



DIAGNOSIS & TREATMENT OF HUMAN PRION DISEASES

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OUTLINE



SOME GENERAL POINTS ABOUT DIAGNOSIS

RECENT DIAGNOSTIC DEVELOPMENTS

SOME GENERAL POINTS ABOUT TREATMENT

TREATMENT POSSIBILITIES

SUMMARY: A GUIDE TO LISTENING TO EXPERTS

THE DIAGNOSTIC PROCESS

THINK OF POSSIBILITY

EXCLUDE OTHER POSSIBILITIES

CONFIRMATORY TESTS

THE DIAGNOSTIC PROCESS

THINK OF POSSIBILITY

EXCLUDE OTHER POSSIBILITIES

SOMETIMES THE PASSAGE OF TIME IS HELPFUL

THE DIAGNOSTIC PROCESS

EXCLUDE OTHER POSSIBILITIES

CONFIRMATORY TESTS

SOME TESTS HAVE BOTH ROLES

[BRAIN MRI, LUMBAR PUNCTURE]

THE DIAGNOSTIC PROCESS

CONFIRMATORY TESTS

ESSENTIALLY NON-SPECIFIC TESTS

NOT RELATED TO BASIC DISEASE MECHANISMS

ESSENTIALLY SPECIFIC TESTS

RELATED TO BASIC DISEASE MECHANISMS

**ESSENTIALLY NON-SPECIFIC TESTS
NOT RELATED TO BASIC DISEASE MECHANISMS**

EEG

BRAIN MRI

CSF 14-3-3

**ABNORMALITIES MAY BE SEEN IN OTHER DISEASES
UTILITY DEPENDS GREATLY ON CLINICAL CONTEXT**

THE DIAGNOSTIC PROCESS

CONFIRMATORY TESTS

ESSENTIALLY NON-SPECIFIC TESTS

NOT RELATED TO BASIC DISEASE MECHANISMS

ESSENTIALLY SPECIFIC TESTS

RELATED TO BASIC DISEASE MECHANISMS

ESSENTIALLY SPECIFIC TESTS

I

DETECTION OF GENETIC MUTATION

IN

GENETIC PRION DISEASES

ESSENTIALLY SPECIFIC TESTS

II

DETECTION OF PrP^{Sc}

BRAIN

ESSENTIALLY SPECIFIC TESTS

III

DETECTION OF PrP^{Sc}

BRAIN: BIOPSY or AUTOPSY

ESSENTIALLY SPECIFIC TESTS

III

**DETECTION OF PrP^{Sc}
ELSEWHERE IN BODY ?**

TONSIL: variant CJD



OUTLINE



SOME GENERAL POINTS ABOUT DIAGNOSIS

RECENT DIAGNOSTIC DEVELOPMENTS

SOME GENERAL POINTS ABOUT TREATMENT

TREATMENT POSSIBILITIES

SUMMARY: A GUIDE TO LISTENING TO EXPERTS

**TWO BROAD DEVELOPMENTS
RELATED TO BASIC DISEASE MECHANISMS**

IMPROVED DETECTION OF PrP^{Sc}

SIMPLER METHODS TO OBTAIN NEURAL TISSUE

**ESSENTIALLY SPECIFIC TESTS
RELATED TO BASIC DISEASE MECHANISMS**

PrP^{Sc} CAN BE FOUND OUTSIDE OF BRAIN

IN SPORADIC CJD

BUT AT LOW LEVELS

**ESSENTIALLY SPECIFIC TESTS
RELATED TO BASIC DISEASE MECHANISMS**

PrP^{Sc} DETECTABLE

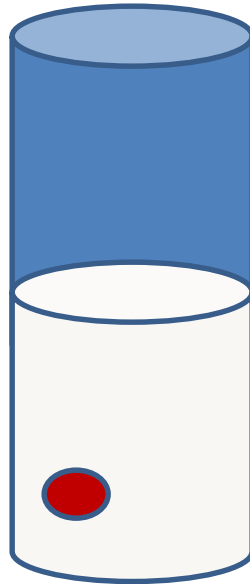
**IF LOW LEVELS INCREASED
USING
AMPLIFICATION TECHNIQUES**

AMPLIFICATION

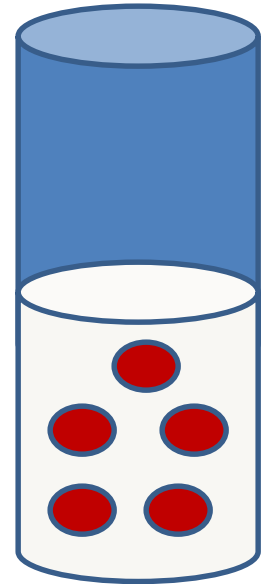
SAMPLE



PrP^{Sc}



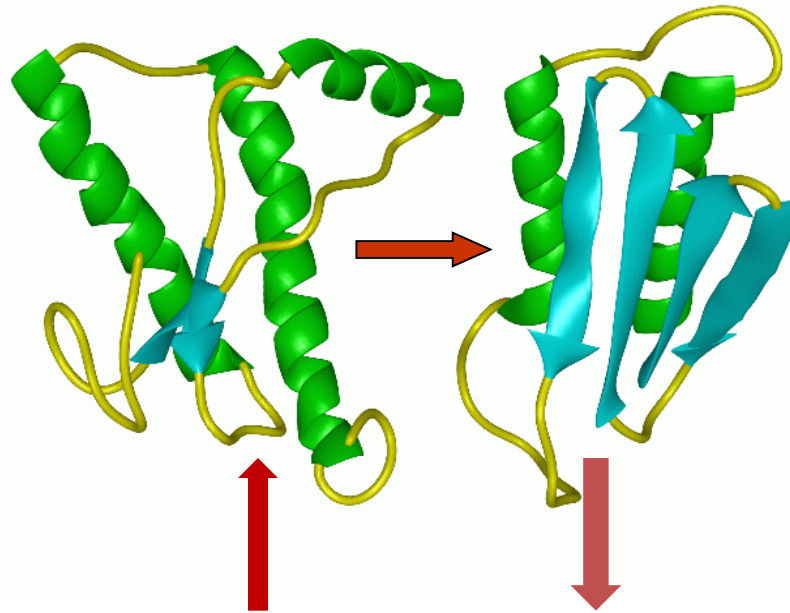
AMPLIFICATION



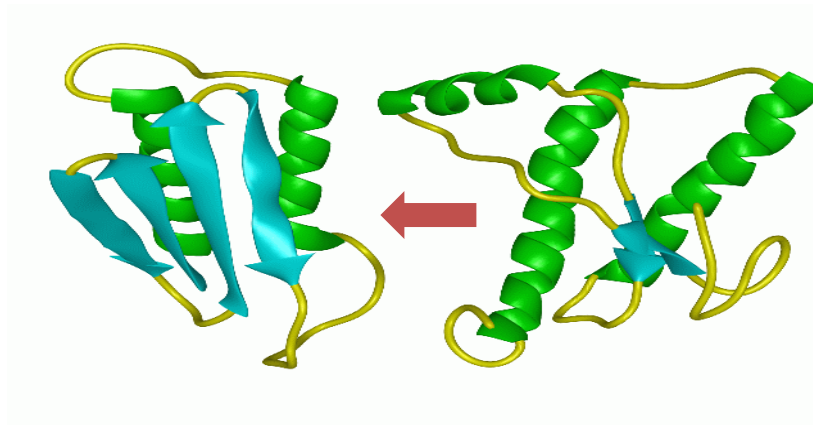
AMPLIFY THE AMOUNT
SO BECOMES DETECTABLE
BY AVAILABLE METHODS

ESSENTIALLY BASED ON AUTO-CATALYTIC CONVERSION OF PRION PROTEIN

PrP^C



PrP^{Sc}



TWO BASIC PrP^{Sc} AMPLIFICATION TECHNIQUES

PMCA

PROTEIN MISFOLDING CYCLIC AMPLIFICATION

RT-QuIC

REAL-TIME QUAKING-INDUCED CONVERSION

[SOME REFINEMENTS OF THESE METHODS]

PrP^{Sc} AMPLIFICATION: WHAT TISSUES?

