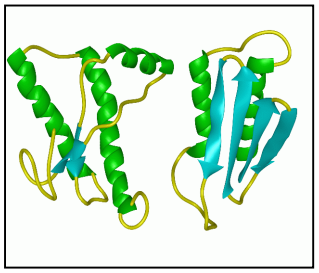
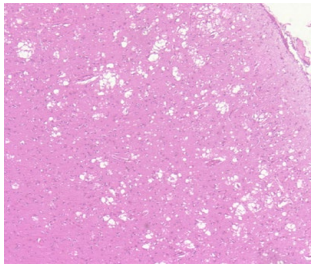
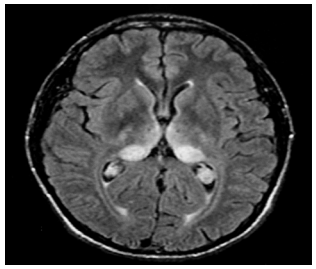
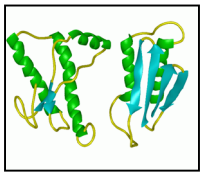
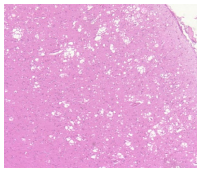
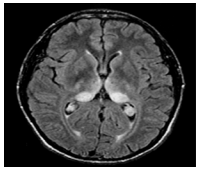
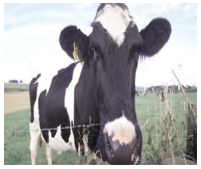




PRION DISEASES: AN OVERVIEW

Richard Knight

NCJDRSU CCBS University of Edinburgh


PRION DISEASES: AN OVERVIEW

WHAT ARE THEY ?

WHY DO THEY HAPPEN ?

HOW DO WE DIAGNOSE THEM ?

HOW MIGHT WE TREAT THEM ?

AND ALONG THE WAY: *SOME* OF THE HISTORY

SCRAPIE

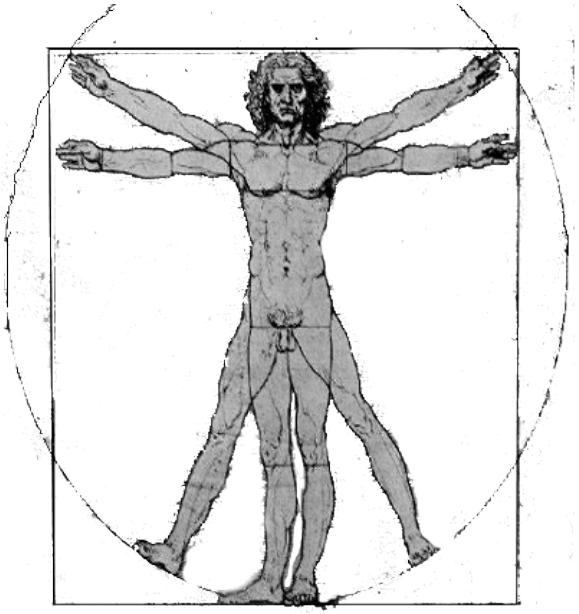
TME

CWD

ALGERIAN DROMEDARIES

BSE

BSE-RELATED



VARIOUS FORMS OF CJD

SOME RARE GENETIC DISEASES

VPSPr

KURU

WHAT IS COMMON TO ALL THESE DIFFERENT FORMS OF ILLNESS ?

ALL OF THEM:

BRAIN DISEASES

PROGRESSIVE & FATAL

SIMILAR PATHOLOGY: 'NEURODEGENERATIVE'

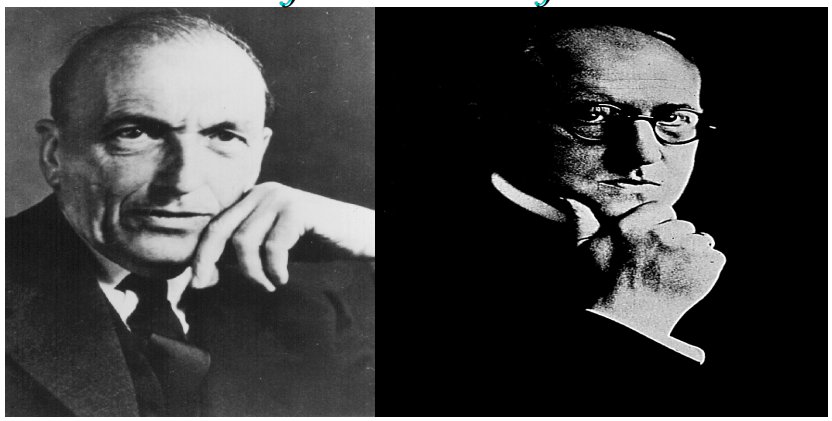
RELATED TO A SPECIFIC PROTEIN ABNORMALITY

