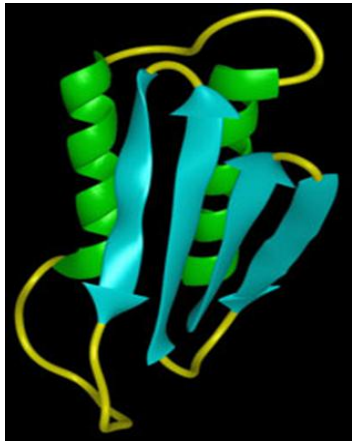


The PRION

INFECTION REQUIRES AN INFECTIVE AGENT

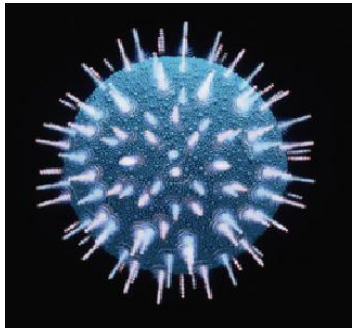


The PRION



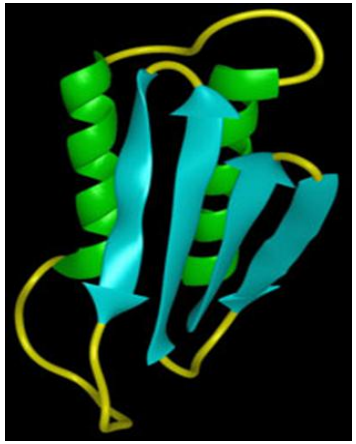
PRECISE NATURE ?
PROTEIN-ONLY ?

DETECTING INFECTIVITY
WHAT ARE WE DETECTING & HOW ?



The PRION

ANIMAL TRANSMISSION EXPERIMENTS



PrP^{Sc} PrP^{RES}

SCRAPIE

TME

CWD

PRION DISEASES ANIMALS

BSE

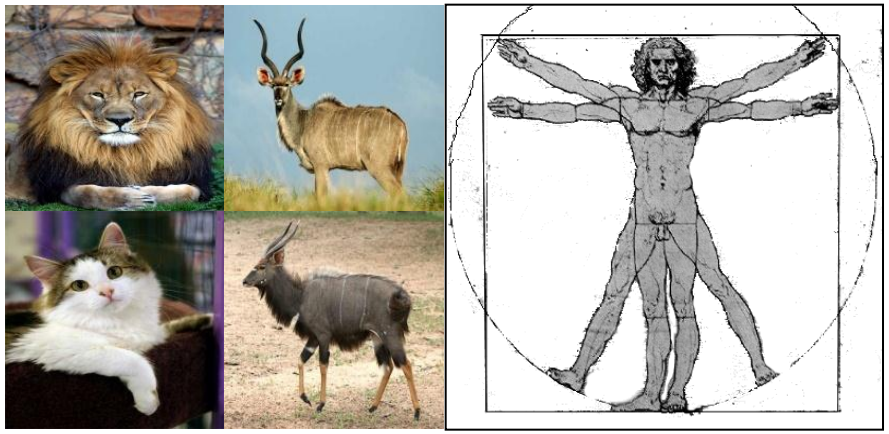
SCRAPIE

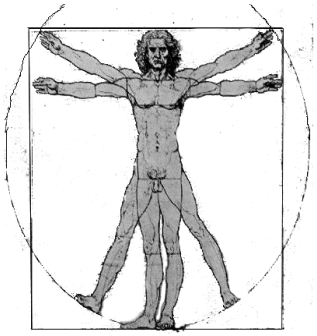
TME

CWD

PRION DISEASES ANIMALS

BSE

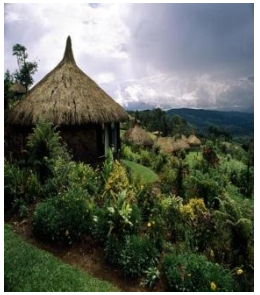




HUMAN PRION DISEASE

RARE:

1-2 deaths/million/year



IDIOPATHIC

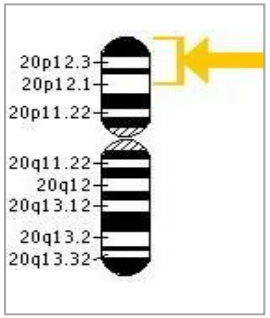
- SPORADIC CJD

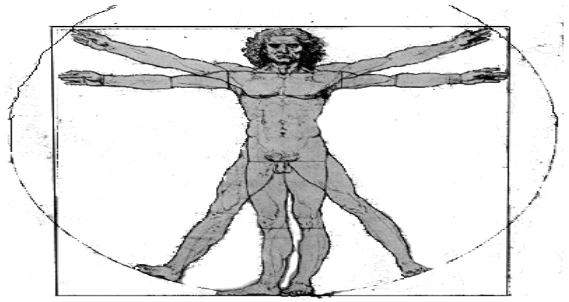
ACQUIRED

- KURU
- IATROGENIC CJD
- VARIANT CJD

GENETIC

- DIFFERENT *PRNP* MUTATIONS

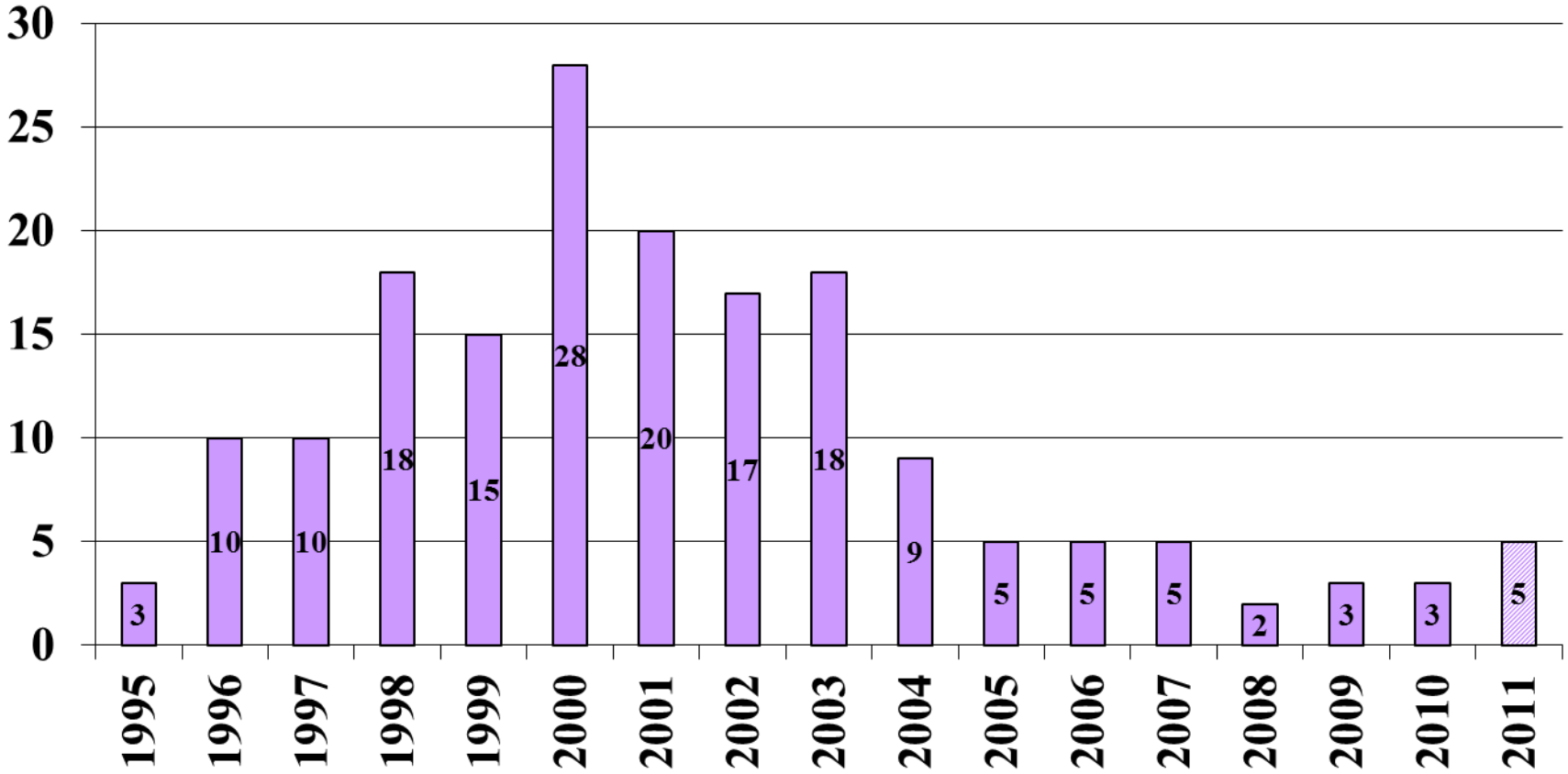




VARIANT CJD: ORIGIN

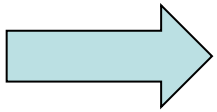
ACQUIRED
ZOONOTIC
PRION DISEASE

NUMBER OF DEATHS PER ANNUM OF vCJD IN THE UK



PRIOR TO 1989

460,000-482,000
BSE CATTLE



Valleron et al Science 2001

PRIOR TO 1989

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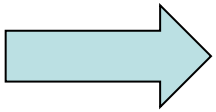
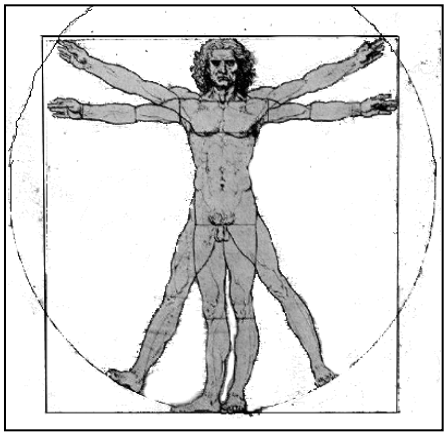
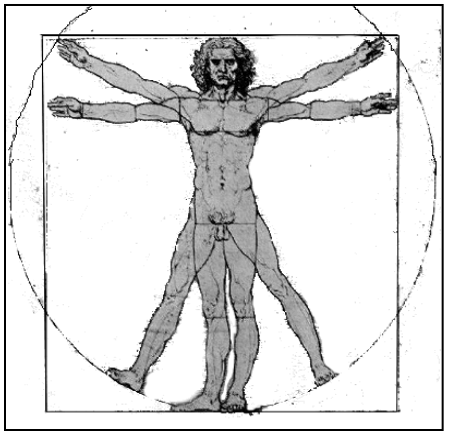


Valleron et al Science 2001

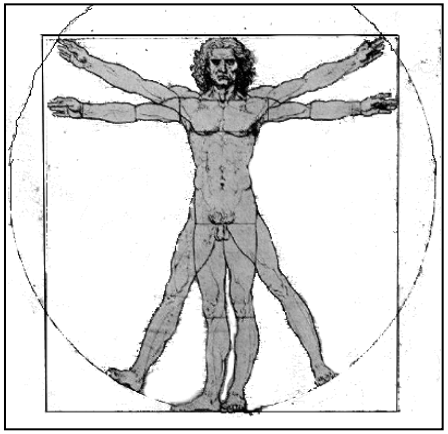


176
vCJD

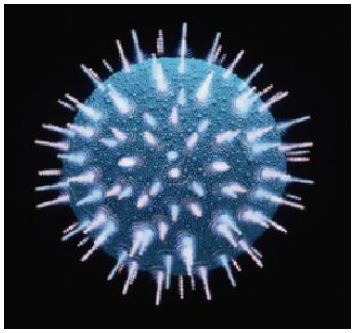


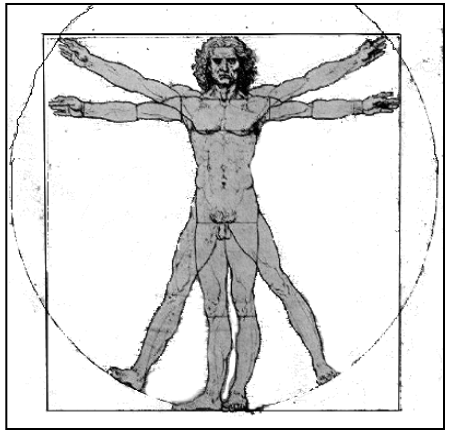
WHY SO FEW CASES ?

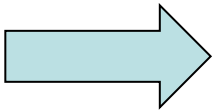
THE SPECIES BARRIER

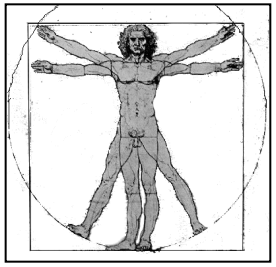


EXPOSURE TO INFECTION

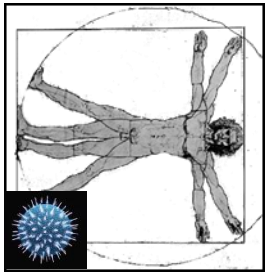




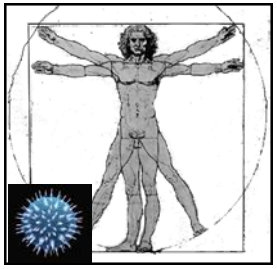




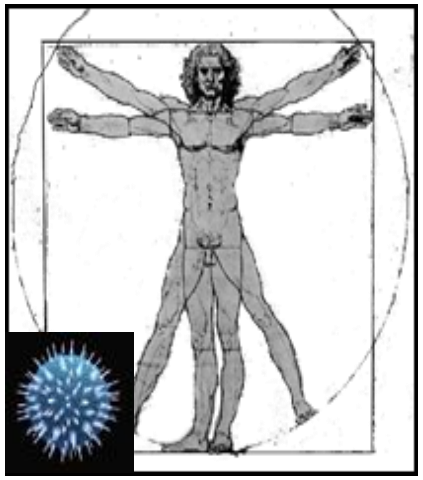
NOT INFECTED



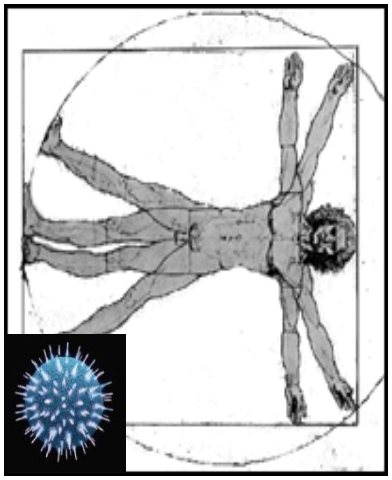
CLINICALLY INFECTED



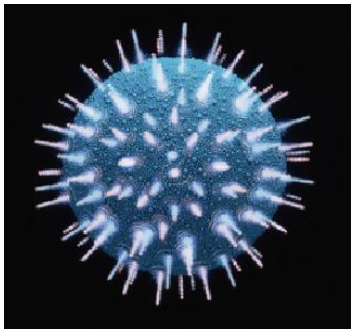
SUB CLINICALLY INFECTED

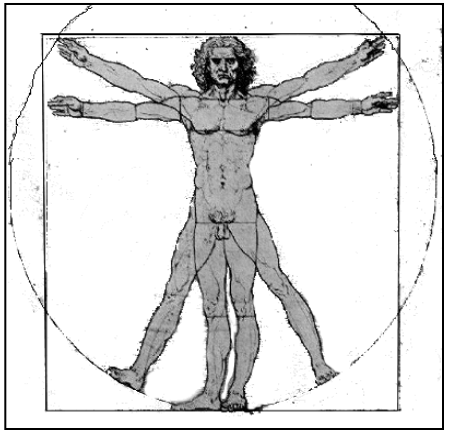


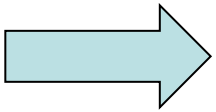
INCUBATION PERIOD

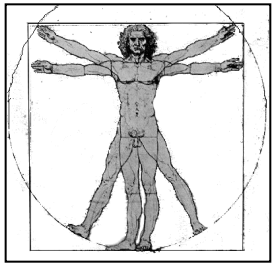


BSE EXPOSURE









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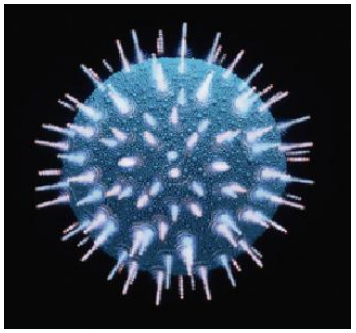
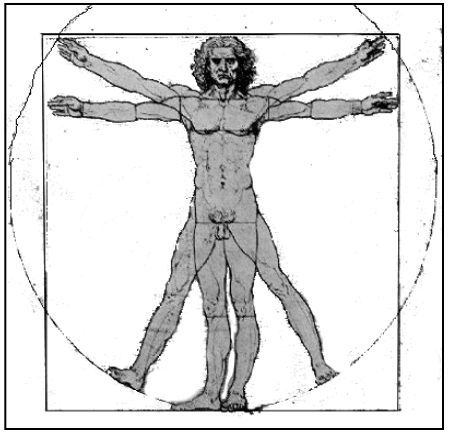
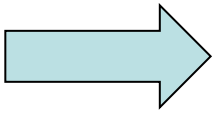
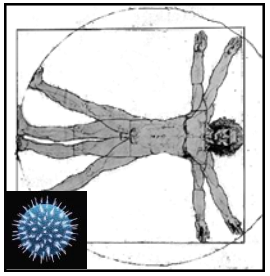