CSF: RT-QuIC in SPORADIC CJD

BLOOD: in VARIANT CJD

URINE: in VARIANT CJD

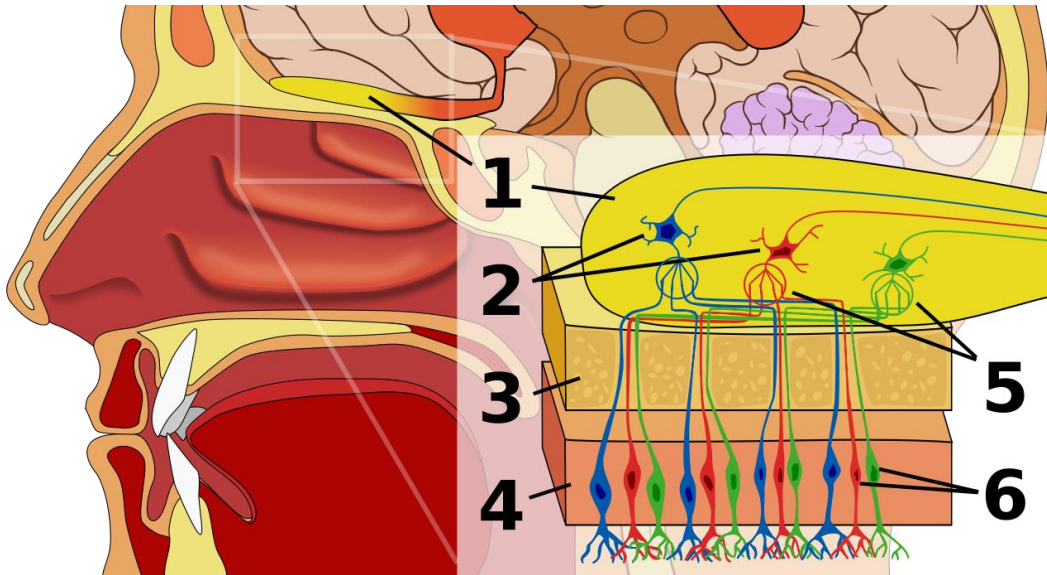
SKIN: in SPORADIC CJD

**TWO BROAD DEVELOPMENTS
RELATED TO BASIC DISEASE MECHANISMS**

IMPROVED DETECTION OF PrP^{Sc}

SIMPLER METHODS TO OBTAIN NEURAL TISSUE

BRUSHING TO OBTAIN OLFACTORY NEURONES



USING AMPLIFICATION METHODS
TO AID PrP^{Sc} DETECTION

TESTS IN PRACTICE

NO MATTER HOW TECHNICALLY GOOD THEY ARE

**THEY NEED TO BE USED
IN AN APPROPRIATE PERSON
AT AN APPROPRIATE TIME**

THEY REMAIN *PART* OF THE CLINICAL PROCESS

PrP^{Sc} IN BLOOD, URINE & SKIN IS IT A RISK ?

DETECTING ABNORMAL PrP IS NOT NECESSARILY DETECTING INFECTIVITY

INFECTIVITY IN EXPERIMENTS IS NOT NECESSARILY NATURAL INFECTION RISK

**NO EVIDENCE OF 'ORDINARY' INFECTION WITH HUMAN PRION DISEASES
EVEN WITH INTIMATE CONTACT**



OUTLINE



SOME GENERAL POINTS ABOUT DIAGNOSIS

RECENT DIAGNOSTIC DEVELOPMENTS

SOME GENERAL POINTS ABOUT TREATMENT

TREATMENT POSSIBILITIES

SUMMARY: A GUIDE TO LISTENING TO EXPERTS

WE ALL WANT SUCCESSFUL TREATMENT

SUPERFICIALLY STRAIGHTFORWARD:

GIVE A TREATMENT

DO THEY GET BETTER OR NOT ?

TWO TREATMENT SITUATIONS



CLINICAL ILLNESS



PREVENTION

GENETIC MUTATION CARRIERS

TWO TREATMENT SITUATIONS



CLINICAL ILLNESS

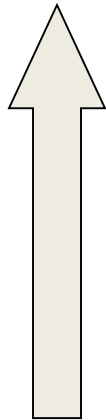
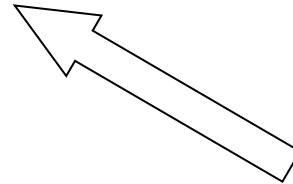


PREVENTION

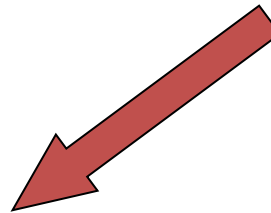
A TREATMENT
MAY BE EFFECTIVE IN ONE ROLE
BUT NOT THE OTHER

WHAT DO TREATMENTS DO ?

SYMPTOMS



NOT ALWAYS
EASY TO TELL
THE DIFFERENCE



DISEASE
PROCESS

WHAT DO TREATMENTS DO ?