POTENTIALLY **TRANSMISSIBLE***

***Generally only in certain specific circumstances**

IN THE PAST:
DISEASES OFTEN NAMED AFTER PEOPLE

Hans Creutzfeldt *Alfons Jakob*



CREUTZFELDT-JAKOB DISEASE:
THE COMMONEST HUMAN PRION DISEASE

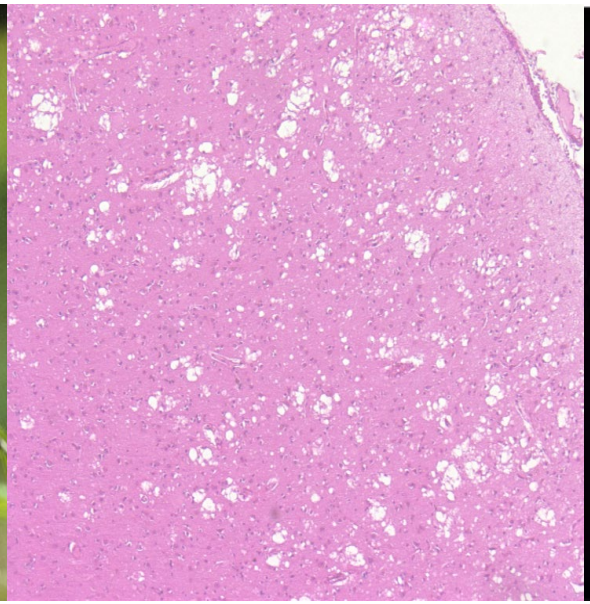
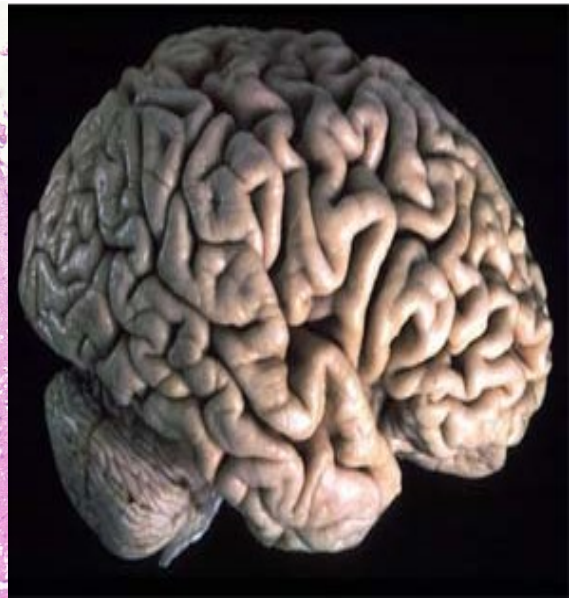
1920s

GERSTMANN STRÄUSSLER SCHEINKER SYNDROME
A GENETIC HUMAN PRION DISEASE

1936

DESCRIPTIVE NAMES THEN BECAME POPULAR

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

FIRST EXPERIMENTAL TRANSMISSION OF CJD 1968

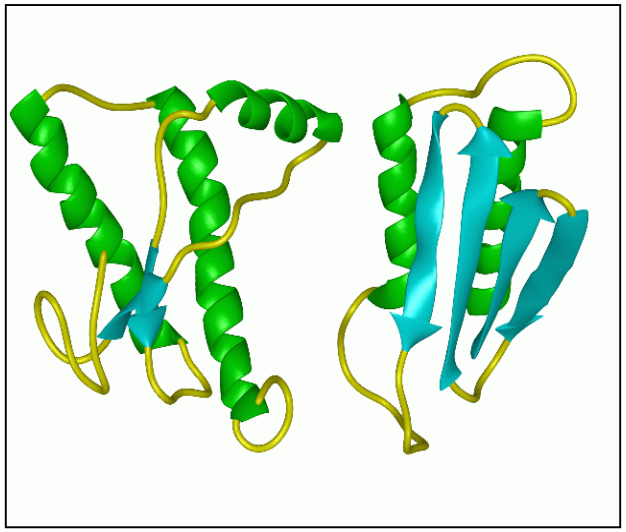
Gibbs
Gajdusek
Asher
Alpers
Beck
Daniel
Matthews

THEN IN THE 1980s

PRION PROTEIN, ITS GENE

& THEIR ROLE IN THESE DISEASES

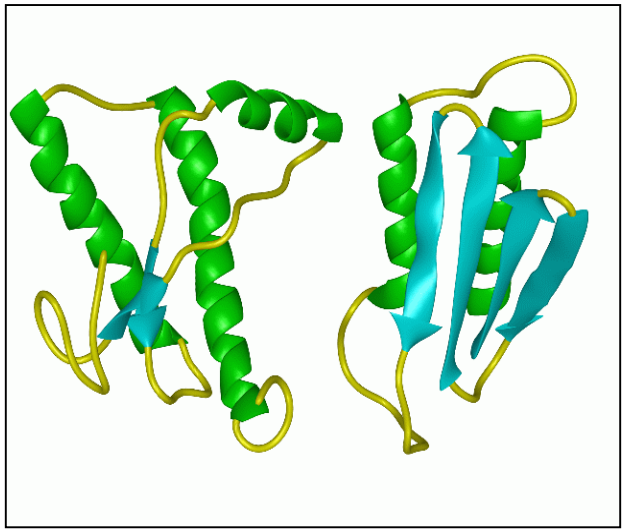
IDENTIFIED



Prusiner & Others

THE MODERN ERA:
A NAME REFLECTING THE PROTEIN UNDERPINNING

PRION DISEASES



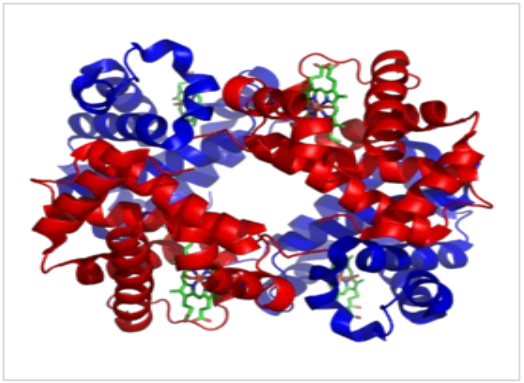
PROTEINS:
COMPLEX CHEMICAL STRUCTURES

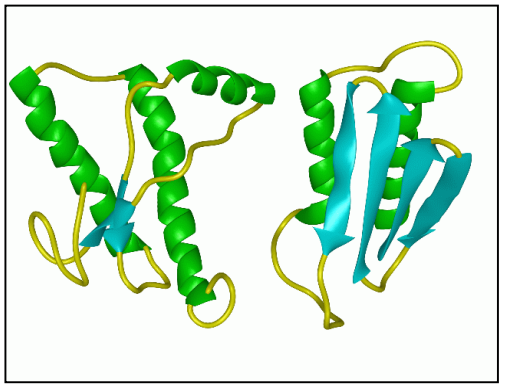
~50,000 PROTEINS IN HUMAN BODY

STRUCTURAL ROLES

FUNCTIONAL ROLES

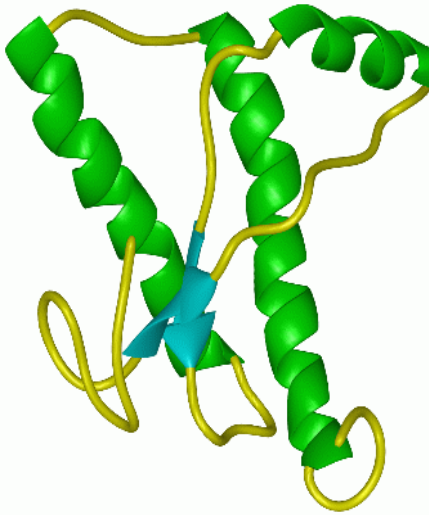
THEIR SHAPE (THEIR FOLDING) VERY IMPORTANT