CLINICALLY INFECTED

January						
S	M	T	W	T	F	S
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

February						
S	M	T	W	T	F	S
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

March						
S	M	T	W	T	F	S
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30

April						
S	M	T	W	T	F	S
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

May						
S	M	T	W	T	F	S
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

June						
S	M	T	W	T	F	S
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30

July						
S	M	T	W	T	F	S
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

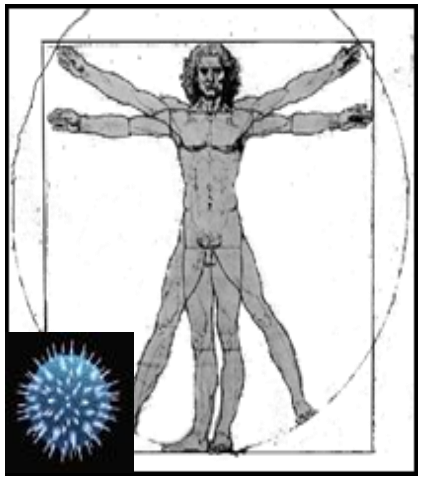
August						
S	M	T	W	T	F	S
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

September						
S	M	T	W	T	F	S
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30

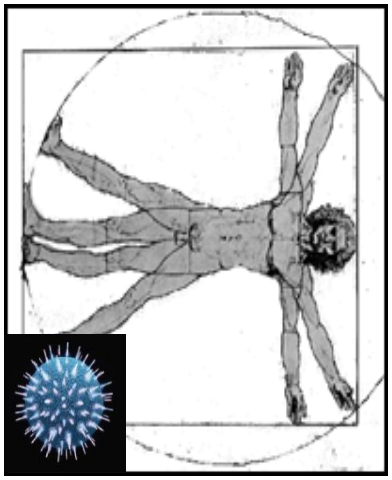
October						
S	M	T	W	T	F	S
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

November						
S	M	T	W	T	F	S
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

December						
S	M	T	W	T	F	S
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30



INCUBATION PERIOD



DO WE KNOW

WHAT DETERMINES

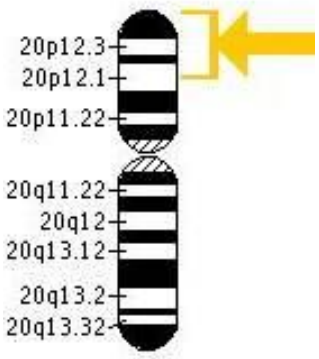
OVERALL SUSCEPTIBILITY
OR
INCUBATION PERIOD ?

DO WE KNOW

WHAT DETERMINES

OVERALL SUSCEPTIBILITY
OR
INCUBATION PERIOD ?

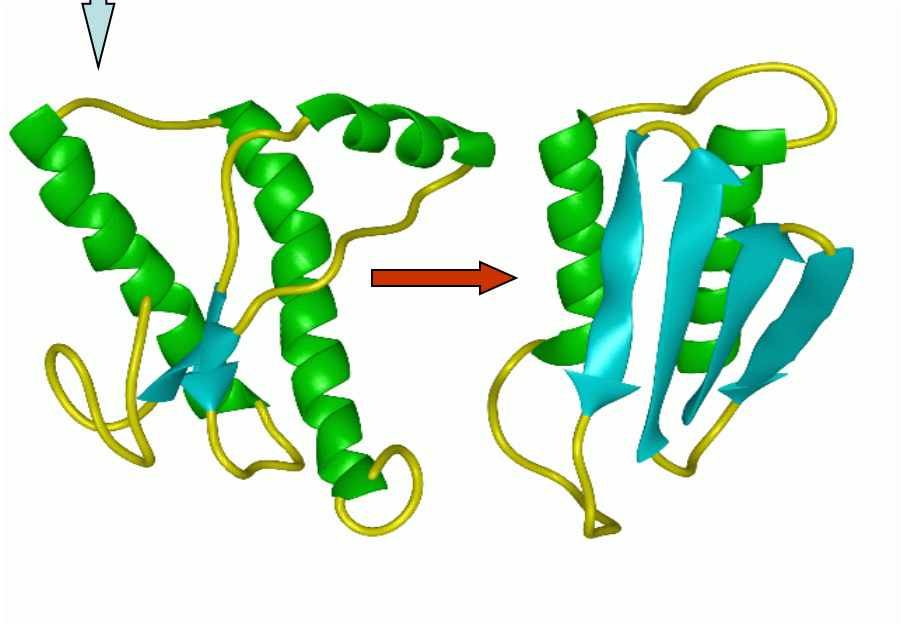
WE KNOW AT LEAST ONE MAJOR FACTOR

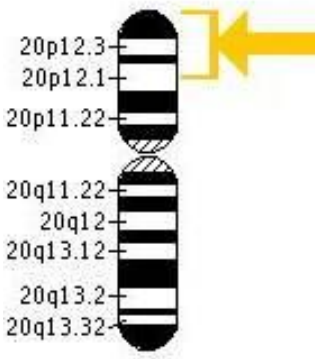


PRNP:

CODON 129 M/V POLYMORPHISM

PrP^C



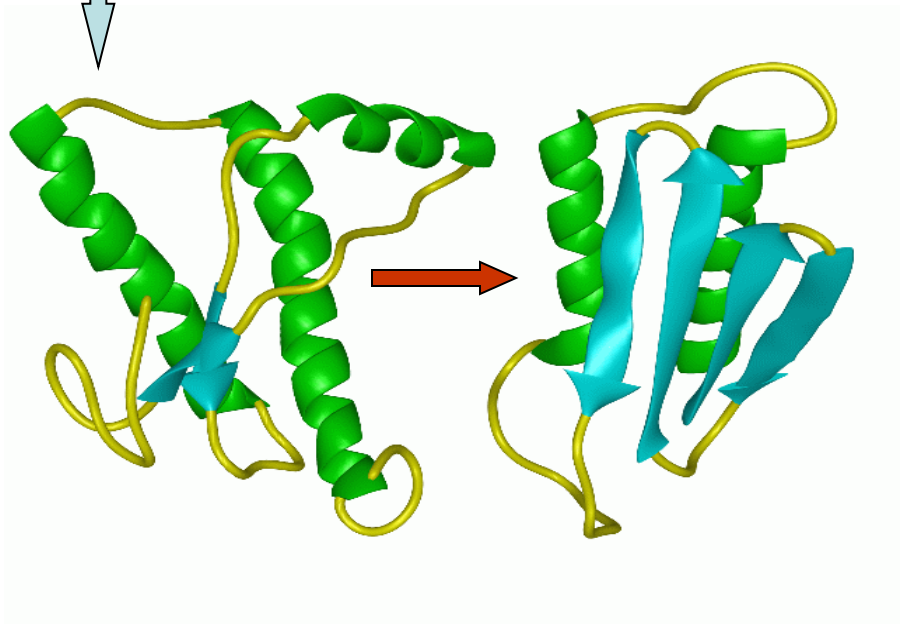


PRNP:

CODON 129 M/V POLYMORPHISM

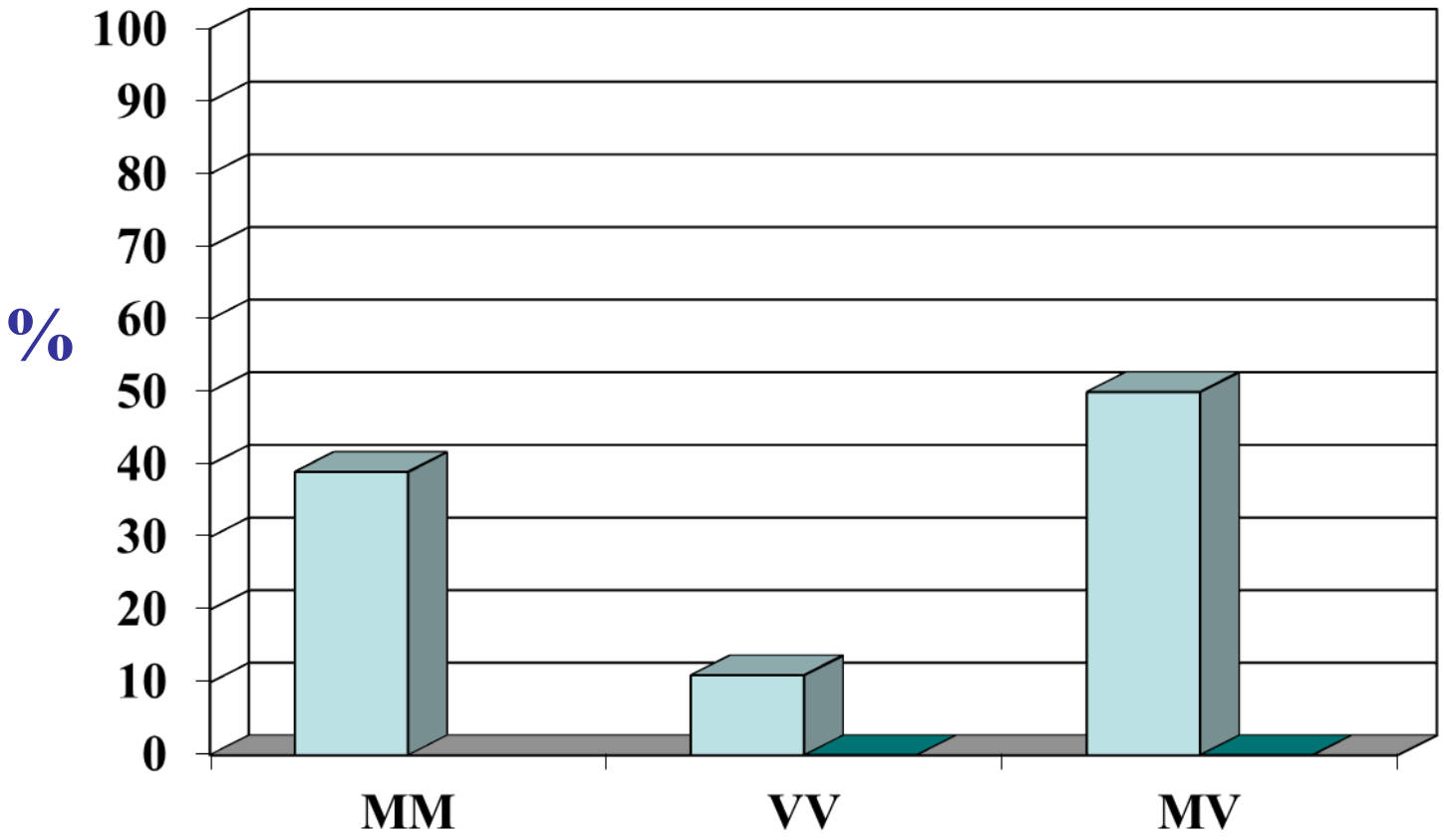
- SUSCEPTIBILITY
- INCUBATION PERIOD

PrP^C



CODON 129 POLYMORPHISM

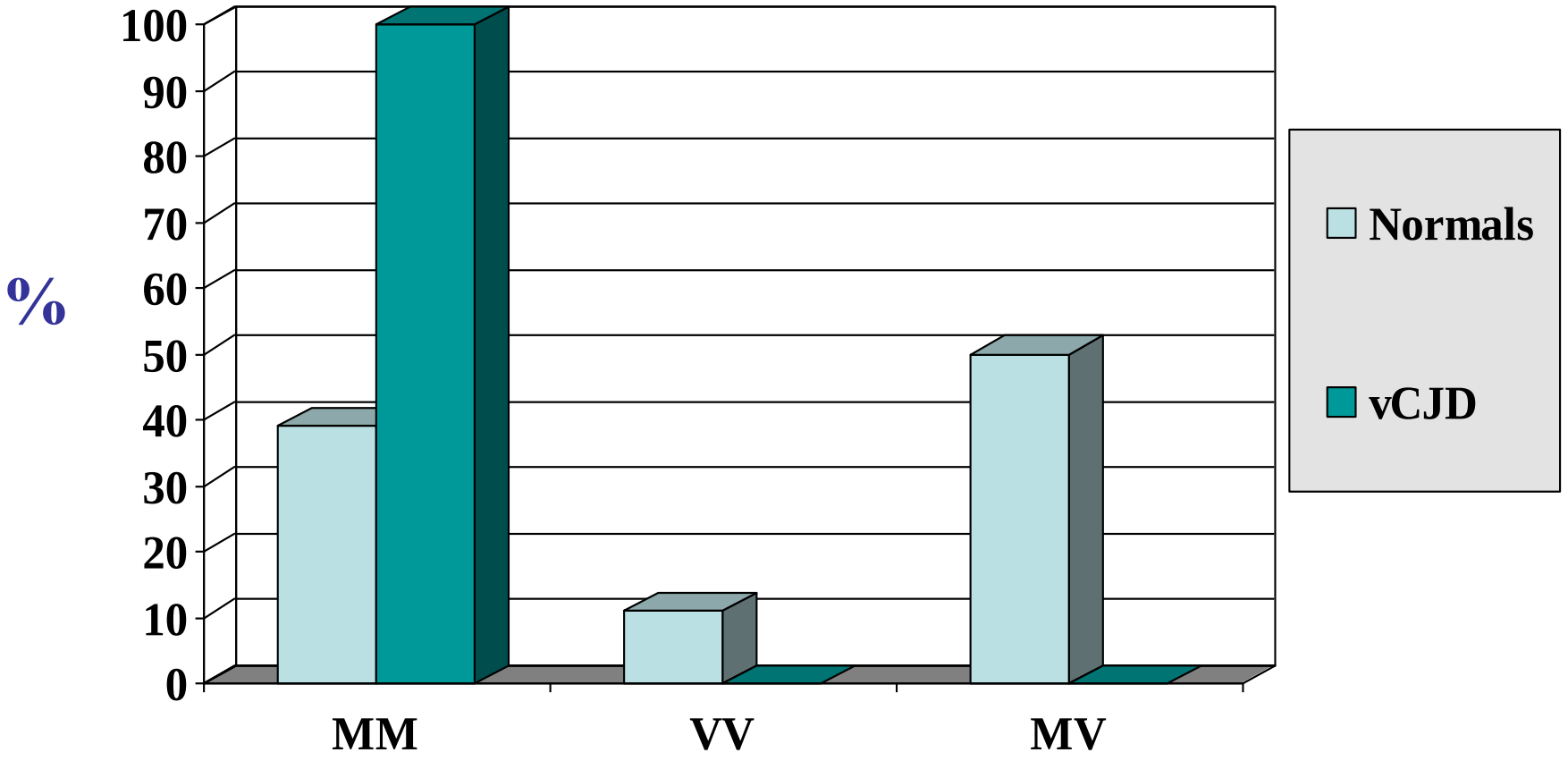
Normal Population



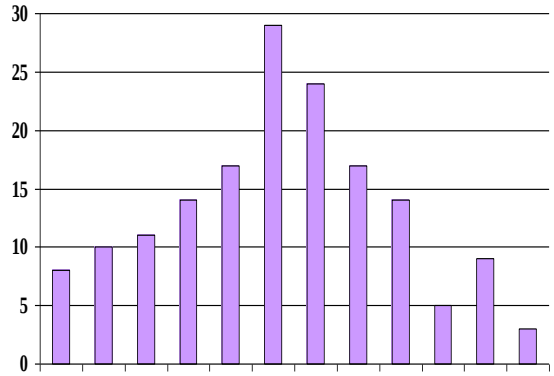
CODON 129 POLYMORPHISM

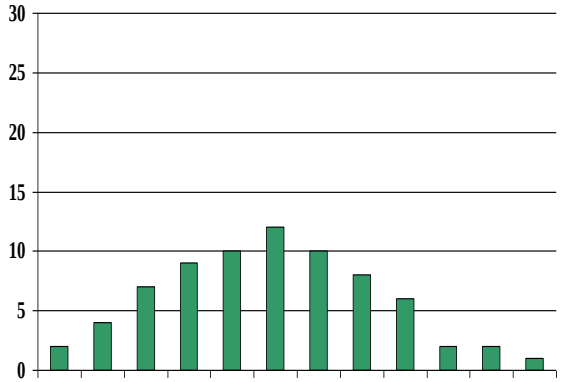
Normal Population & vCJD (Def & Prob)