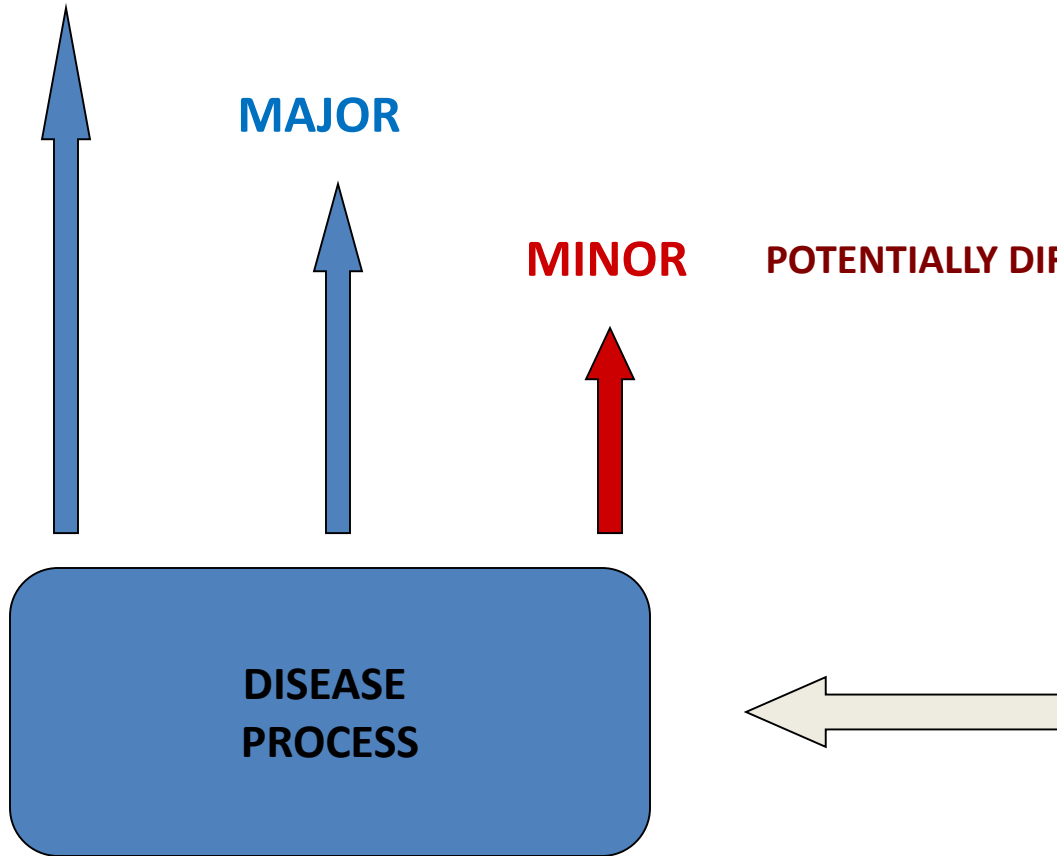
CURE

MAJOR

MINOR

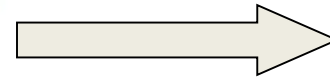
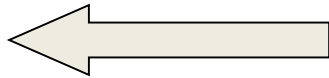
POTENTIALLY DIFFICULT TO DETECT

**DISEASE
PROCESS**



WHAT DO TREATMENTS DO ?

BENEFIT



HARM

TWO TREATMENT SITUATIONS

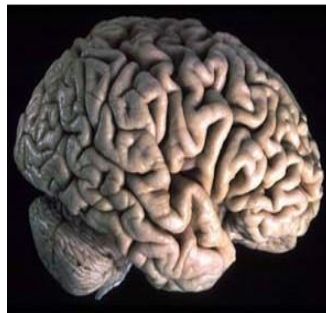
CLINICAL ILLNESS

PREVENTION

**SIDE EFFECTS
MAY HAVE DIFFERENT SIGNIFICANCE**

A POTENTIAL 'HARM' OF SUCCESSFUL TREATMENT

**DISEASE PROCESS HALTED
DAMAGED BRAINS CANNOT BE REPAIRED**



**POTENTIAL TREATMENTS:
*HOW DO YOU EVALUATE THEM?***

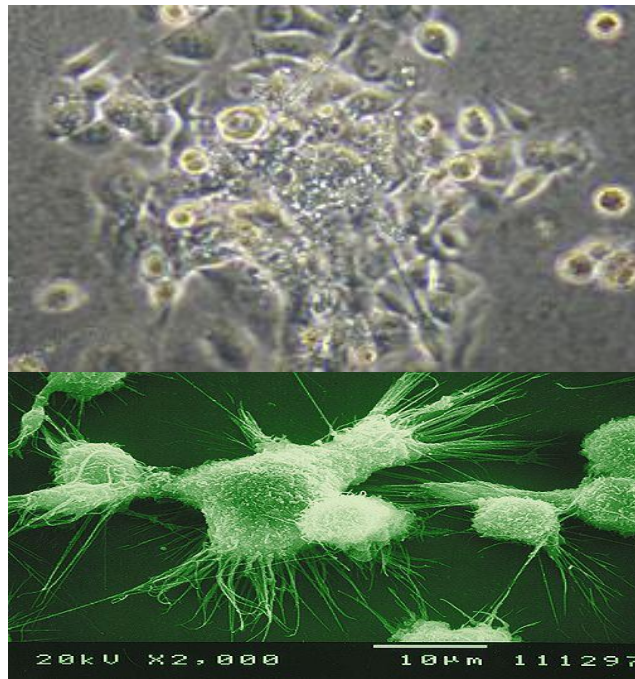
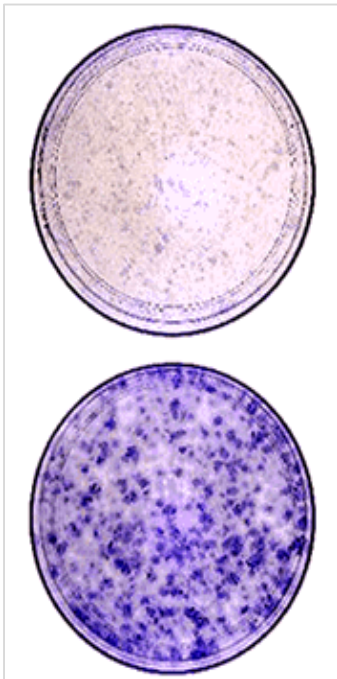
IN THE LABORATORY



LEVEL OF PROTEIN MOLECULES

**POTENTIAL TREATMENTS:
*HOW DO YOU EVALUATE THEM?***

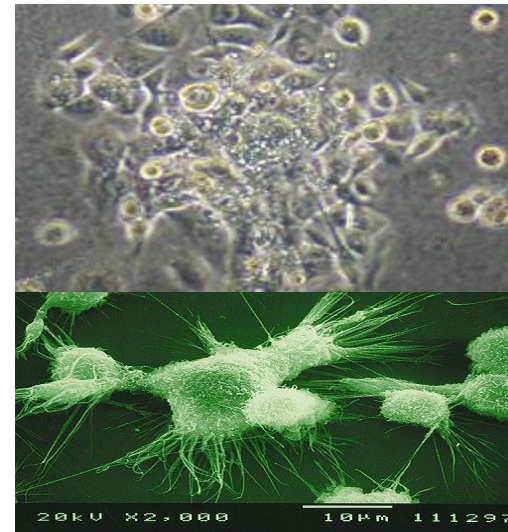
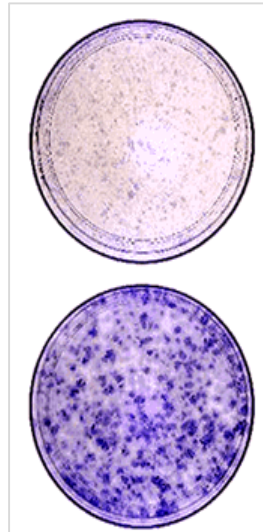
IN THE LABORATORY



LEVEL OF CELLS

**POTENTIAL TREATMENTS:
*HOW DO YOU EVALUATE THEM?***

IN THE LABORATORY



BUT WILL THEY WORK IN WHOLE LIVING ANIMALS ?