PRION DISEASES

INVOLVE ABNORMALITY IN A SPECIFIC PROTEIN: THE PRION PROTEIN



NORMAL PRION PROTEIN

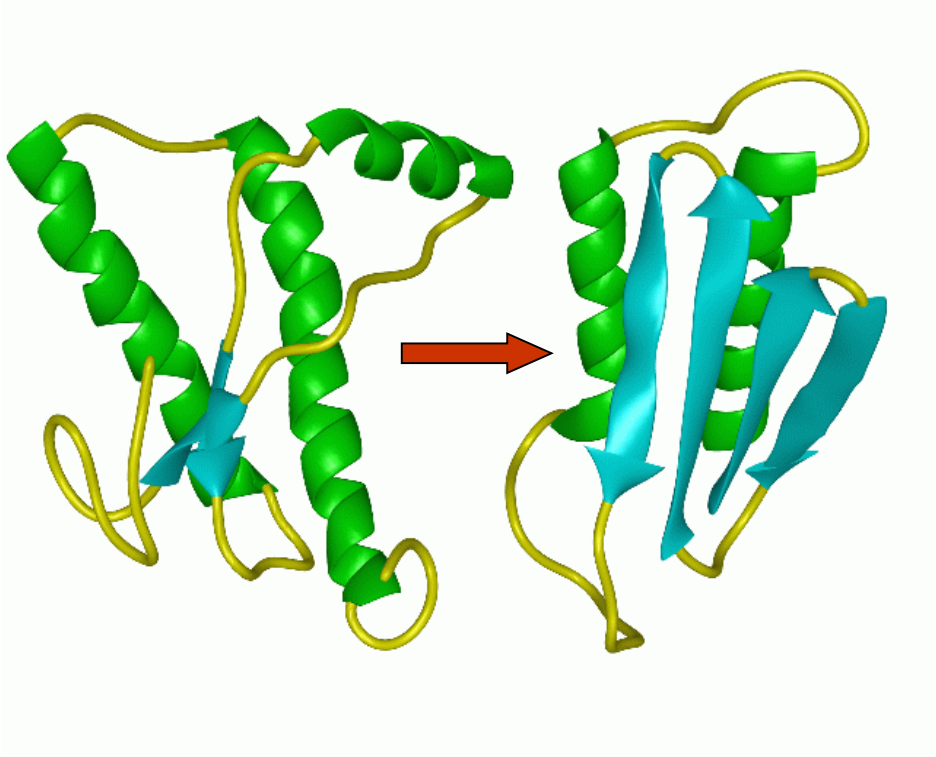
FOUND IN MANY ANIMALS

FOUND IN MANY TISSUES

IMPORTANT
BUT
PRECISE FUNCTION ?