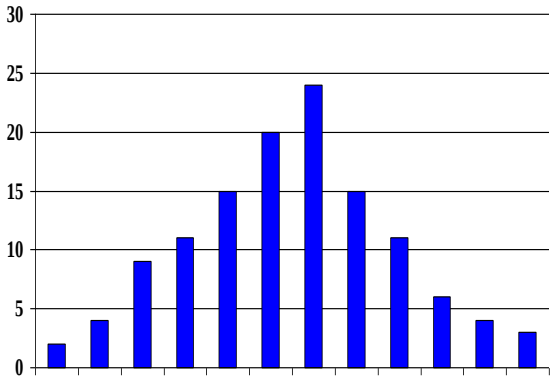
1996-2012



VARIANT CJD
OTHER *PRNP*-129 GENOTYPES
LONGER INCUBATION PERIODS

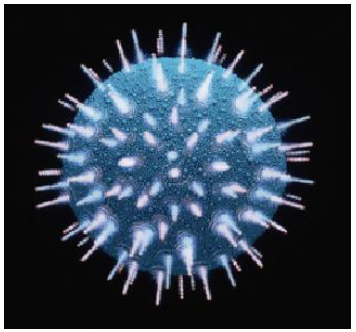


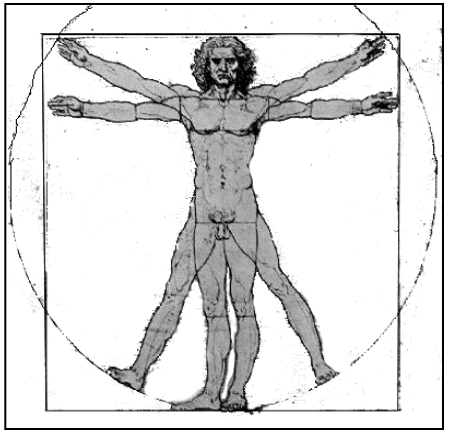


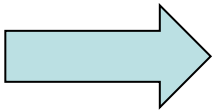


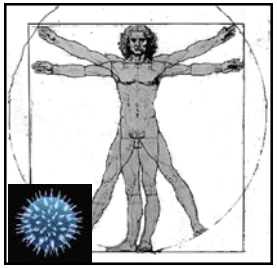
MM VV MV

time





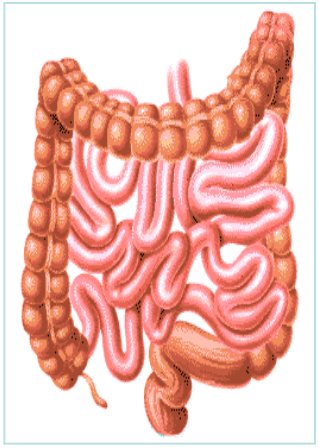


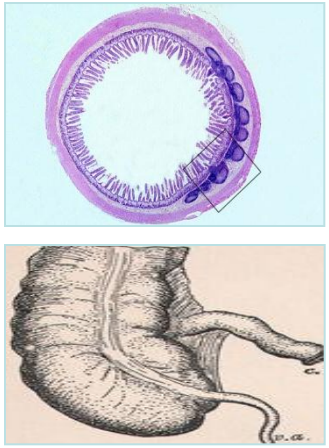


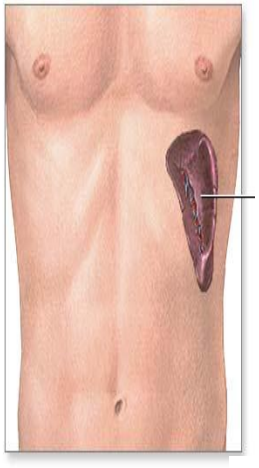
SUB CLINICALLY INFECTED

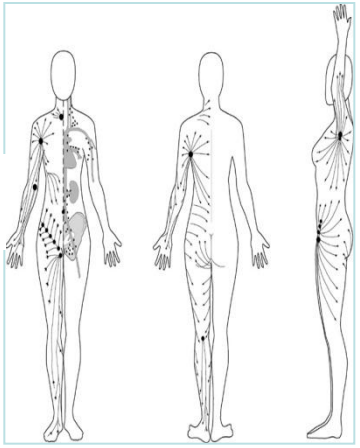
VARIANT CJD: *DISEASE* CONFINED TO BRAIN

PrP^{Sc} DEPOSITION (*& INFECTIVITY)*
NOT CONFINED TO BRAIN

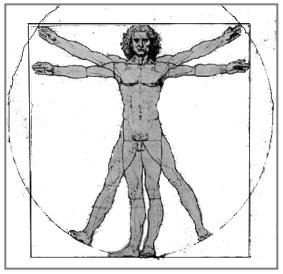




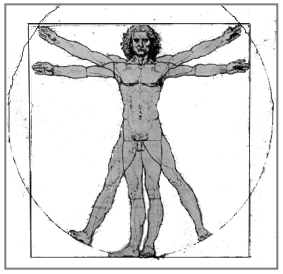


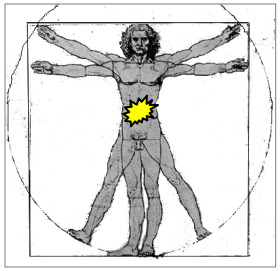


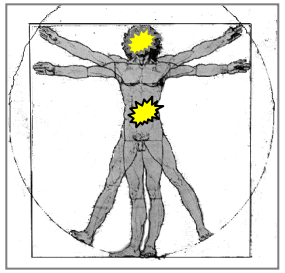
PRESENT UNDERSTANDING



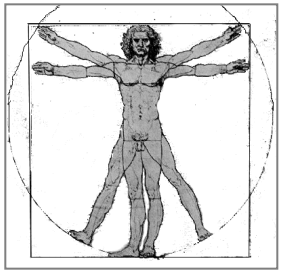
PRESENT UNDERSTANDING

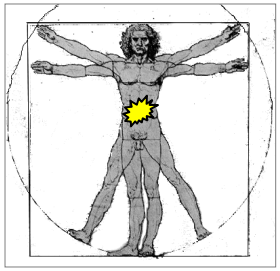


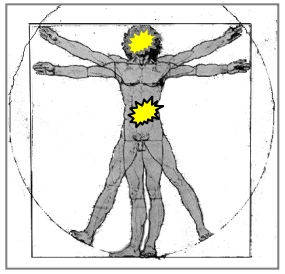


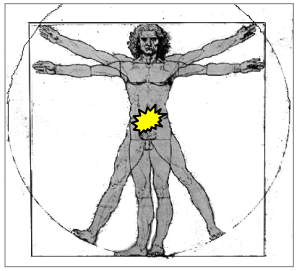


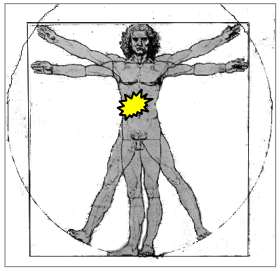
PRESENT UNDERSTANDING



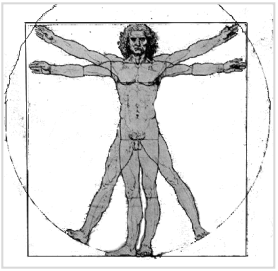


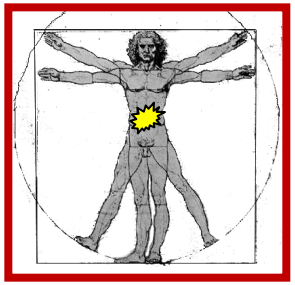


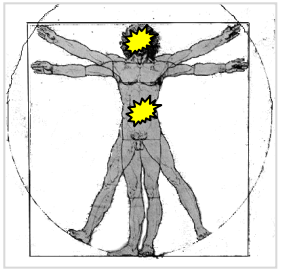


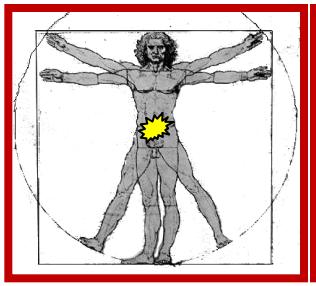


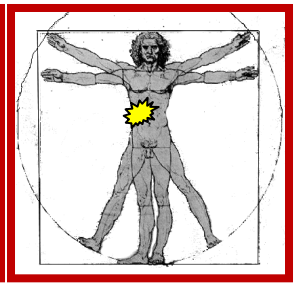
SUB-CLINICAL INFECTION



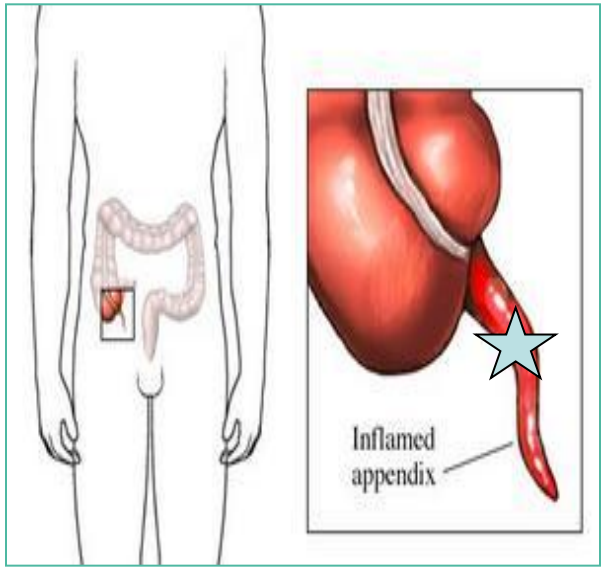






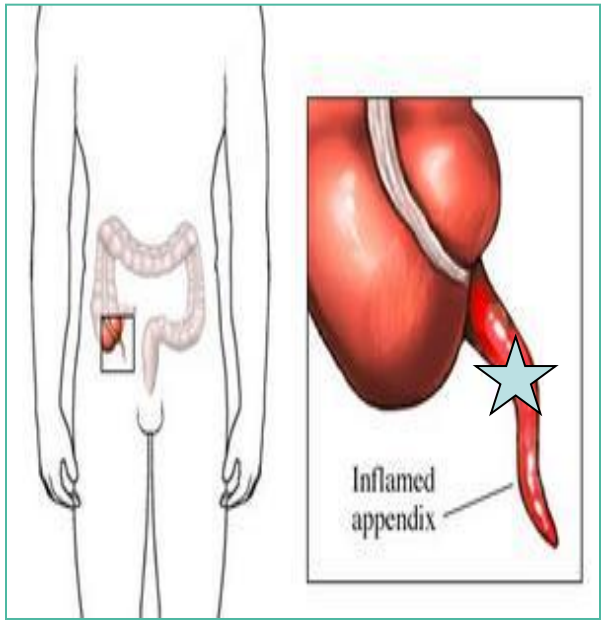


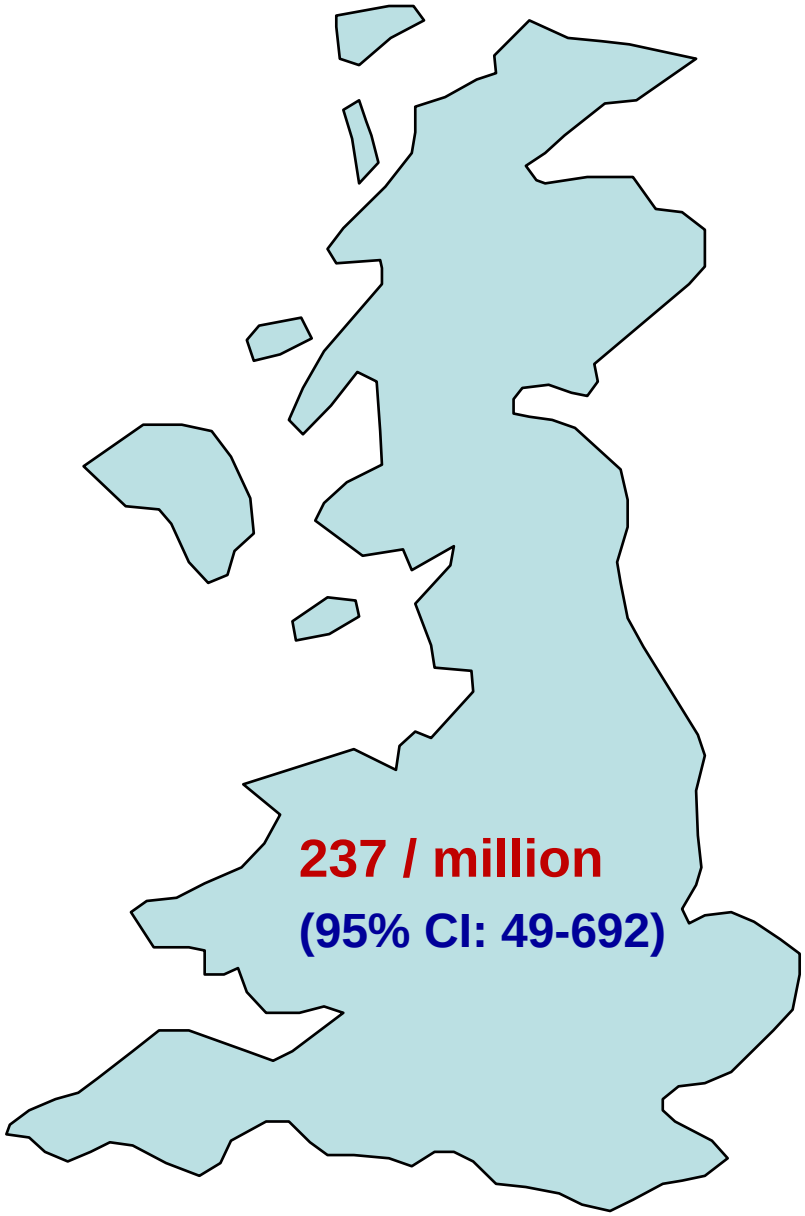
A MEANS OF ESTIMATING SUBCLINICAL INFECTION PREVALACE IN THE POPULATION



ANALYSIS OF ROUTINE SURGICAL SPECIMENS FOR PrP^{RES}

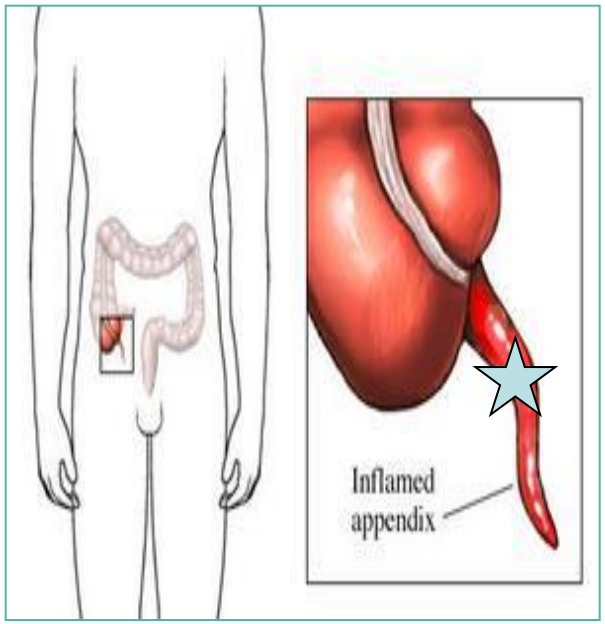
LYMPHORETICULAR SURVEILLANCE IN THE UK
Hilton DA et al J Path 2004