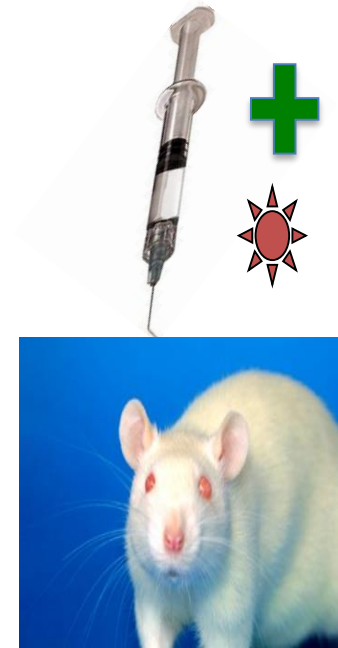
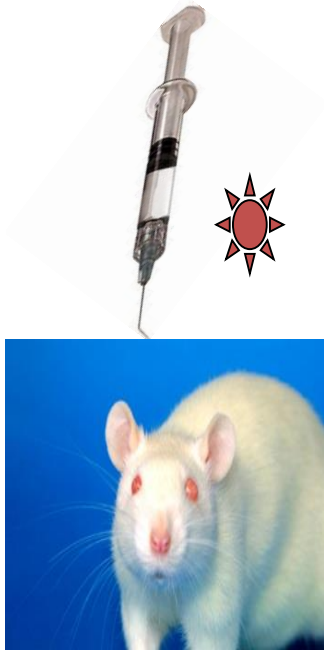
**POTENTIAL TREATMENTS:
*HOW DO YOU EVALUATE THEM?***