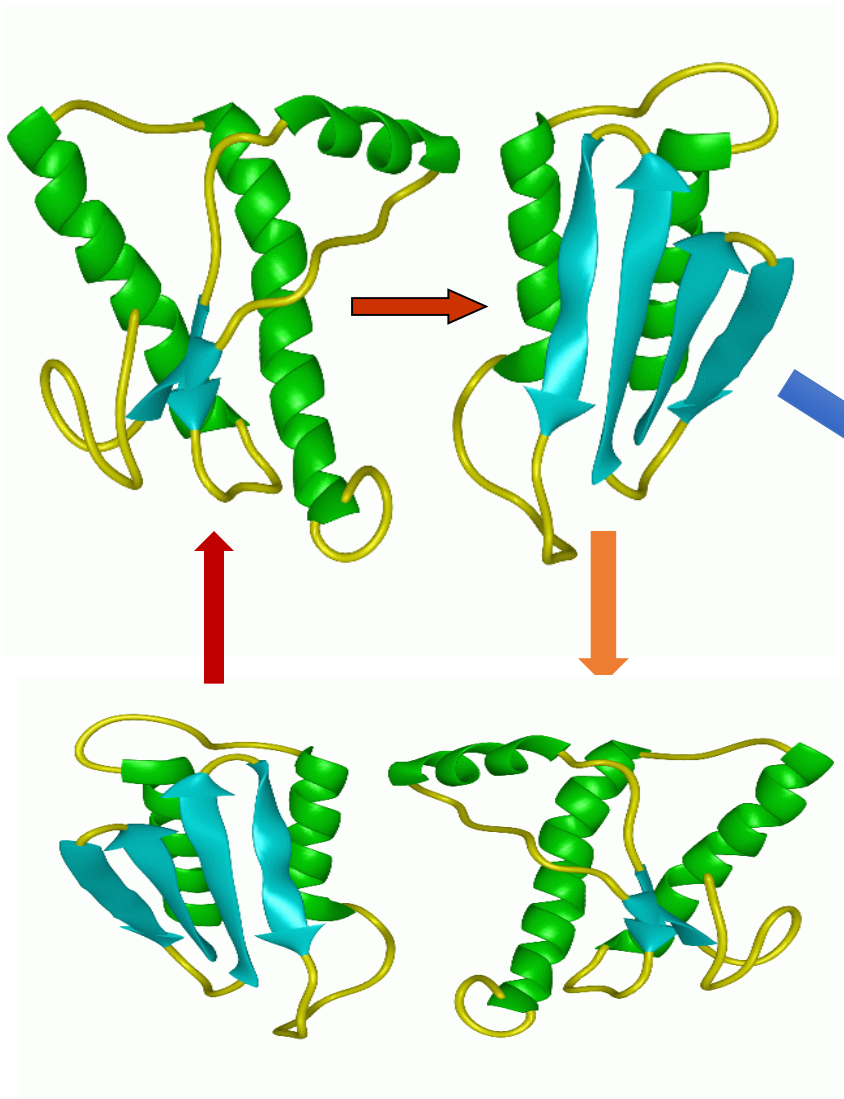
PRION DISEASES

DISEASES IN WHICH THE PRION PROTEIN UNDERGOES A CHANGE IN CONFORMATION: ABNORMAL FINAL STRUCTURE



PrP^{Sc}

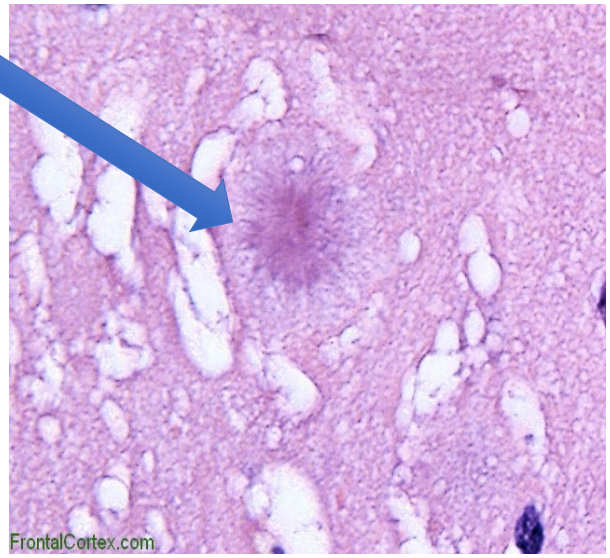
ABNORMAL PRION PROTEIN

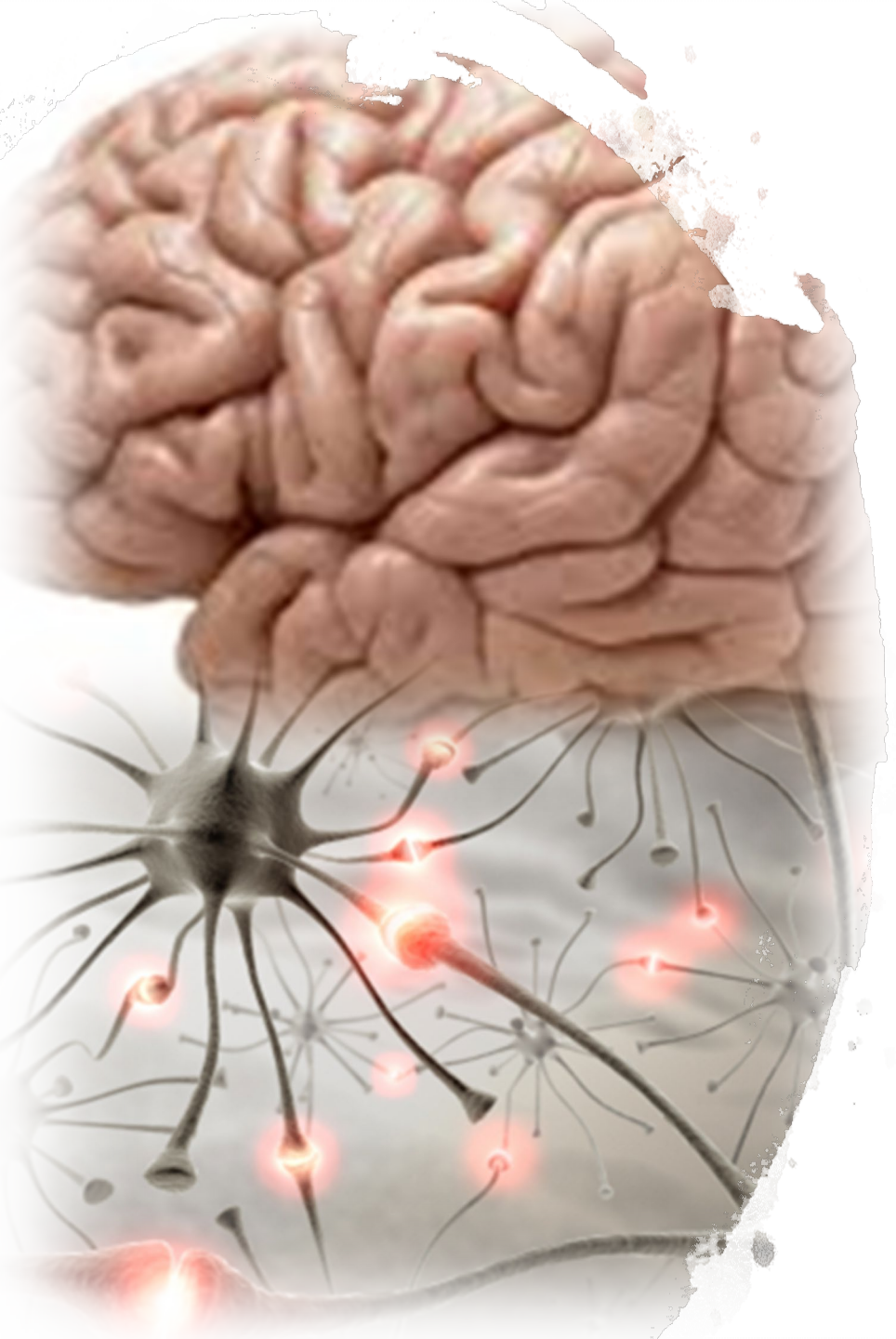


ACCUMULATES

AGGREGATES

DEPOSITED IN TISSUE





WHAT MAKES HUMANS HUMAN ?