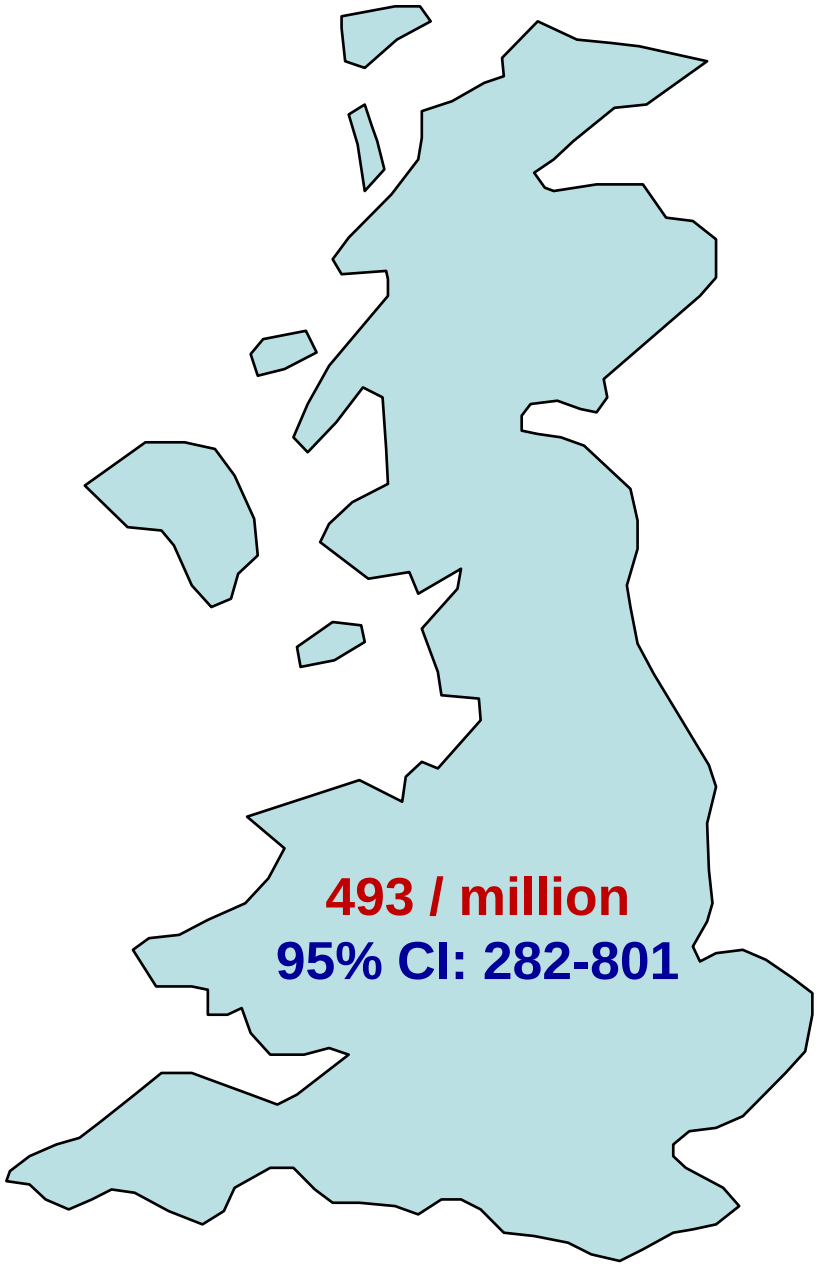




LYMPHORETICULAR SURVEILLANCE IN THE UK

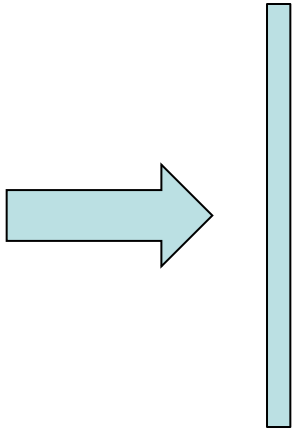
Health Protection Agency

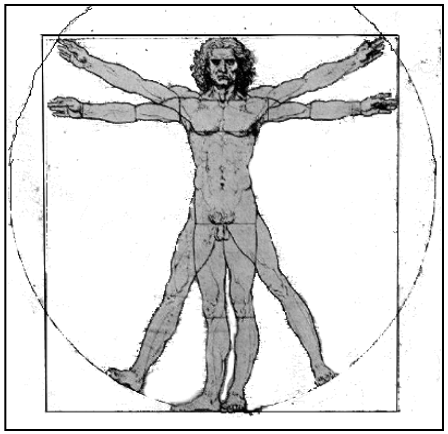




II

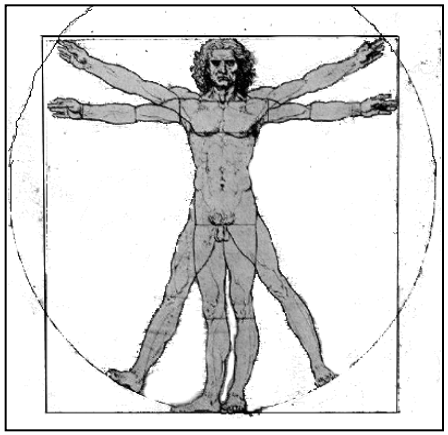
HUMAN TO HUMAN SECONDARY TRANSMISSION

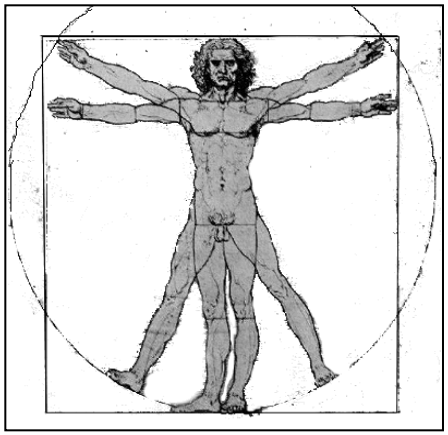




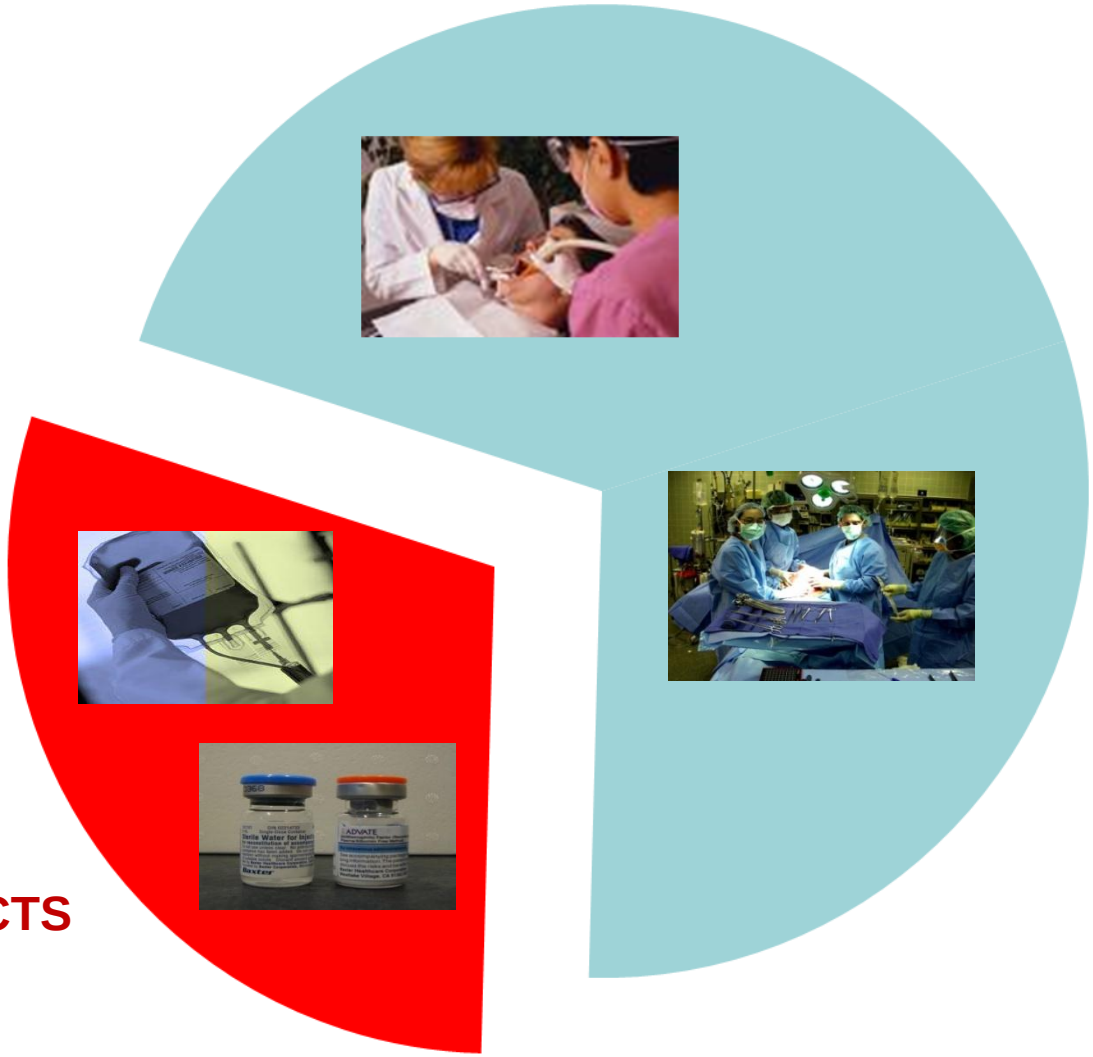
SPECIES BARRIER

SPECIES ADAPTATION





SECONDARY HUMAN-HUMAN TRANSMISSION



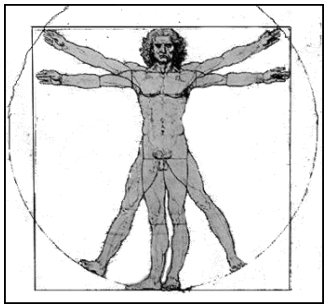
BLOOD
&
BLOOD PRODUCTS

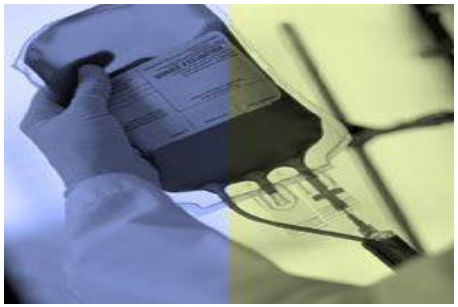
TRANSFUSION MEDICINE EPIDEMIOLOGICAL REVIEW

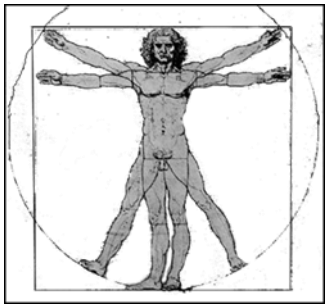
UK NBS & NCJDRSU

UK HAEMOPHILIA STUDY

UK HCDO & NCJDRSU







TMER 1996-2012
ACTUAL CASES

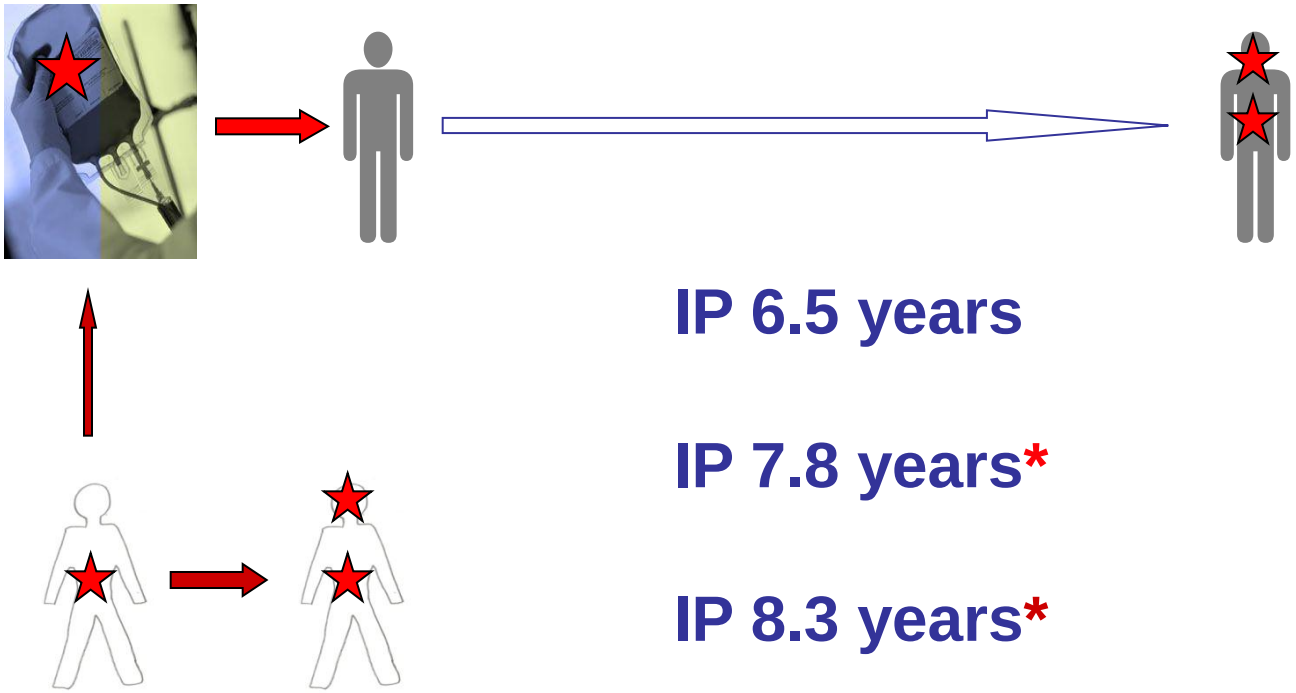
4 INSTANCES
NON-LEUCODEPLETED RBCs: 1996-1999