IN THE LABORATORY



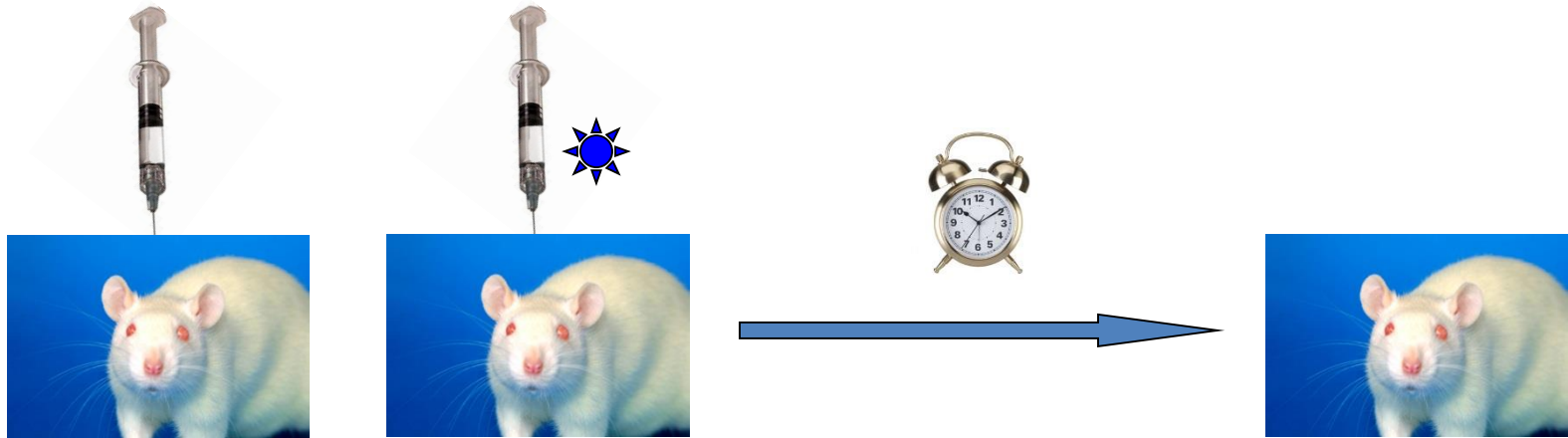
LEVEL OF LABORATORY ANIMALS

TYPICAL ANIMAL EXPERIMENT METHODOLOGY



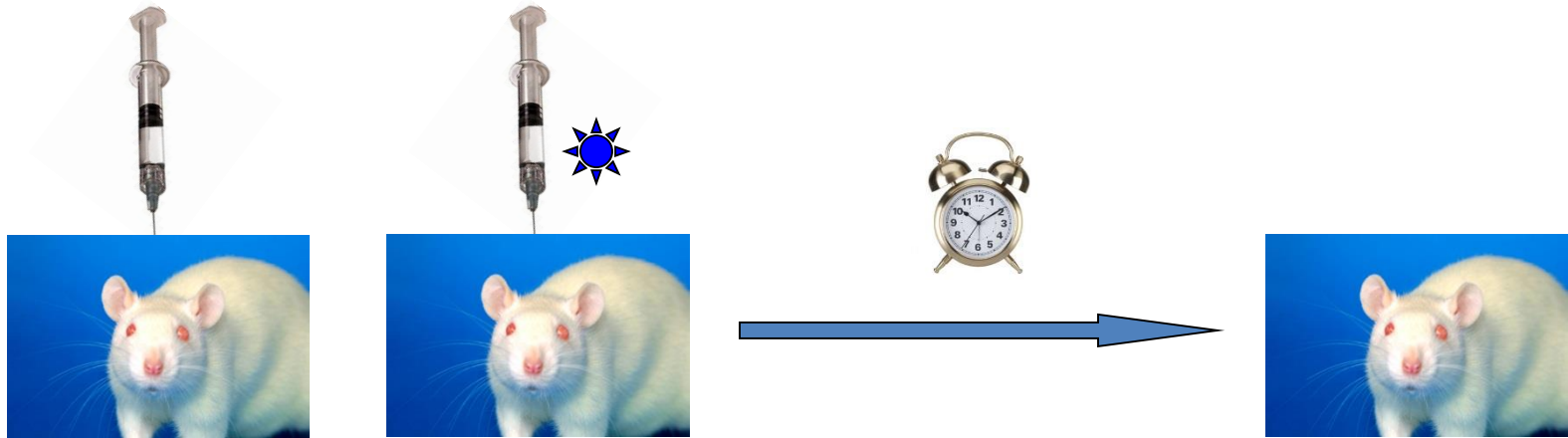
NUMBER BECOMING ILL
INCUBATION PERIOD
PATHOLOGICAL FINDINGS

ANIMAL EXPERIMENTS: POTENTIAL PROBLEMS



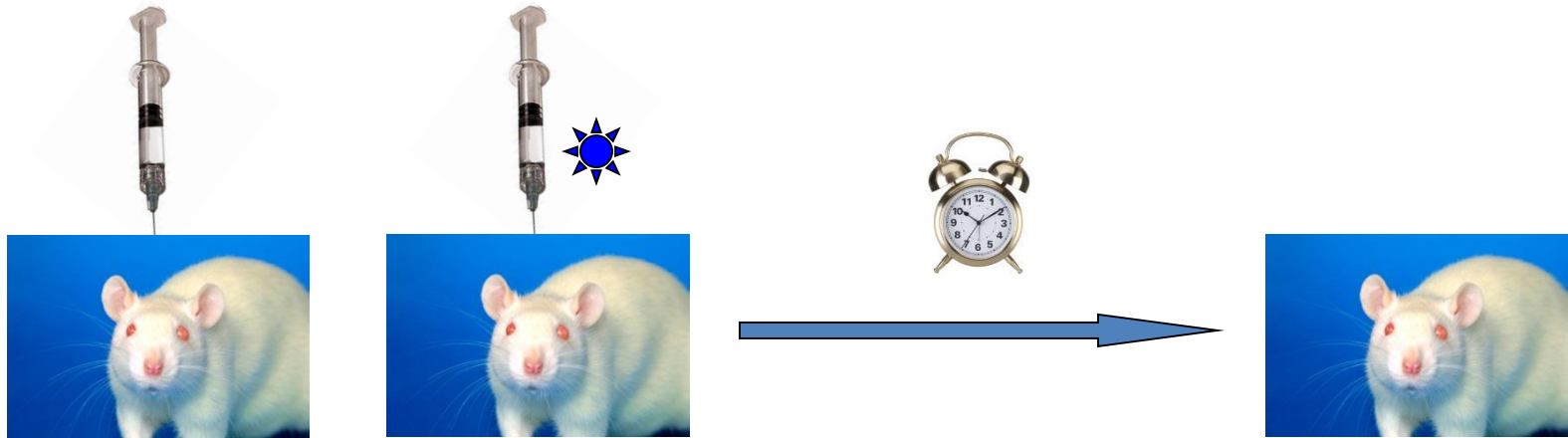
**INFECTION BY SPECIFIC ROUTE
OF UNCERTAIN HUMAN SIGNIFICANCE**

ANIMAL EXPERIMENTS: POTENTIAL PROBLEMS



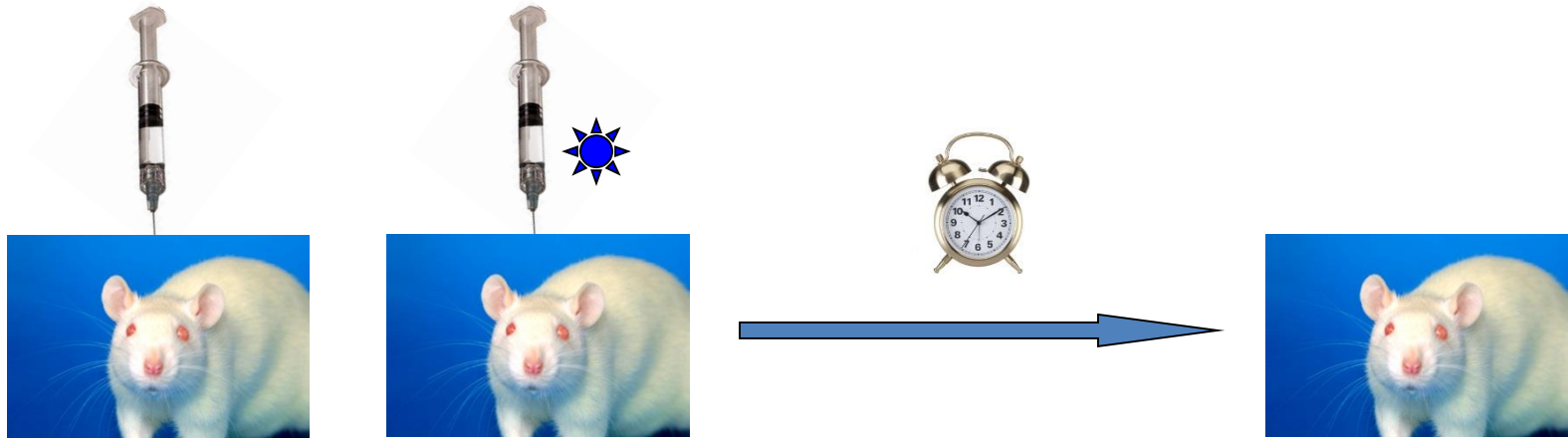
AN INFECTION WITH A SPECIFIC FORM OF DISEASE

ANIMAL EXPERIMENTS: POTENTIAL PROBLEMS



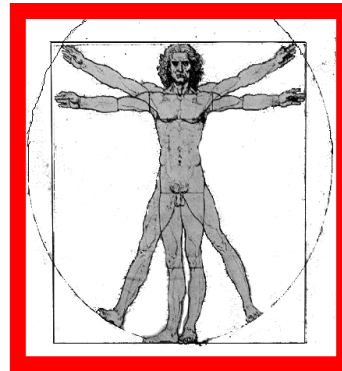
**TREATMENT GIVEN NEAR TIME OF INFECTION
EITHER PREVENTATIVE
OR VERY EARLY DISEASE**

ANIMAL EXPERIMENTS: POTENTIAL PROBLEMS



**RODENTS ARE NOT HUMANS
[NOT EVEN TRANSGENIC ANIMALS]**

TREATING HUMANS IS THE REAL AIM



MOST RELEVANT & IMPORTANT
***BUT:* POTENTIALLY MOST DIFFICULT**



THE PROBLEM OF MEASUREMENT



DIRECTLY OBSERVED CLINICAL IMPROVEMENT

SPECIFIC MEASUREABLE DISEASE ACTIVITY MARKERS

THE PROBLEMS OF MEASUREMENT

DIRECTLY OBSERVED CLINICAL IMPROVEMENT

OBJECTIVE MEASUREMENT OF SEVERE & MULTIMODAL NEUROLOGICAL DISABILITY

THE PROBLEMS OF MEASUREMENT

DIRECTLY OBSERVED CLINICAL IMPROVEMENT

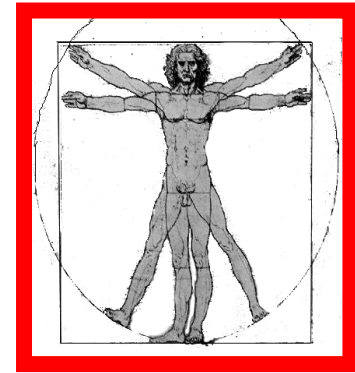
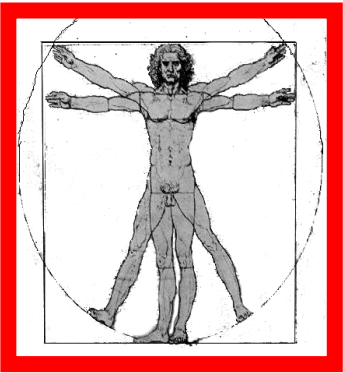
TIME TAKEN TO REACH CERTAIN CLINICAL POINTS

TIME TO DEATH

THE PROBLEMS OF MEASUREMENT

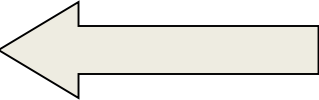
SPECIFIC MEASUREABLE DISEASE ACTIVITY MARKERS

LACK OF THESE IN PRION DISEASE

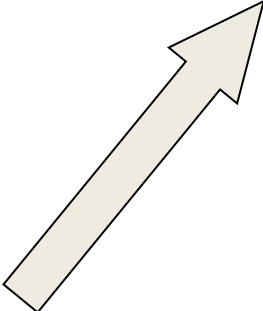
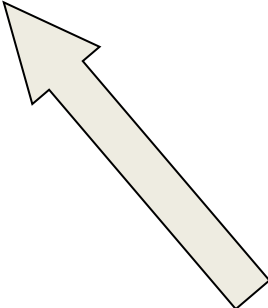


THE PROBLEM OF VARIABILITY

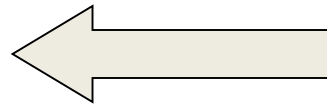
INDIVIDUAL



DISEASE



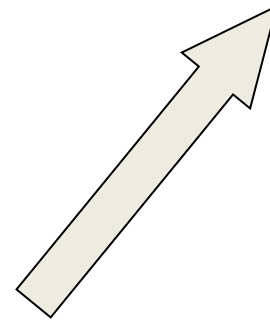
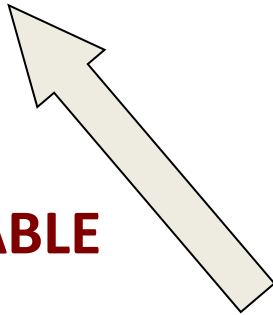
TREATMENT