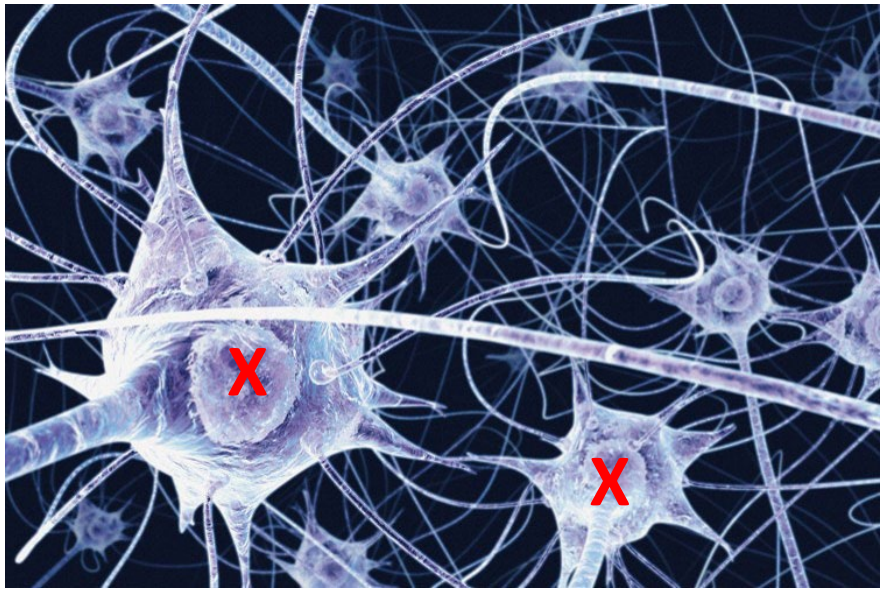
OUR BRAINS

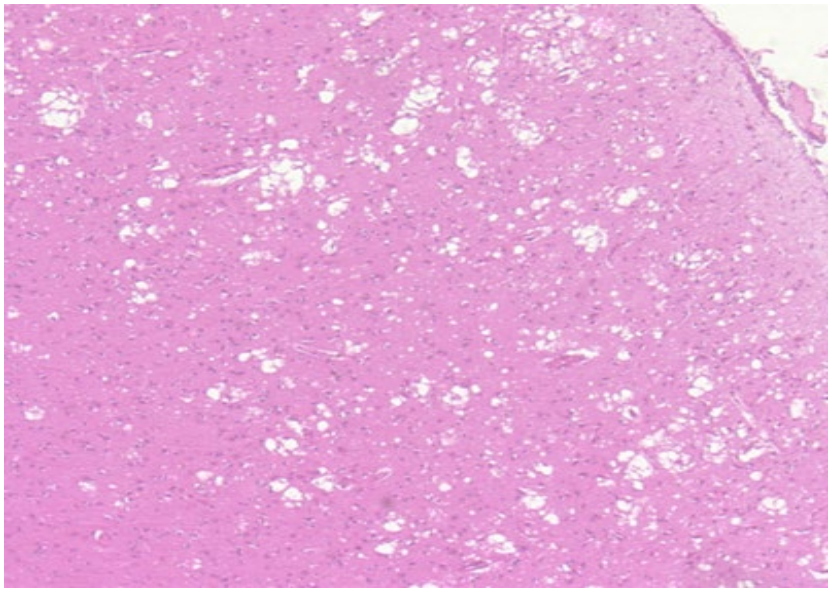
AND ITS MILLIONS OF NEURONES

CONNECTED ELECTRICALLY IN NETWORKS

THE FUNDAMENTAL DISEASE QUESTION:

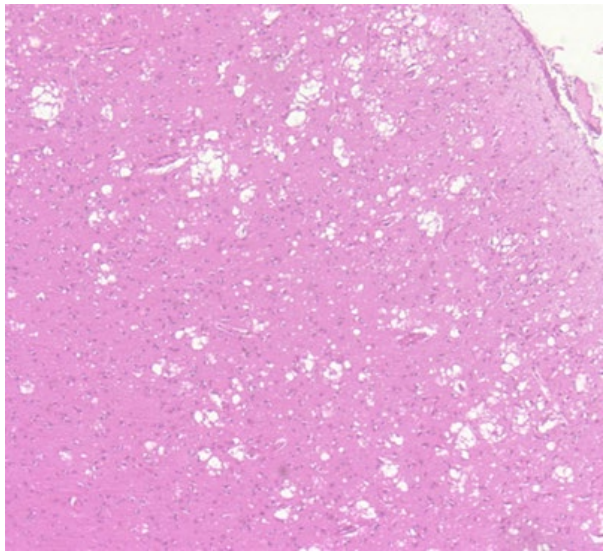
WHAT CAUSES NEURONAL DYSFUNCTION & LOSS?





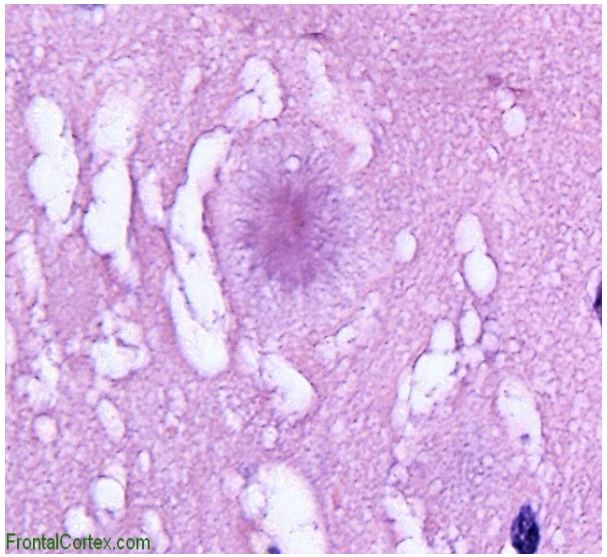
OUR UNDERSTANDING OF THIS IS INCOMPLETE & UNCERTAIN

IN PARTICULAR….