3 CLINICAL
1 SUBCLINICAL

1 SUBCLINICAL CASE

DIED 5 YEARS
NON-NEUROLOGICAL DISEASE

3 CLINICAL CASES



IP 6.5 years

IP 7.8 years*

IP 8.3 years*

*** SAME DONOR**

THE DONORS:
TIME OF DONATION BEFORE vCJD ONSET

17 MONTHS*

18 MONTHS

21 MONTHS*

3.5 YEARS

*** SAME DONOR**

THE DONORS:
TIME OF DONATION BEFORE vCJD ONSET

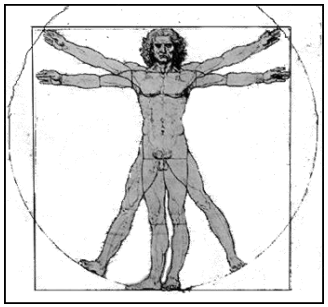
17 MONTHS

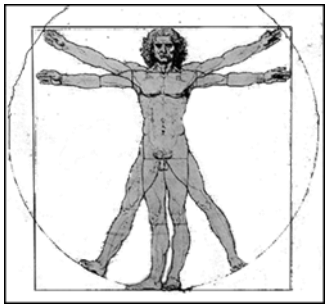
18 MONTHS

21 MONTHS

3.5 YEARS

BLOOD INFECTIVITY PRESENT
AT LEAST 3.5 YEARS
BEFORE ANY CLINICAL SIGN OF DISEASE





UK HAEMOPHILIA STUDY

ACTUAL CASES

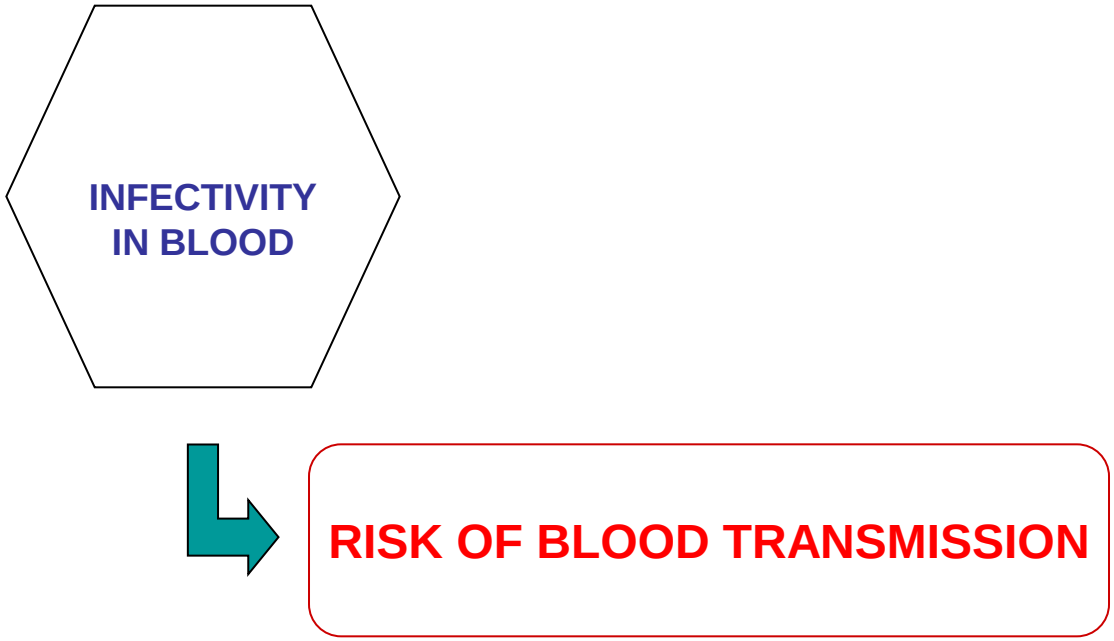
1 INSTANCE
FACTOR VIII

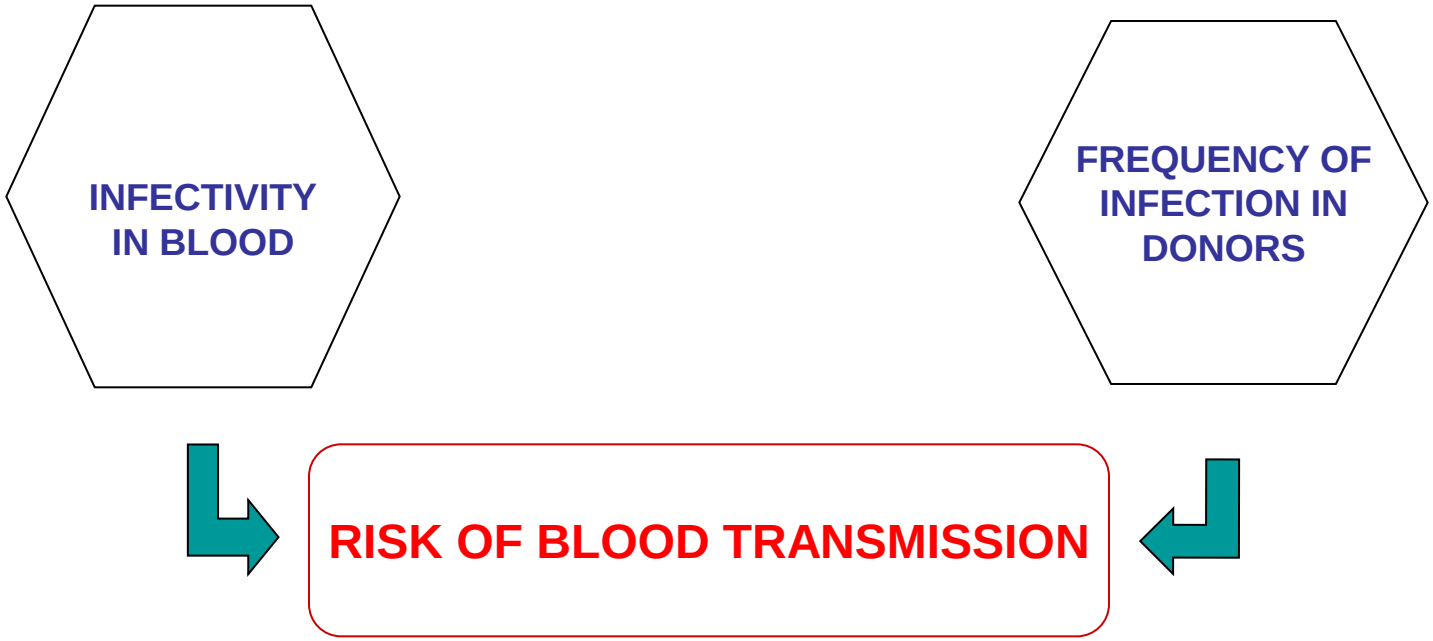
SUBCLINICAL

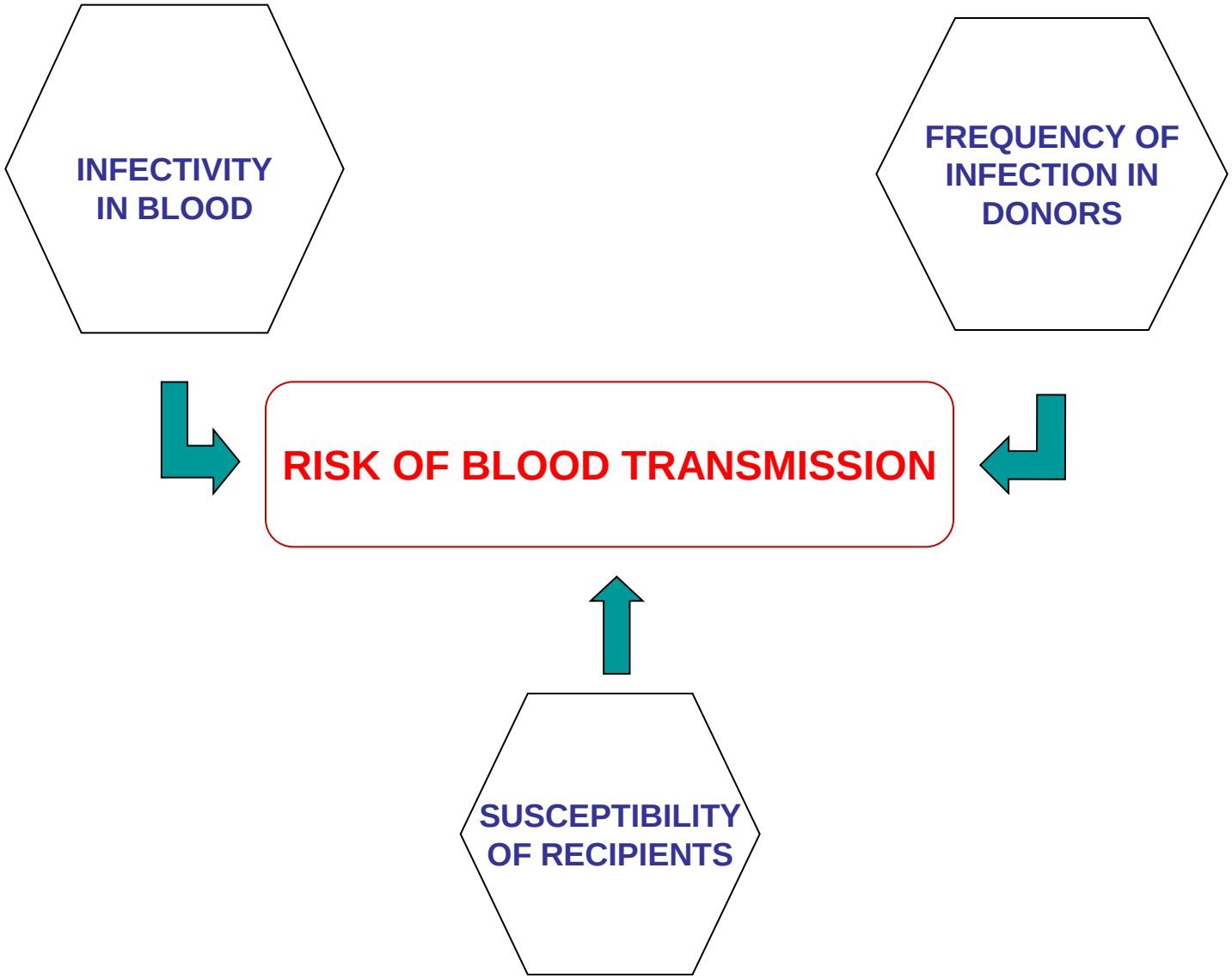
III

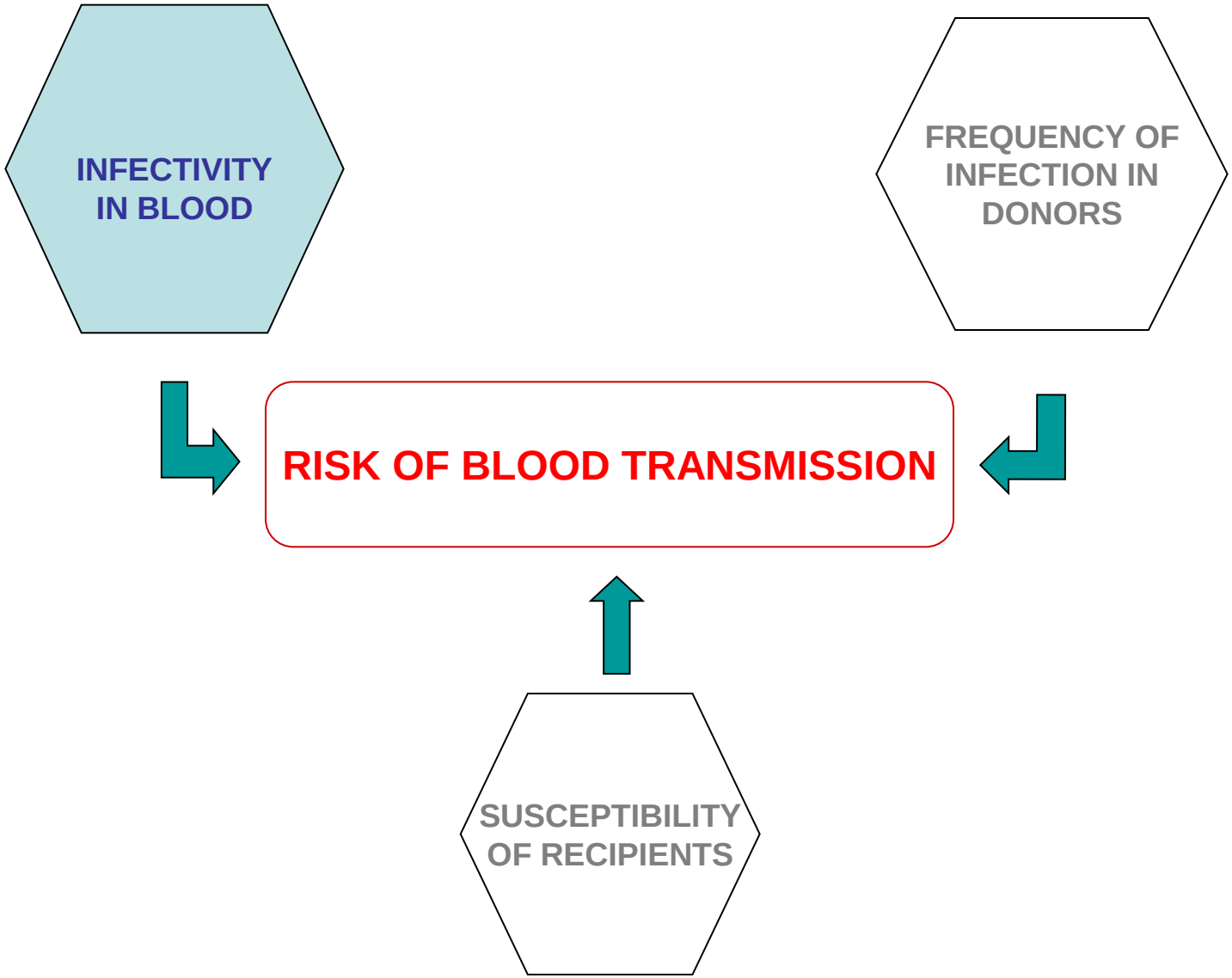
ASPECTS OF INFECTION & TRANSMISSION

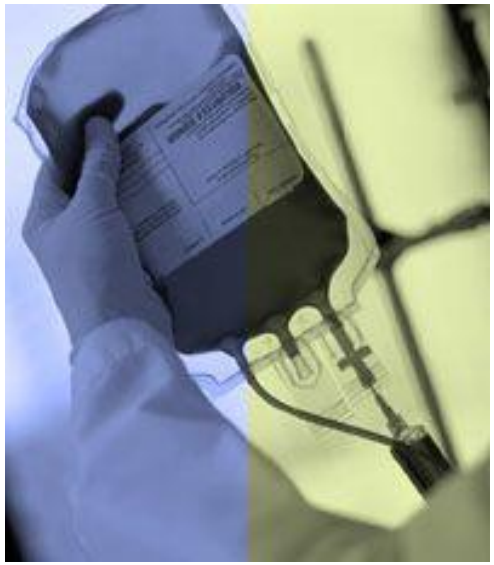
RISK OF BLOOD TRANSMISSION

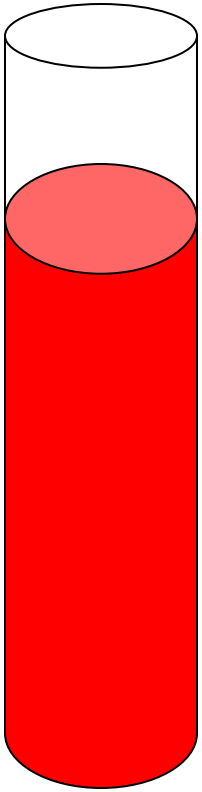

INFECTIVITY
IN BLOOD
RISK OF BLOOD TRANSMISSION


INFECTIVITY IN BLOOD
FREQUENCY OF INFECTION IN DONORS
RISK OF BLOOD TRANSMISSION


INFECTIVITY IN BLOOD
FREQUENCY OF INFECTION IN DONORS
RISK OF BLOOD TRANSMISSION
SUSCEPTIBILITY OF RECIPIENTS


INFECTIVITY IN BLOOD
FREQUENCY OF INFECTION IN DONORS
RISK OF BLOOD TRANSMISSION
SUSCEPTIBILITY OF RECIPIENTS

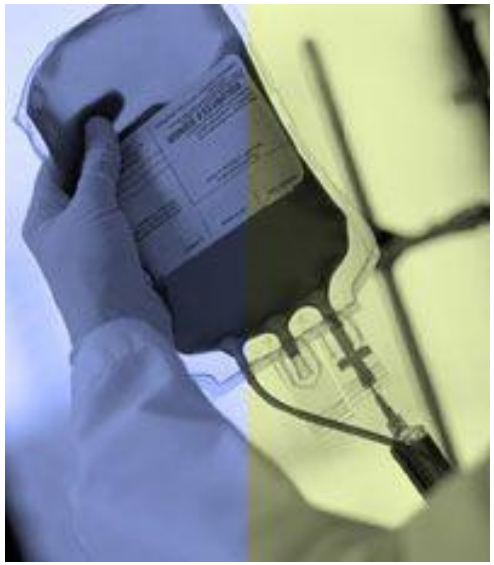


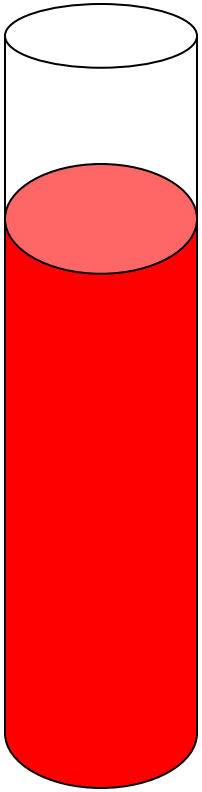


VARIANT CJD INFECTIVITY IN BLOOD

EXISTS

BUT WITH IMPORTANT UNCERTAINTIES





VARIANT CJD INFECTIVITY IN BLOOD

EXISTS

BUT WITH IMPORTANT UNCERTAINTIES

MANY STUDIES:

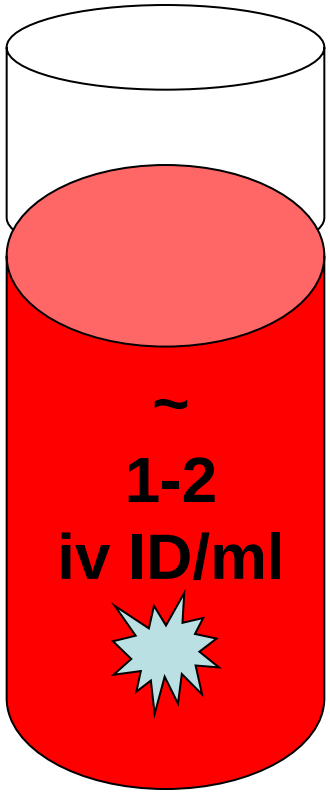
LABORATORY

ANIMAL

NOT vCJD

EXACT LEVEL OF INFECTIVITY IN *HUMAN vCJD* BLOOD UNCERTAIN

PREVIOUS ESTIMATES BASED ON ANIMAL TSE EXPERIMENTS:



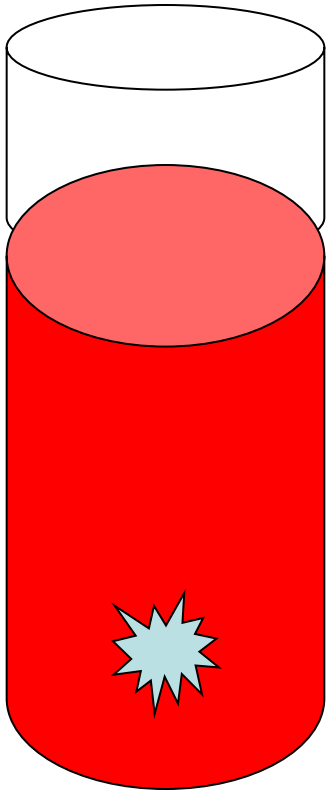
450 ml WB

450-900 iv ID

Hamster & Mouse: Brown et al 1998, 1999; Cervenakova et al 2003; Gregori et al 2004

EXACT LEVEL OF INFECTIVITY IN *HUMAN vCJD* BLOOD UNCERTAIN

CURRENT ESTIMATES
BASED ON
SHEEP TSE EXPERIMENTS
&
HUMAN CASE REPORTS:



450 ml WB

~1 iv ID per unit

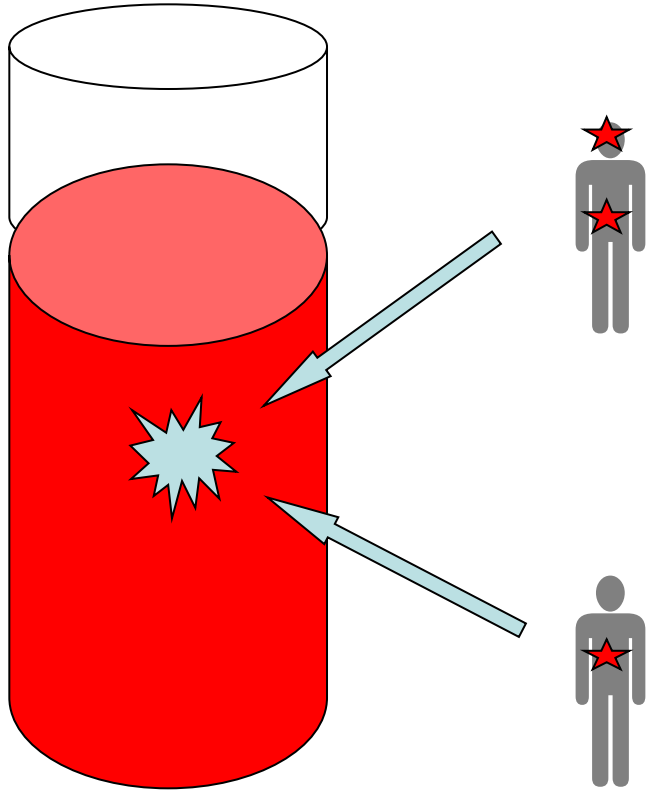
Gregori et al Transfusion 2011 51:2596-2602

EXACT TIMING OF INFECTIVITY IN *HUMAN vCJD* BLOOD UNCERTAIN

ANIMAL EXPERIMENTS
&
HUMAN CASE DATA:

PRESENT *BOTH*

IN CLINICAL ILLNESS
&
AT LEAST PART OF PRECLINICAL PHASE



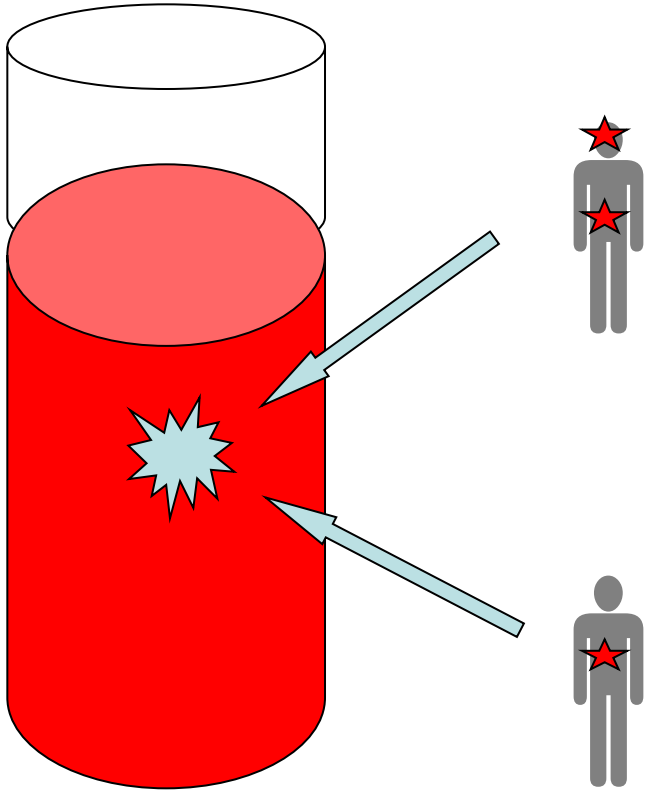
EXACT TIMING OF INFECTIVITY IN *HUMAN vCJD* BLOOD UNCERTAIN

ANIMAL EXPERIMENTS
&
HUMAN CASE DATA:

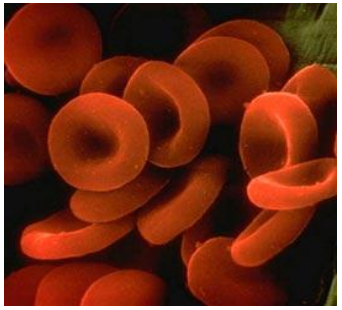
PRESENT *BOTH*

IN CLINICAL ILLNESS
&
AT LEAST PART OF PRECLINICAL PHASE

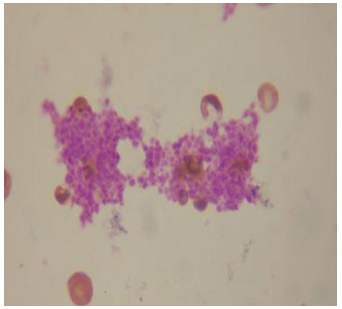
BUT HOW CONSISTENTLY ?

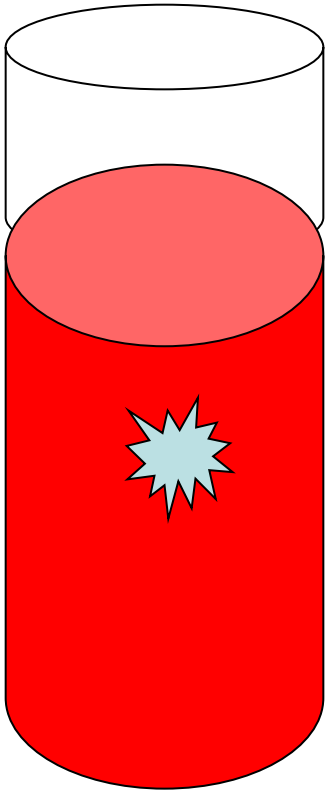


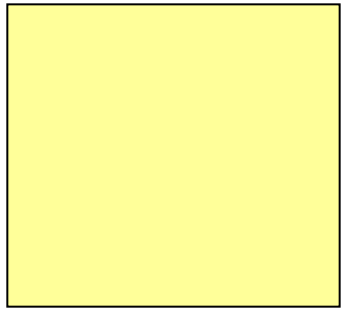
DISTRIBUTION OF INFECTIVITY IN *HUMAN vCJD* BLOOD SOMEWHAT UNCERTAIN



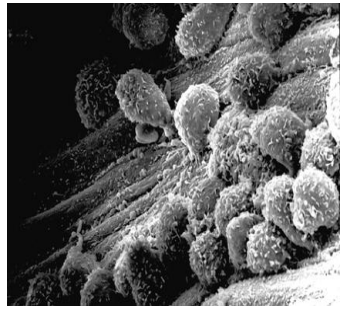
RBCs
&
PLATELETS





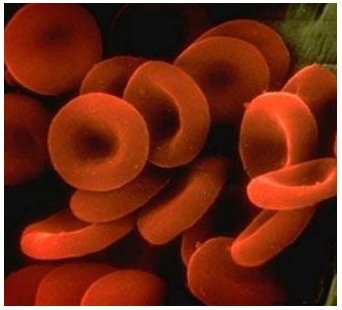


PLASMA

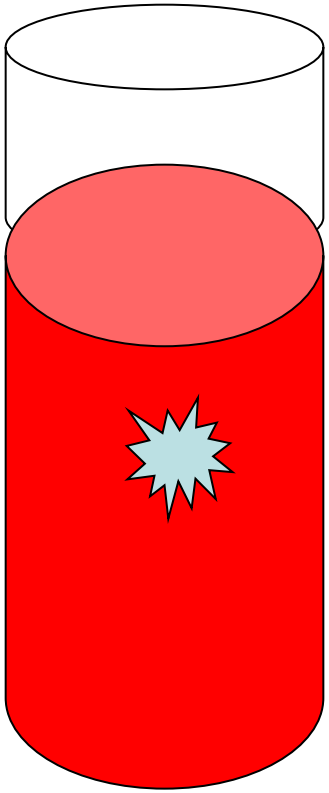


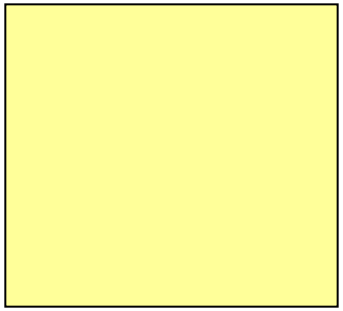
WBCs

DISTRIBUTION OF INFECTIVITY IN *HUMAN vCJD* BLOOD SOMEWHAT UNCERTAIN

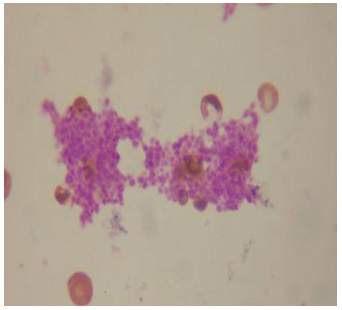


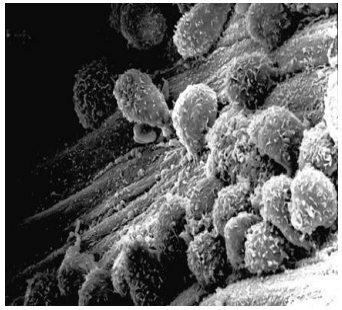
RBCs*
&
PLATELETS*





PLASMA ~50%



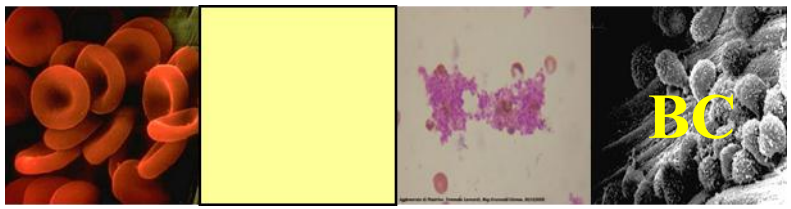


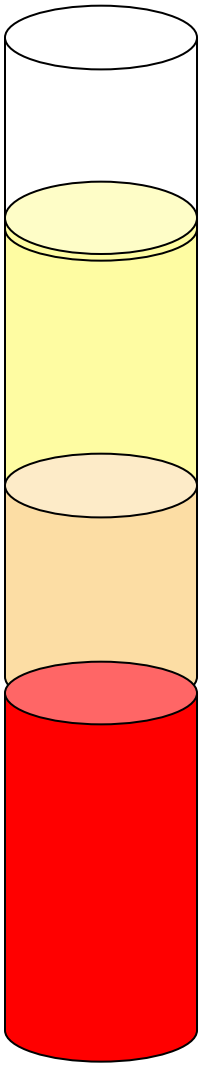
WBCs ~50%

***INFECTIVITY**
ASSOCIATED WITH RESIDUAL PLASMA / WBCs

All Clinically-Relevant Blood Components Transmit Prion Disease following a single Blood Transfusion: A Sheep Model of vCJD