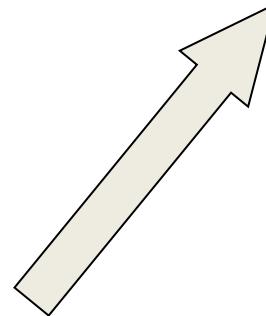
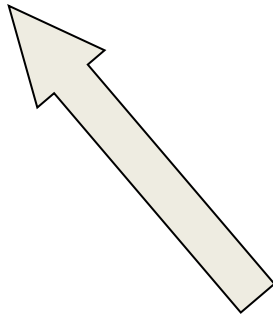
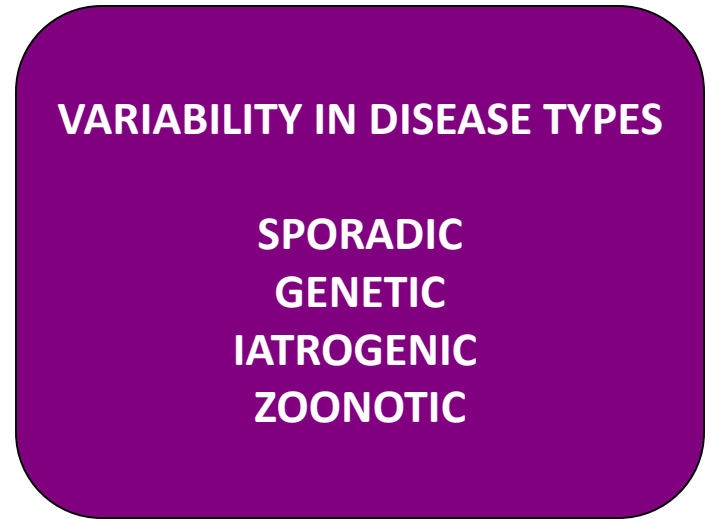
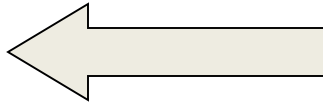
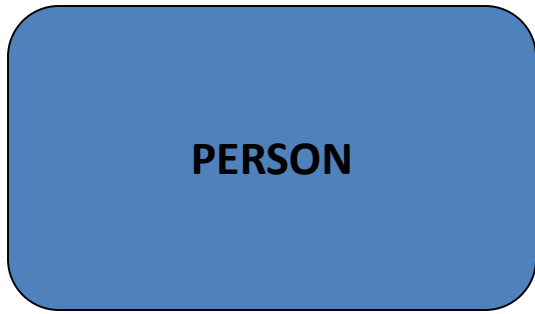


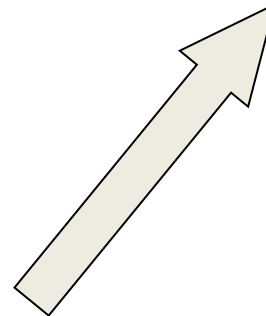
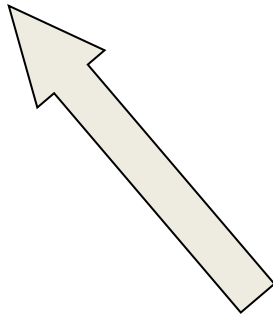
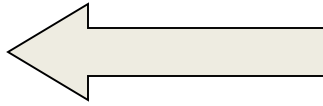
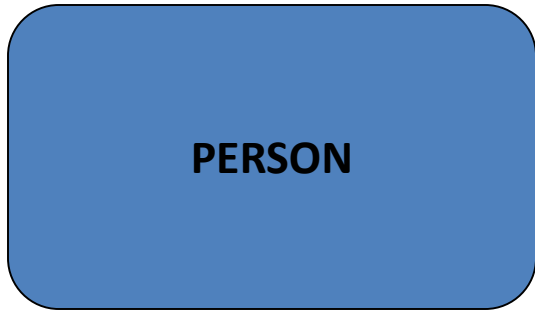
VARIABLE



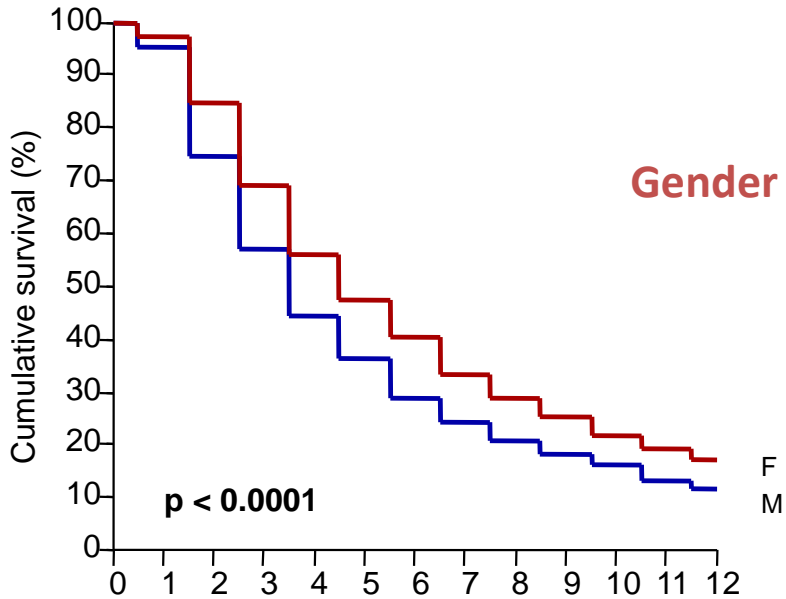
VARIABLE







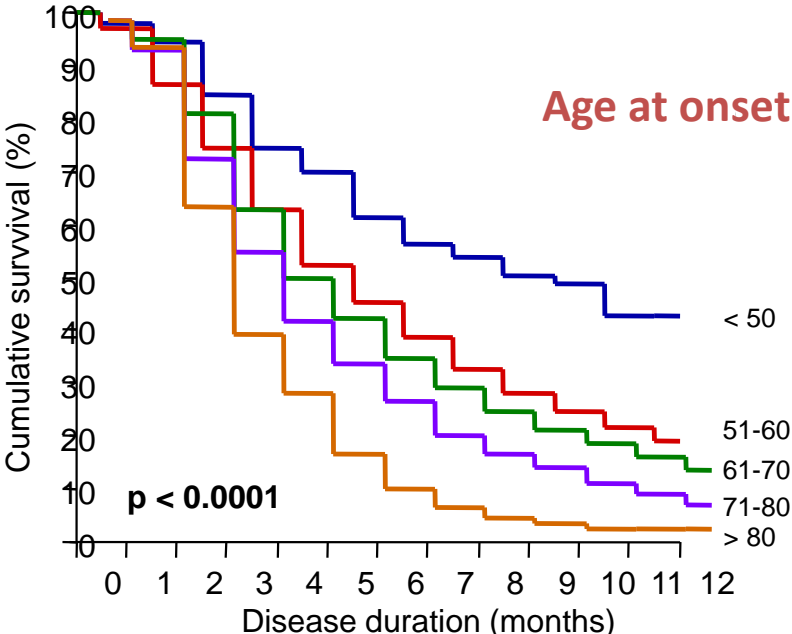
USING SURVIVAL AS A END-POINT ?



Pocchiari et al BRAIN 2004

Kaplan-Meier survival curves

Sporadic CJ D

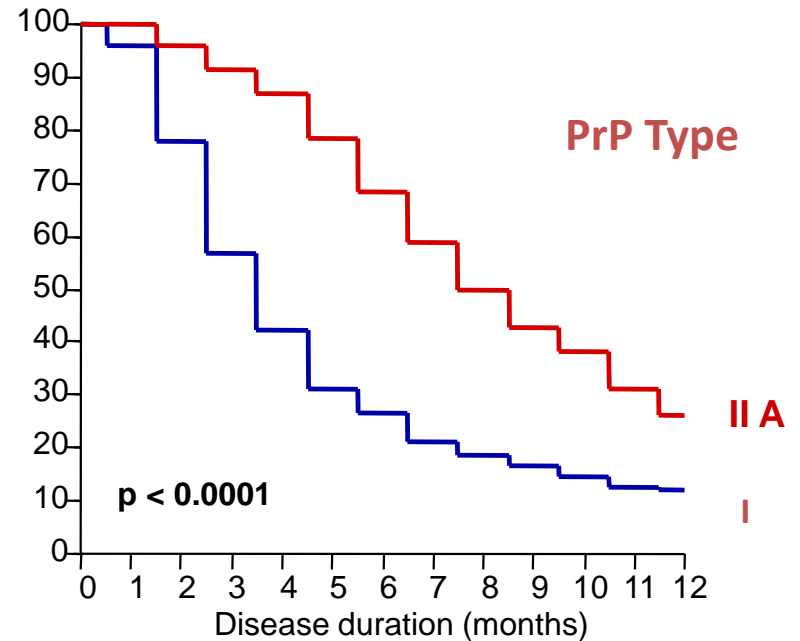
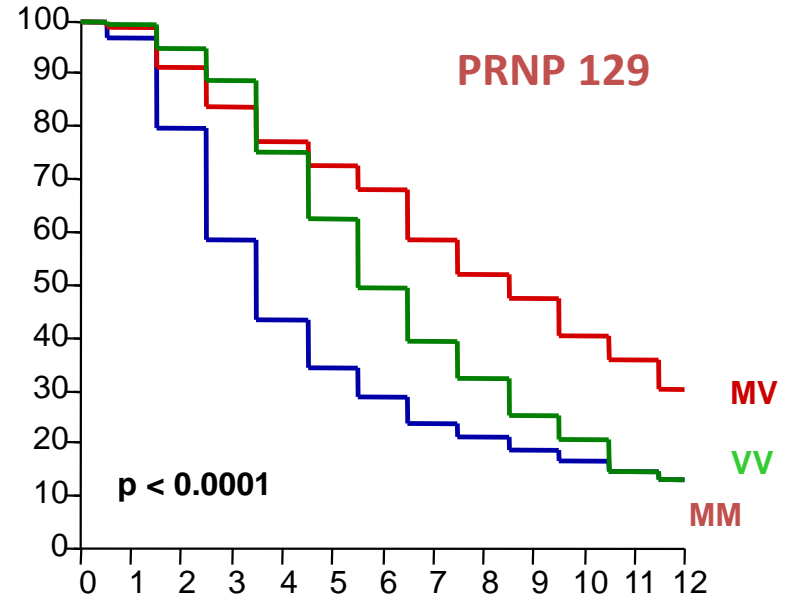


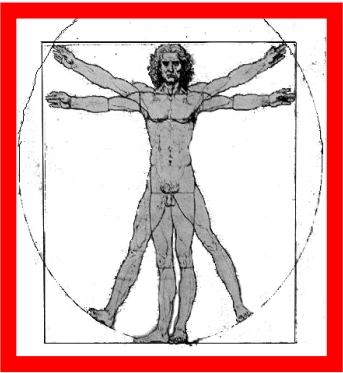
USING SURVIVAL AS A END-POINT ?

Pocchiari et al BRAIN 2004

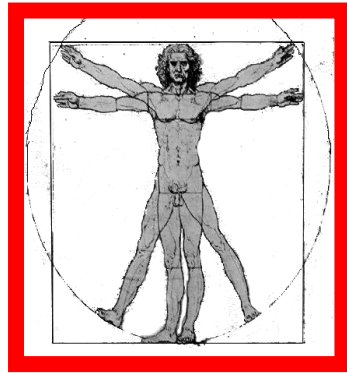
Kaplan-Meier survival curves

Sporadic CJ D



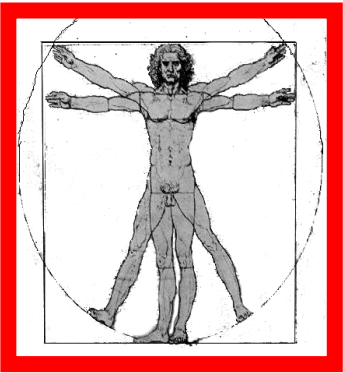


THE PROBLEM OF BIAS

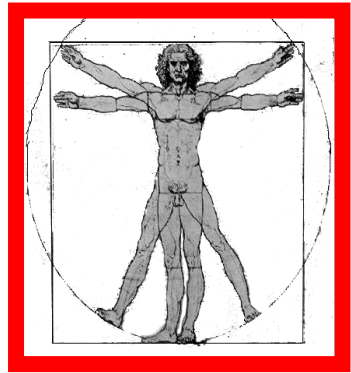


**SEEING BENEFIT THAT ISN'T THERE
ATTRIBUTING SPONTANEOUS CHANGES TO TREATMENT**

**BELIEF IN TREATMENT
WISH TO SEE IMPROVEMENT**

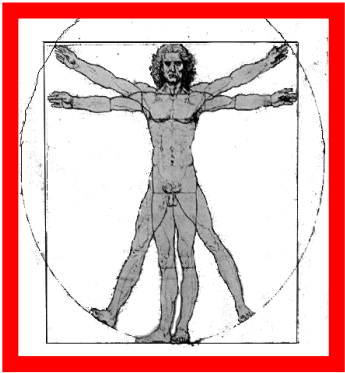


CONFOUNDING FACTORS

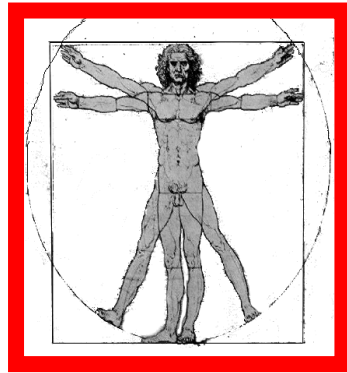


IMPROVEMENT NOT RELATED DIRECTLY TO DRUG

**THOSE IN A DRUG TRIAL
MAY GET BETTER GENERAL CARE**



THE STANDARD SCIENTIFIC SOLUTION

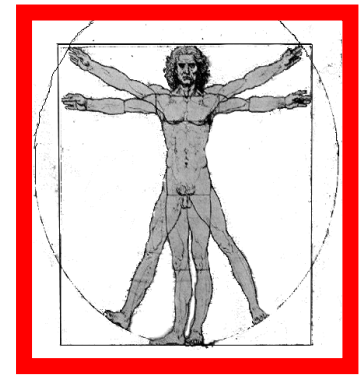
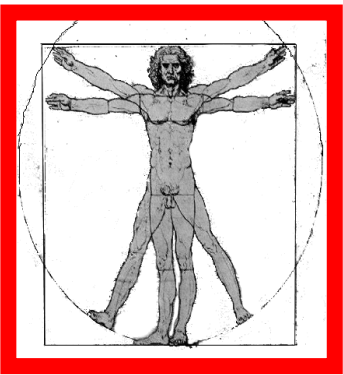