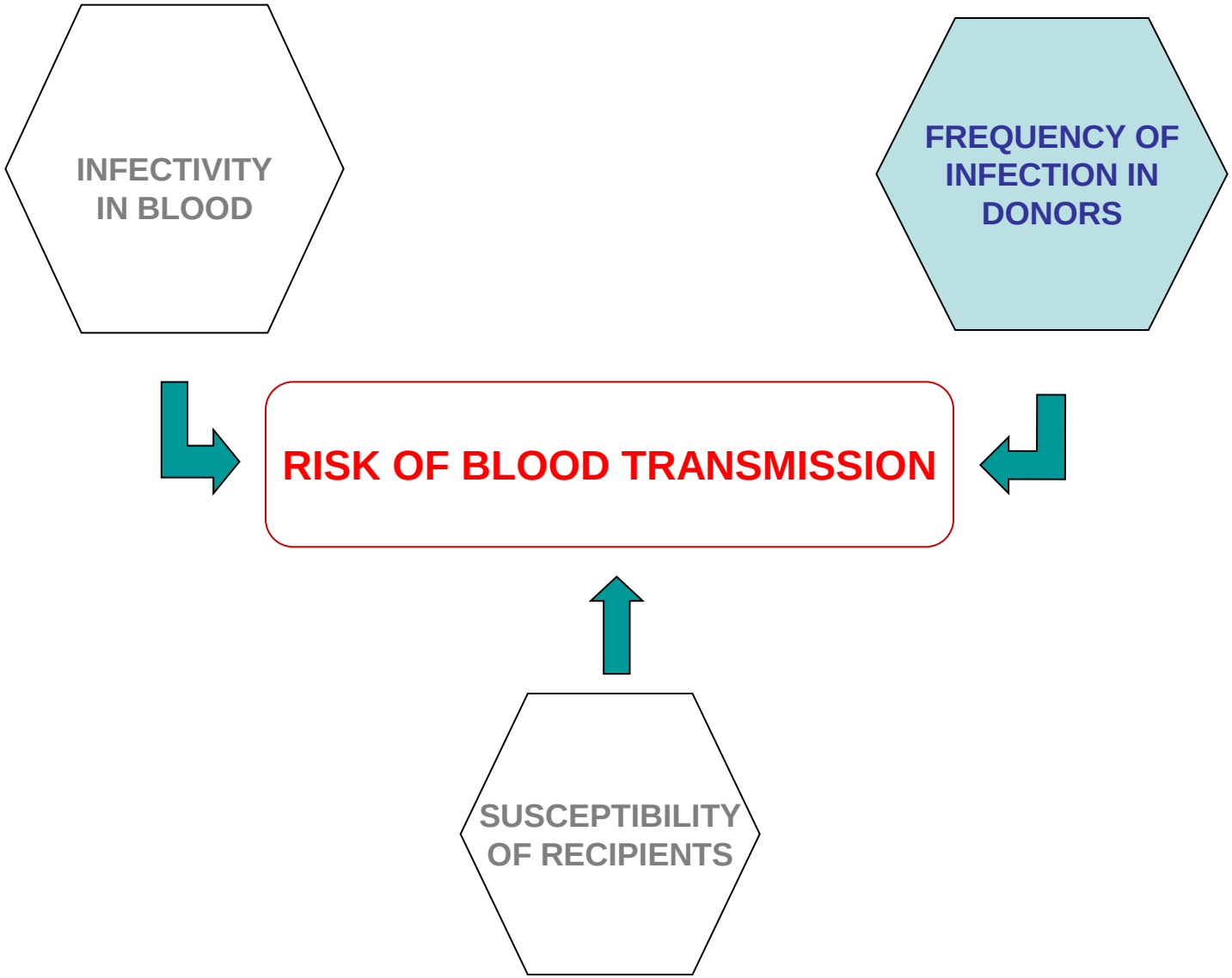
McCutcheon et al PloS ONE 2011 6(8): e23169



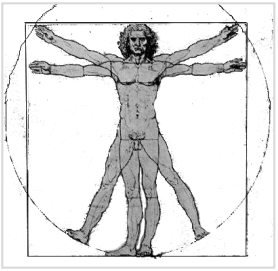


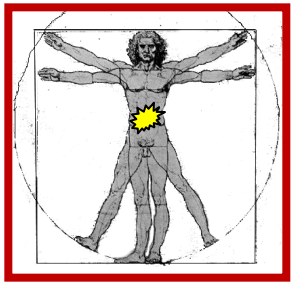
PLASMA: 50%

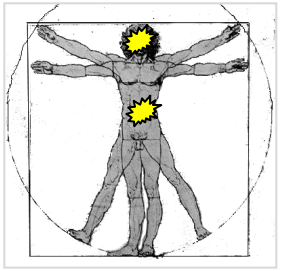
FRACTIONS & PRODUCTS

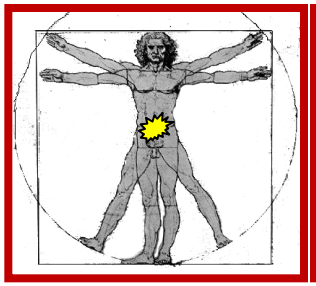

INFECTIVITY IN BLOOD
FREQUENCY OF INFECTION IN DONORS
RISK OF BLOOD TRANSMISSION
SUSCEPTIBILITY OF RECIPIENTS

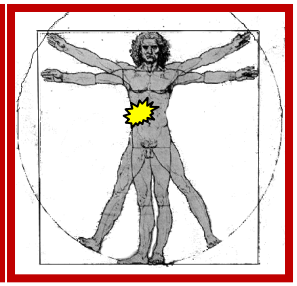
THE DONOR RISK: SUBCLINICAL CASES







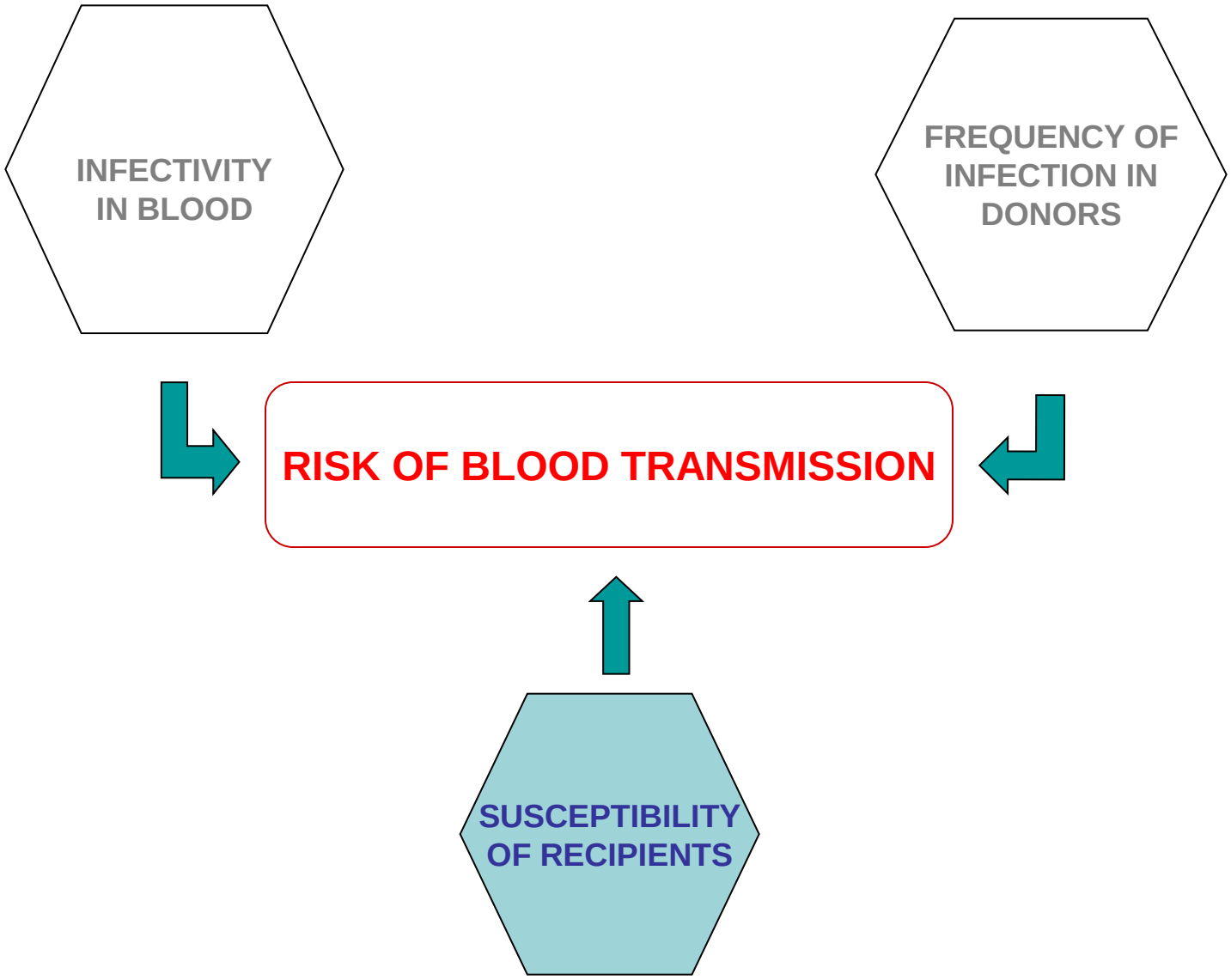




DEFINITE PREVALENCE OF SUBCLINICAL INFECTION IN THE UK
UNKNOWN

CENTRAL FIGURES FOR DONORS INFECTED
Hilton et al: 1:4,000
HPA: 1:2,000

OTHER COUNTRIES ?


INFECTIVITY IN BLOOD
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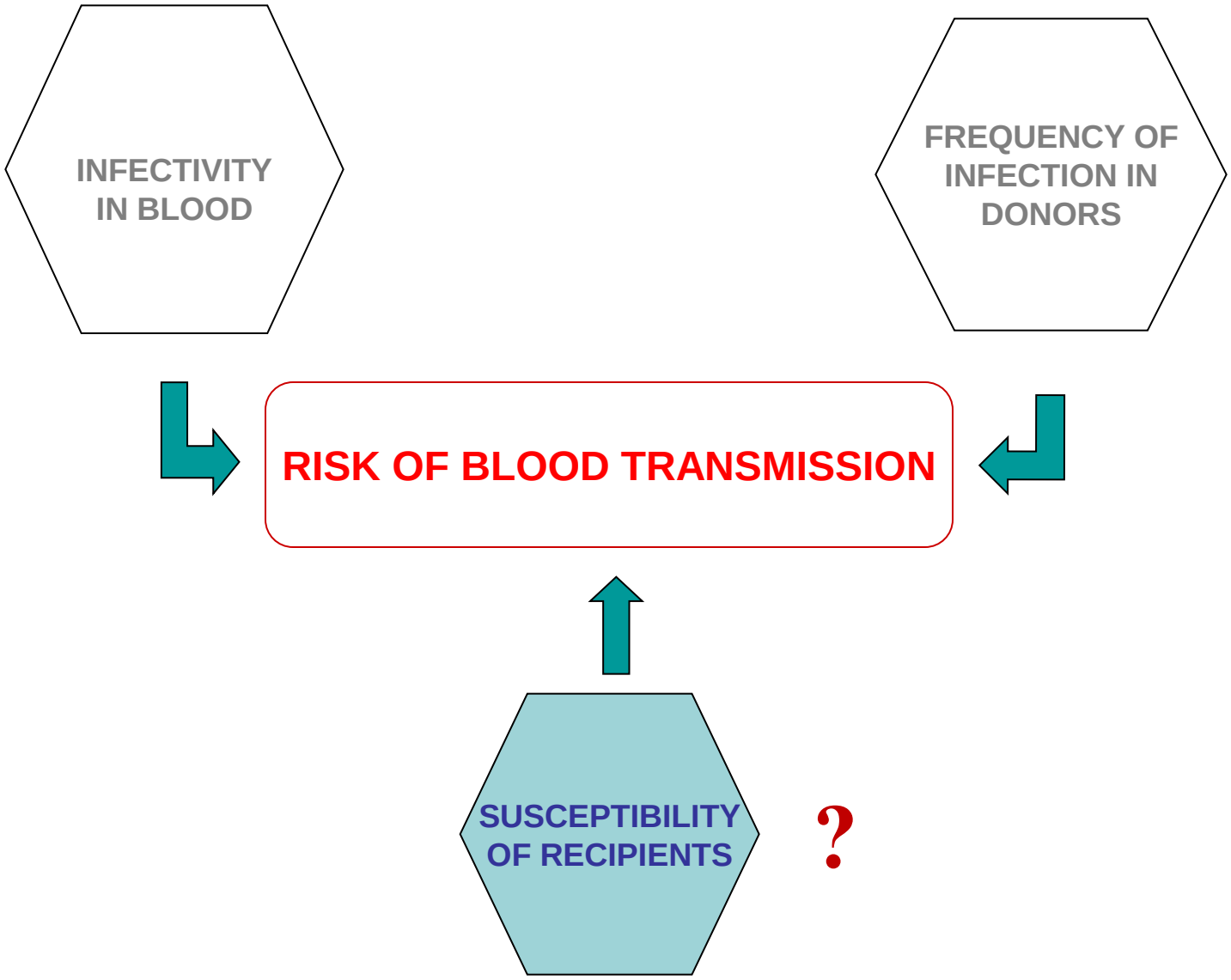

INFECTIVITY IN BLOOD
FREQUENCY OF INFECTION IN DONORS
RISK OF BLOOD TRANSMISSION
SUSCEPTIBILITY OF RECIPIENTS
?

IV

WHAT HAS HAPPENED ?
AND WHY ?

ACTIONS

A VARIETY OF DONOR SELECTION MEASURES

UNIVERSAL LEUCOREDUCTION

[NO BLOOD SCREENING TEST YET]

INFECTIVITY IN PRECLINICAL vCJD BLOOD

TRANSFUSION AN EFFICIENT TRANSMISSION MEANS

SIGNIFICANT NUMBERS OF SUBCLINICAL DONORS

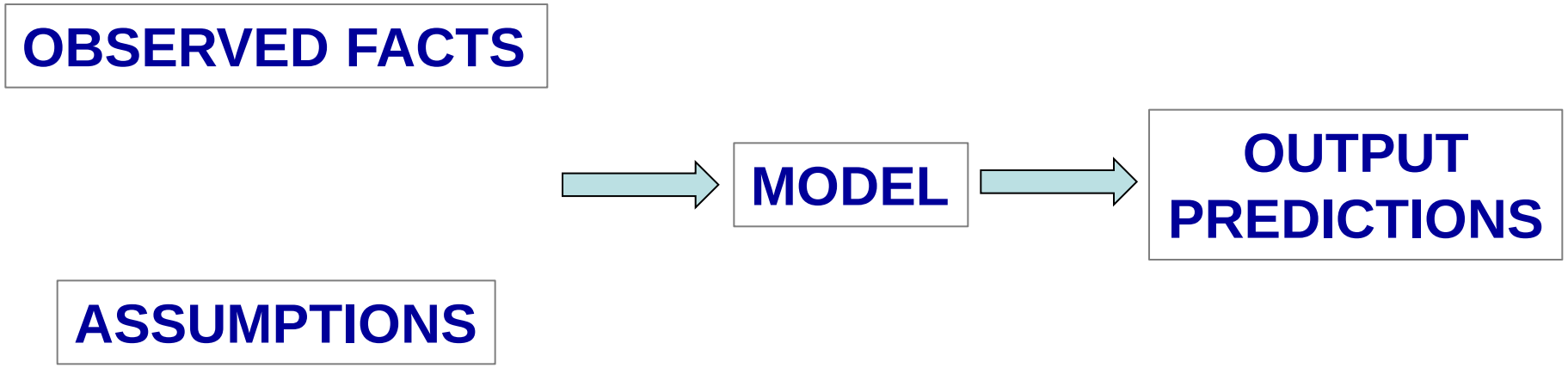
LEUCOREDUCTION NOT TOTALLY EFFECTIVE

YET

ONLY 4 INSTANCES IDENTIFIED
NONE SINCE 1999

MODELLING THE BLOOD PROBLEM

Dr Peter Bennett, Health Protection, DH



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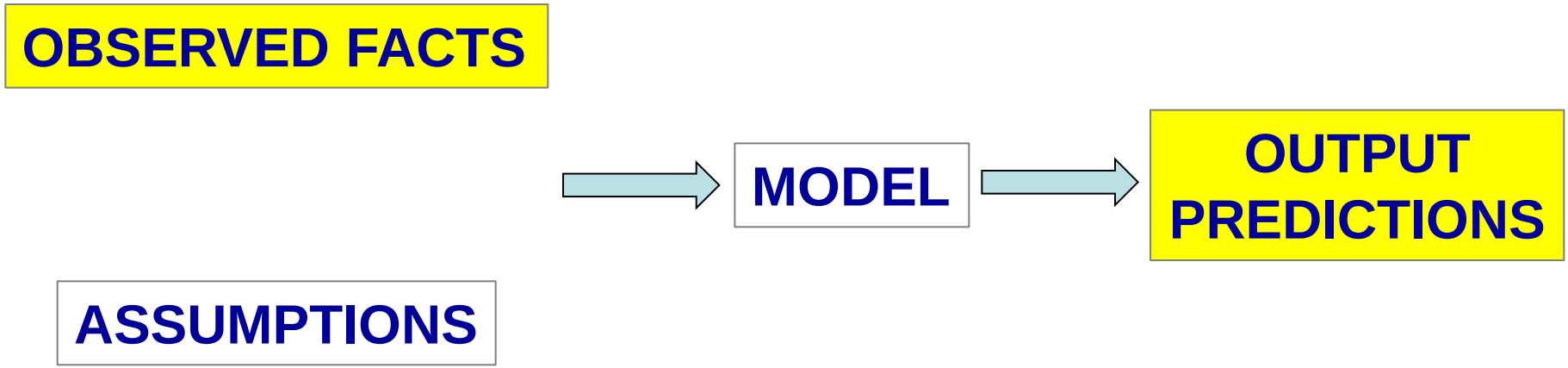