TRIALS WITH LARGE NUMBERS

PLACEBO-CONTROLLED or COMPARATIVE

RANDOMISATION

BLINDING



THE STANDARD SCIENTIFIC SOLUTION

THE LARGE RCT

RARE DISEASE ? INTERNATIONAL COLLABORATION





**IS PLACEBO TREATMENT & RANDOMISATION
ACCEPTABLE
IN AN INEVITABLY FATAL DISEASE ?**

DIFFERENCES OF OPINION ON THIS

THE WEIGHT OF HISTORY

DETECTION OF MINOR CHANGE

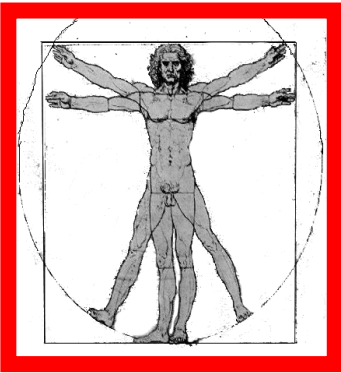
POSSIBLE HARM OF TREATMENT



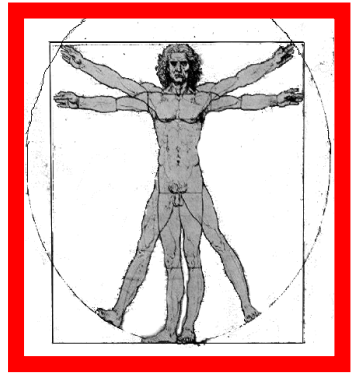
BLINDING

DIFFERENCES OF OPINION ON THIS ALSO

GENERALLY AN IMPORTANT PRINCIPLE



HISTORY



SINCE 1971

**40+ Reports of Attempted Treatments
Involving some 15 Drugs**

Many: small numbers

Until recently: most poor methodologically

Very few RCTs



OUTLINE



SOME GENERAL POINTS ABOUT DIAGNOSIS

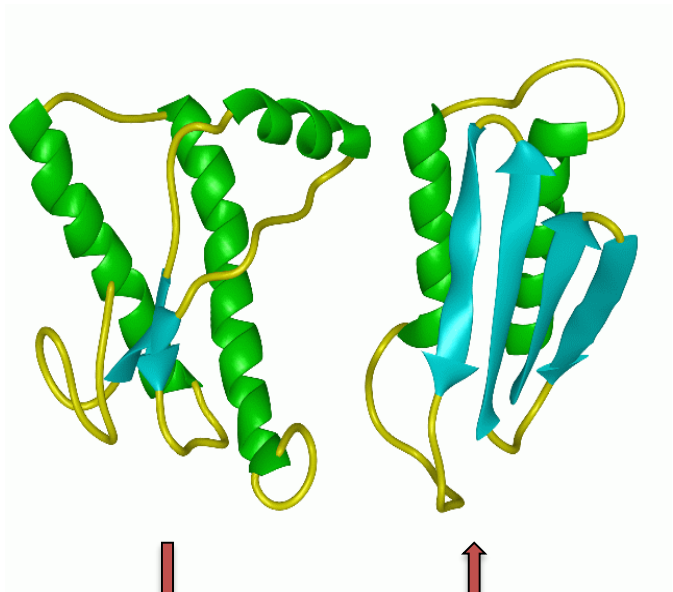
RECENT DIAGNOSTIC DEVELOPMENTS

SOME GENERAL POINTS ABOUT TREATMENT

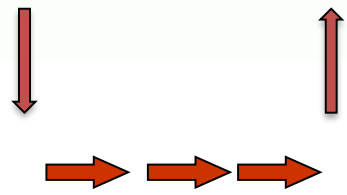
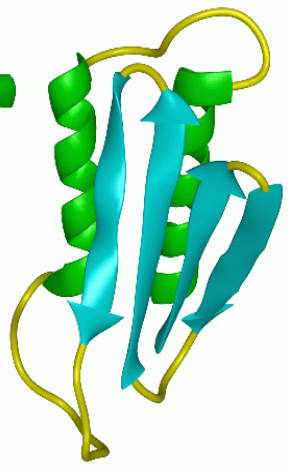
TREATMENT POSSIBILITIES

SUMMARY: A GUIDE TO LISTENING TO EXPERTS

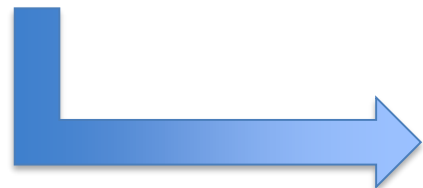
PrP^C



PrP^{Sc}



INTERMEDIATE FORMS



PROCESS OF NEURONAL DEATH



UNDERSTANDING PROCESSES OF NEURONAL DEATH



**PROBABLE EARLIEST CHANGES
IN SYNAPSES**

**EXPERIMENTAL EVIDENCE
THAT THESE EARLY CHANGES
ARE REVERSIBLE**

DIAGNOSIS & TREATMENT OF HUMAN PRION DISEASES

EARLY TREATMENT USUALLY BETTER

EARLY TREATMENT REQUIRES EARLY DIAGNOSIS

TWO TREATMENT SITUATIONS

CLINICAL ILLNESS



CAN WE DIAGNOSE EARLY ENOUGH ?

STOP DISEASE BUT SEVERELY DISABLED

PREVENTION

GENETIC MUTATION CARRIERS

A LONG-TERM ITALIAN STUDY

DOXYCYCLINE IN FAMILY MEMBERS

FOLLOW-UP TO SEE IF DISEASE DEVELOPS



OUTLINE



SOME GENERAL POINTS ABOUT DIAGNOSIS

RECENT DIAGNOSTIC DEVELOPMENTS

SOME GENERAL POINTS ABOUT TREATMENT

TREATMENT POSSIBILITIES

SUMMARY: A GUIDE TO LISTENING TO EXPERTS



DIAGNOSIS

DIAGNOSTIC TESTS

HOW SENSITIVE ?

**HOW LIKELY IS TEST TO BE POSITIVE IF YOU
HAVE CJD ?**

ESSENTIALLY RELATED TO TEST & DISEASE

DIAGNOSTIC TESTS

HOW SPECIFIC ?

**HOW LIKELY IS A POSITIVE TEST DUE TO CJD
AND NOT SOMETHING ELSE ?**

ESSENTIALLY RELATED TO TEST & CONTEXT

DIAGNOSTIC TESTS

TESTS RESULTS MAY BE

FALSE POSITIVES

FALSE NEGATIVES



TREATMENT

TREATMENT I

THE LIKELY HUMAN RELEVANCE OF THE EXPERIMENTAL MODEL ?

TEST TUBE / CELL CULTURE / ANIMAL ?

WHAT EFFECTS WERE MEASURED ?

TIMING OF TREATMENT ?

RANDOMISATION/BLINDING USED ?

THE LIKELY HUMAN RELEVANCE OF THE TYPE OF PRION DISEASE STUDIED ?

HOW COULD THE DRUG BE GIVEN TO HUMANS ?

SHOULD IT BE STUDIED IN AN RCT ?

TREATMENT II

HUMAN TREATMENT TRIALS

WERE THE PROBLEMS OF MEASUREMENT, VARIABILITY, BIAS &
CONFOUNDING FACTORS ADDRESSED ?

NUMBERS TREATED ?

CONTROLLED ?

MATCHED CONTROL GROUPS ?

RANDOMISED ?

BLINDED ?

WHAT MEASUREMENTS TAKEN ?

WERE MEASUREMENTS MEANINGFUL ?

PESSIMISTIC / OVER-CRITICAL ?

NEED TO UNDERSTAND THE COMPLEXITIES

HOPE MUST BE TEMPERED BY REALISM

CARE NECESSARY:

USELESS TREATMENTS THOUGHT TO BE USEFUL

USEFUL TREATMENTS THOUGHT TO BE USELESS