MODELLING THE BLOOD PROBLEM

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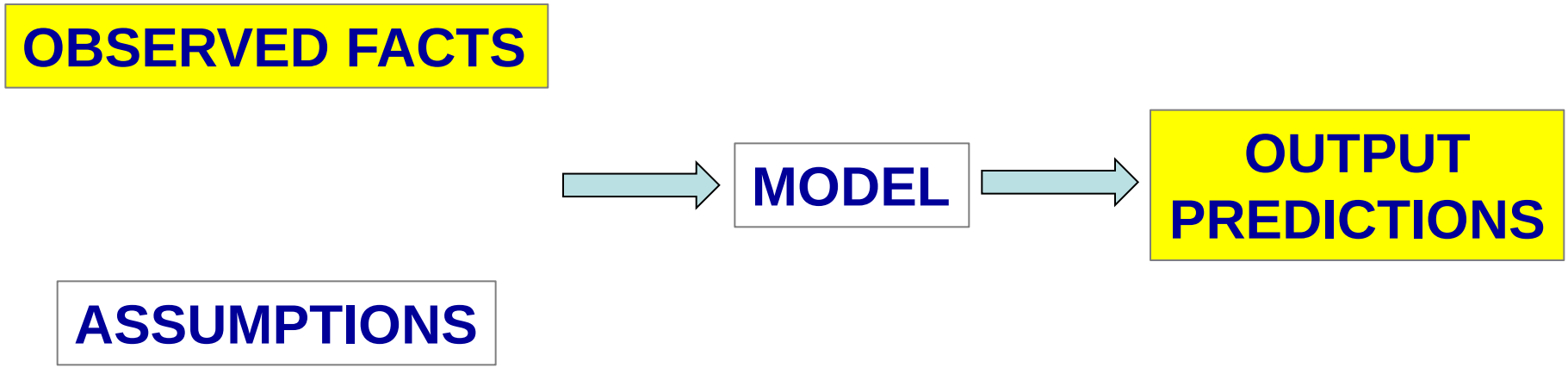

PRECAUTIONS TAKEN HAVE BEEN EFFECTIVE

MODELLING THE BLOOD PROBLEM

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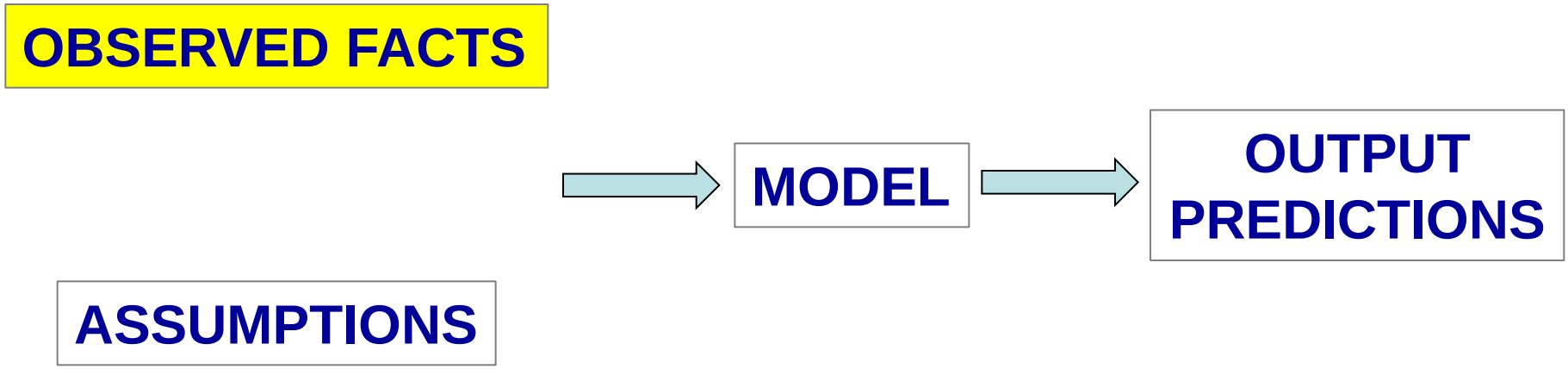

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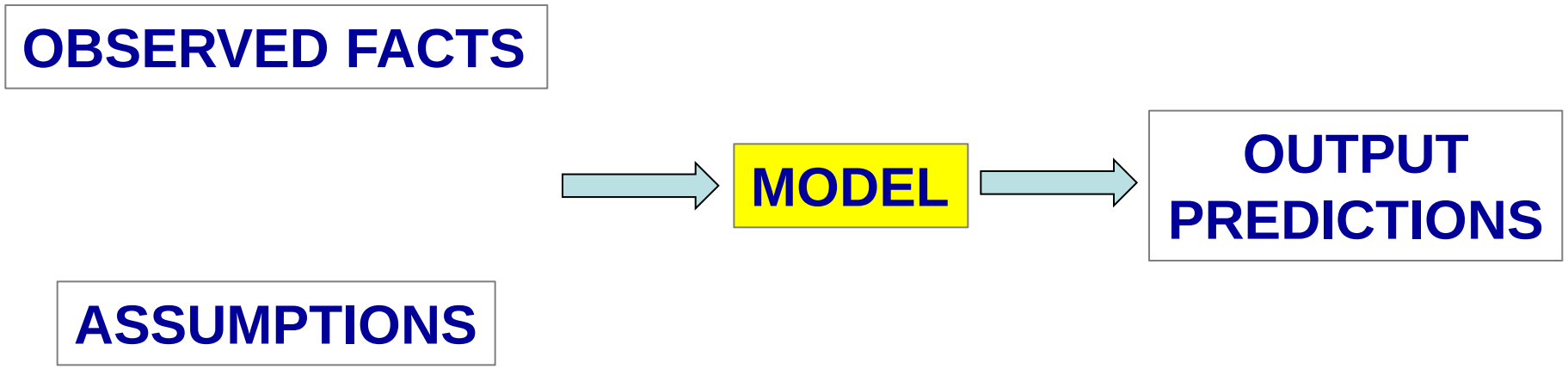

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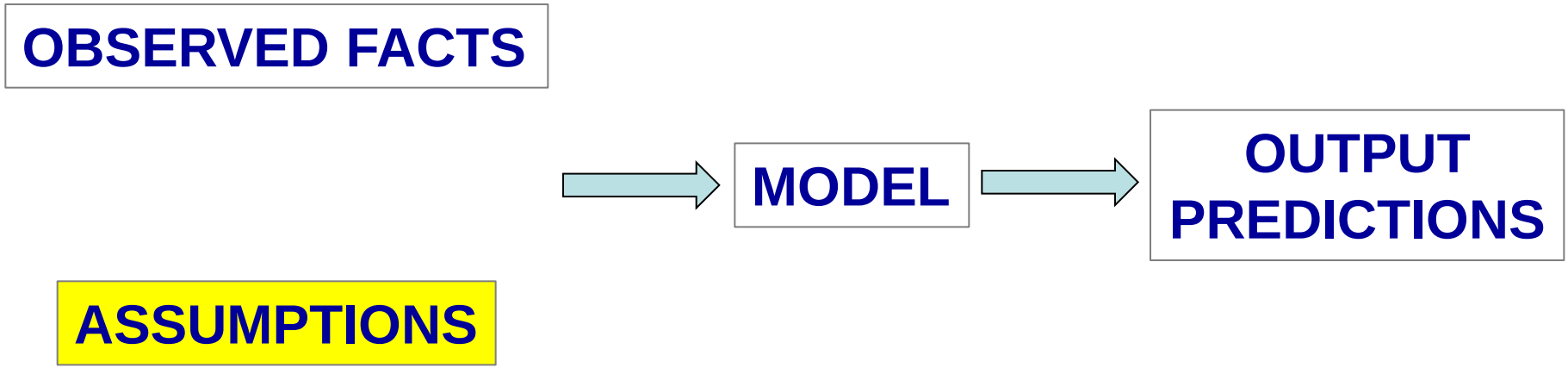

ASSUMPTIONS TO RE-VISIT ?

LESS INFECTIVITY IN BLOOD

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NOT ALL RECIPIENTS SUSCEPTIBLE

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VERY LONG INCUBATION PERIODS
(ONES SEEN HAVE UNUSUALLY SHORT IPs)

ASSUMPTIONS TO RE-VISIT ?

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POSTIVE LR TISSUE IN GENERAL POPULATION MEANS BSE INFECTION

ASSUMPTIONS TO RE-VISIT ?

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NOT ALL RECIPIENTS SUSCEPTIBLE

VERY LONG INCUBATION PERIODS
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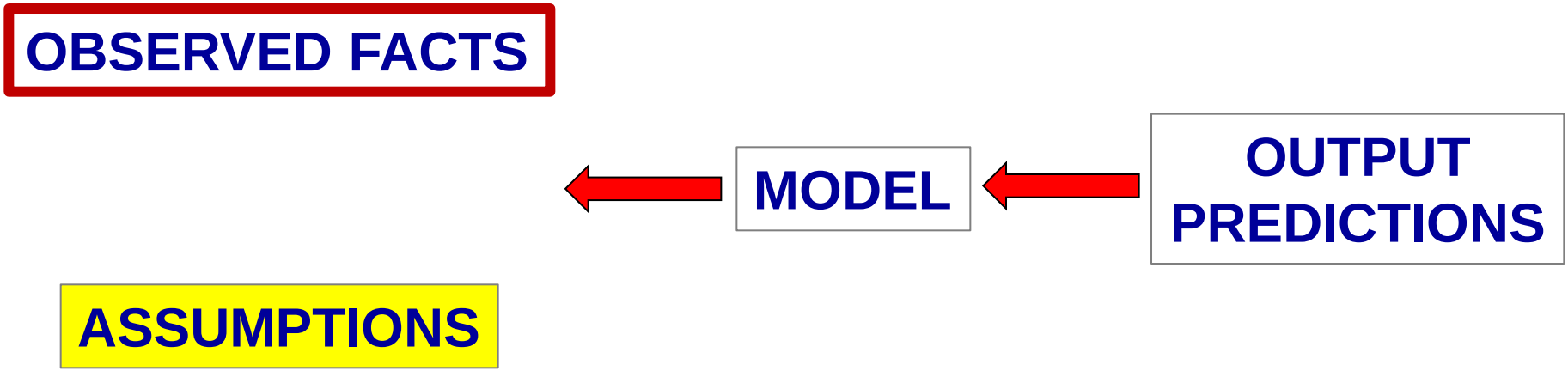
POSTIVE LR TISSUE IN GENERAL POPULATION MEANS BSE INFECTION

POSITIVE LR TISSUE PEOPLE INFECTIOUS

MODELLING THE BLOOD PROBLEM

Dr Peter Bennett, Health Protection, DH



V

CONCLUSION
&
REMAINING UNCERTAINTIES

SUMMARY I

BLOOD IS A RISK IN vCJD

FORTUNATELY FEW CASES SO FAR

REASONS FOR THIS NOT FULLY UNDERSTOOD

SUMMARY II

PREVALENCE OF SUBCLINICAL INFECTION IS A KEY FACTOR

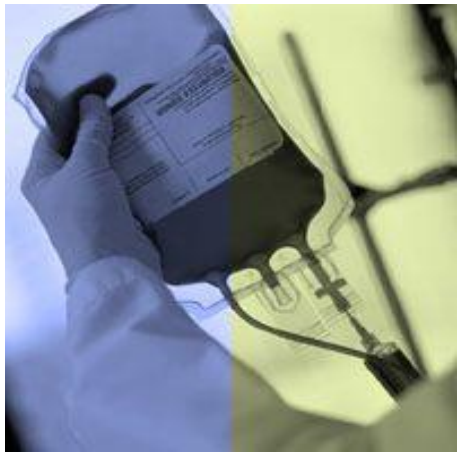
NEEDS FURTHER STUDY

SUMMARY III

A BLOOD SCREENING TEST
WOULD BE A FURTHER PROTECTION

TECHNICAL PROBLEMS

THE SPECIFICITY PROBLEM



UK	**176**
France	**27**
Republic of Ireland	**4**
Italy	**2**
USA	**3**
Canada	**2**
Saudi Arabia	**1**
Japan	**1**
Netherlands	**3**
Portugal	**2**
Spain	**5**
Taiwan	**1**

TMER
LABILE COMPONENTS
REVERSE STUDY

10 vCJD CASES

WITH RELEVANT REPORTS AS BEING RECIPIENTS

209 DONOR EXPOSURES

FROM 192 DONORS

[1 RECEIVED 103 COMPONENTS]

2 DONORS HAD vCJD

TMER
LABILE COMPONENTS
DONORS

32 vCJD REPORTED TO HAVE BEEN DONORS

24 TRACED

18 HAD COMPONENTS ACTUALLY ISSUED

67 TRACED RECIPIENTS

49 DEAD [29 within 2 YEARS]

18 ALIVE [16 >10 YEARS]

TMER
PLASMA PRODUCTS

11 vCJD donors

contributed plasma

to 25 plasma pools

identified by UK fractionators (BPL & PFC) as having been used for

the manufacture of plasma products

prior to 1999.

PLASMA FROM vCJD DONORS SENT FOR FRACTIONATION WITHIN UK

YEAR SENT	NUMBER OF UNITS
1986	1
1987	4
1989	1
1990	2
1991	1
1992	3
1993	2
1994	2
1995	2
1996	4
1997	2
1998	1
TOTAL	**25**

INFECTION IN *PRNP*-129 NON-MM INDIVIDUALS

ASYMPTOMATIC

Appendix Study:	**VV**	**2**
TMER:	**MV**	**1**
Haemophilia Study	**MV**	**1**

SYMPTOMATIC

Possible vCJD	**MV**	**1**

UK HAEMOPHILIA STUDY
UK HCDO & UK NCJDSU

HAEMOPHILIA PATIENTS
'AT RISK'
FROM vCJD-DERIVED PRODUCT

PATHOLOGICAL STUDIES

1 CASE (elderly)

PrP^{Sc} +ve SPLEEN

vCJD implicated treatment 11 years prior to death

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PLASMA DONOR 6 months prior to vCJD onset