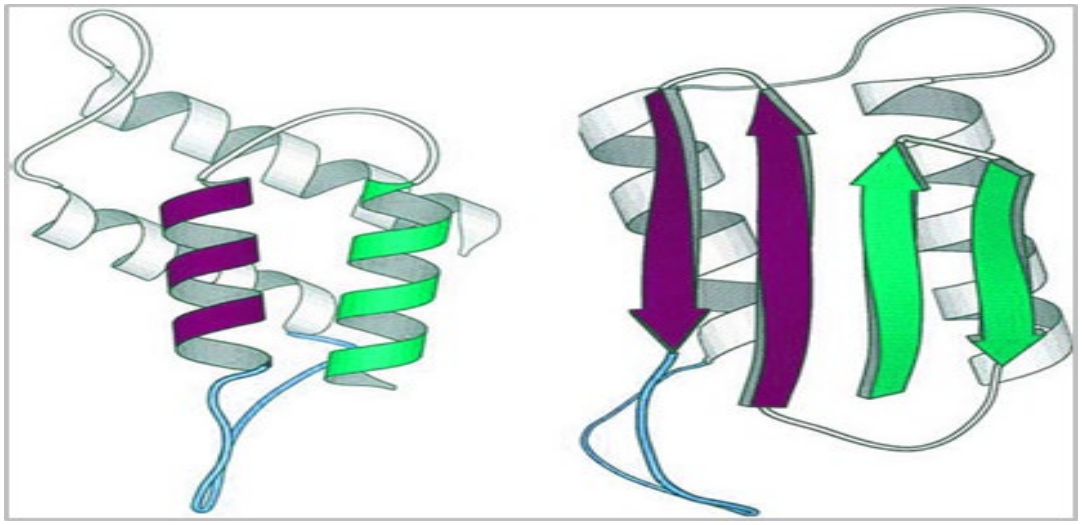
NEURONAL LOSS

Precise
Relationship
?



DEPOSTION
OF
AGGREGATED
ABNORMAL
PRION PROTEIN

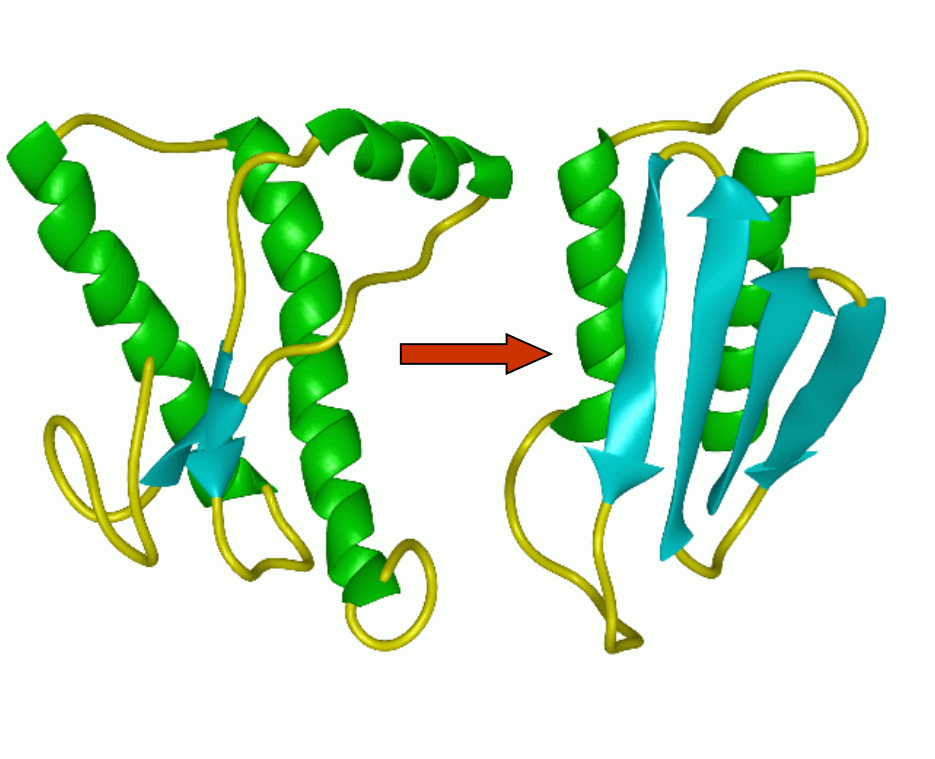
ABNORMAL PRION PROTEIN: CONVERSION NOT ONE STEP



INTERMEDIATE FORMS **MAY BE MOST IMPORTANT IN RELATION TO NEURONAL LOSS & INFECTIVITY**

WHY DOES THIS HAPPEN?
3 BROAD REASONS

PrP^{C}



PrP^{Sc}

I: GENETIC PROBLEM: Abnormal gene-Abnormal Protein

2: INFECTION: Enters & causes change

3: CHANCE: Random Protein Production Mistake
Mistake in Protein Quality Control

MAIN DISEASE TYPES

GENETIC PRION DISEASE

INHERITED MUTATIONS
50:50 CHANCE OF INHERITENCE

CLINICAL COURSE VARIABLE
DEPENDING, IN PART, ON THE PARTICULR MUTATION

MAIN DISEASE TYPES

IATROGENIC CJD

ACCIDENTALLY TRANSMITTED PERSON-PERSON BY MEDICAL/SURGICAL PROCEDURES

MOST CASES PAST EXPOSURE TO
Growth Hormone
Dura Mater Grafts

MAIN DISEASE TYPES

VARIANT CJD

ORIGIN: DIETARY CONTAMINATION WITH BSE
MOST in UK
NO LIVING CASES IN WORLD AT THIS MOMENT

HAS OCCASIONALLY BEEN TRANSMITTED
PERSON-PERSON BY BLOOD

MAIN DISEASE TYPES

SPORADIC CJD

WORLDWIDE
COMMONEST HUMAN PRION DISEASE

MOSTLY MIDDLE AGED & ELDERLY

OFTEN RAPID PROGRESSION

A NOTE ABOUT TERMINOLOGY

PRNP		The NORMAL human gene that produces Prion Protein *Mutations of it: Genetic Disease*
PRION PROTEIN	PrP	A protein
PRION PROTEIN	PrP^{C}	The NORMAL Prion Protein we all have
PRION PROTEIN	PrP^{Sc}	The ABNORMAL Prion Protein in disease That aggregates and is deposited in tissues
PRION PROTEIN	PrP*	ABNORMAL Prion Protein forms intermediate between PrP^{C} and PrP^{Sc}
PRION PROTEIN	PrP^{RES}	The Resistant Core of ABNORMAL Prion Protein
The PRION	Prion	The infectious particle: Composed entirely or mostly of abnormal PrP

DIAGNOSIS OF HUMAN PRION DISEASE

THINK OF IT AS A POSSIBILITY

EXCLUDE OTHER POSSIBILITIES

TESTS THAT SUPPORT THE DIAGNOSIS

PATHOLOGY

DIAGNOSIS OF HUMAN PRION DISEASE

THINK OF IT AS A POSSIBILITY

Rare: May have no knowledge/experience

But a competent clinician

Should recognize a serious illness

Should know how to seek advice

DIAGNOSIS OF HUMAN PRION DISEASE

EXCLUDE OTHER POSSIBILITIES

A very important fact:

Prion disease often presents non-specifically

May be other much more likely diagnoses

May be other *treatable* diagnoses

DIAGNOSIS OF HUMAN PRION DISEASE

EXCLUDE OTHER POSSIBILITIES

Many Tests:

Not initially specifically directed at Prion Disease

But at excluding other possibilities

Even ones that can support a Prion Disease Diagnosis

[eg: Brain MR, Spinal Fluid Analysis]

DIAGNOSIS OF HUMAN PRION DISEASE

TESTS THAT SUPPORT THE DIAGNOSIS

Since the 1980s: Huge Progress

THE DIAGNOSTIC PROCESS

IN THE PAST
CLINICAL DIAGNOSIS RESTED MOSTLY ON:

ESSENTIALLY NON-SPECIFIC TESTS

NOT RELATED TO BASIC DISEASE MECHANISMS

Seeing Suspect Cases in 1980 BEFORE Prion Protein

CLINICAL FEATURES

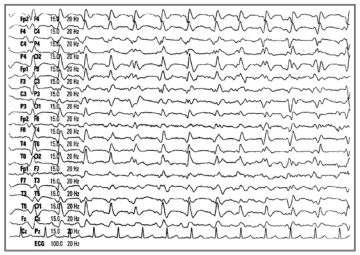
EEG

CT Brain:

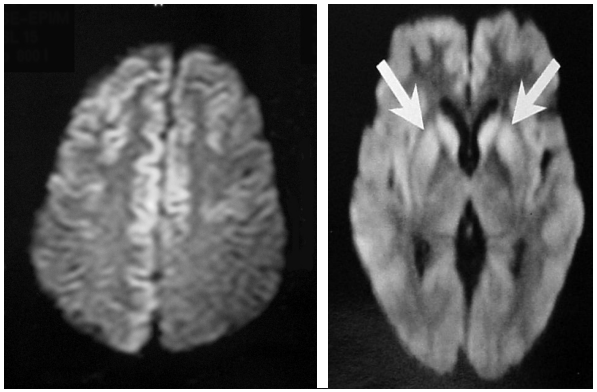
excluding some other diagnoses

But no positive support for diagnosis

ESSENTIALLY NON-SPECIFIC TESTS
NOT RELATED TO BASIC DISEASE MECHANISMS

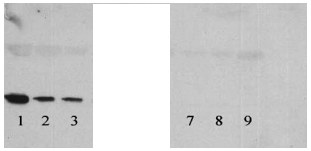


EEG



BRAIN MRI

CSF 14-3-3



THE RELEVANT ABNORMALITIES

CAN BE SEEN IN OTHER DISEASES

UTILITY: DEPENDS HEAVILY ON CLINICAL CONTEXT

For a While,

WE *HAVE* HAD
3 ESSENTIALLY SPECIFIC TESTS

One:

DETECTION OF GENETIC MUTATION

IN

GENETIC PRION DISEASES

For a While,

WE *HAVE* HAD
3 ESSENTIALLY SPECIFIC TESTS

Two:

NEUROPATHOLOGICAL DIAGNOSIS
REQUIRING BRAIN TISSUE

AT AUTOPSY: Diagnosis only after death

BY BRAIN BIOPSY: Not undertaken lightly

For a While,

WE *HAVE* HAD
TWO ESSENTIALLY SPECIFIC TESTS

Three:

DETECTION OF PrP^{Sc} in TONSIL BIOPSY

BUT: RELEVANT ONLY IN VARIANT CJD

BUT IN THE LAST FEW YEARS:

A NUMBER OF
NON-INVASIVE
ESSENTIALLY SPECIFIC TESTS
RELATED TO BASIC DISEASE MECHANISMS

ESSENTIALLY SPECIFIC TESTS:

DETECTION OF ABNORMAL PRION PROTEIN

DETECTION OF PrP^{Sc}

STANDARD METHODS OF DETECTION
DETECT ONLY HIGH LEVELS OF PrP^{Sc}

IN CJD (other than vCJD):
HIGH LEVELS ARE IN BRAIN
[LOW LEVELS CAN BE PRESENT]

ESSENTIALLY SPECIFIC TESTS:

DETECTION OF ABNORMAL PRION PROTEIN

But detection methods would work if

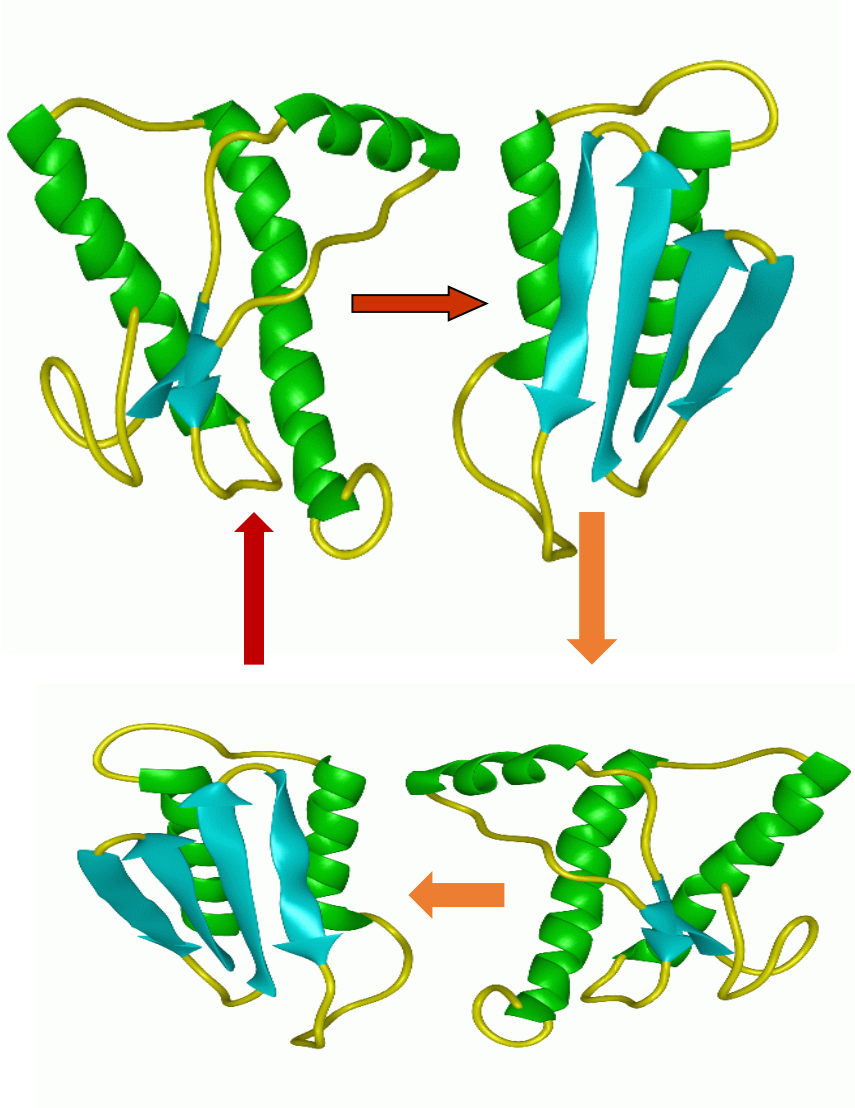
LOW LEVELS INCREASED

USING

AMPLIFICATION TECHNIQUES

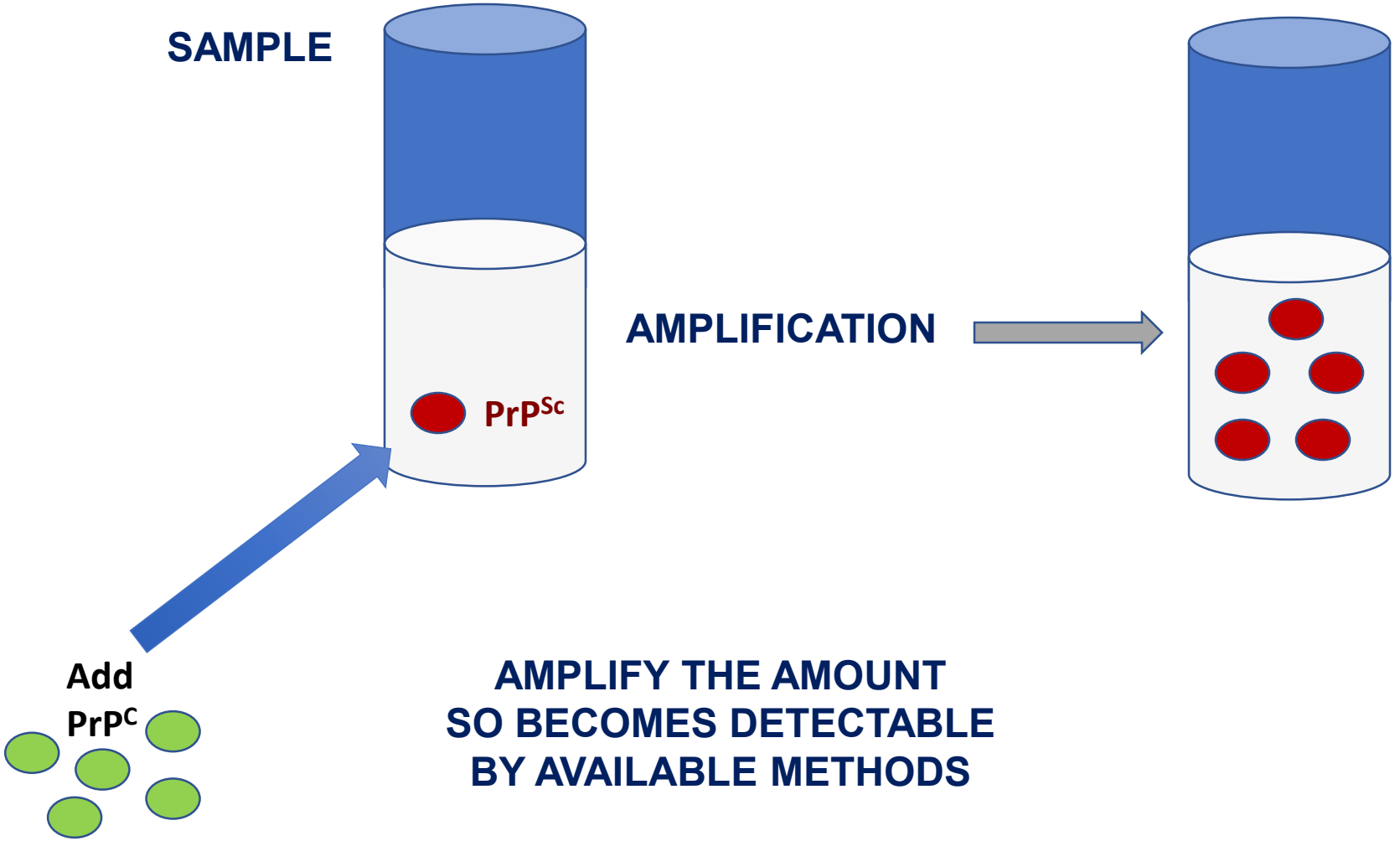
AMPLIFICATION TECHNIQUES HAVE BEEN DEVELOPED ESSENTIALLY BASED ON AUTO-CATALYTIC CONVERSION OF PRION PROTEIN

PrP^{C}



PrP^{Sc}

AMPLIFICATION



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 METHODS HAVE BEEN USED ON:

SPINAL FLUID

BLOOD

URINE

SKIN (BIOPSY)

NASAL BRUSHINGS

PrP^{Sc} AMPLIFICATION TESTS IN CLINICAL DIAGNOSIS
NOTE I

TECHNIQUES
TEND TO BEHAVE DIFFERENTLY
IN DIFFERENT PRION DISEASES

CSF SPORADIC CJD: RT-QuIC
CSF VARIANT CJD: PMCA

PrP^{Sc} AMPLIFICATION TESTS IN CLINICAL DIAGNOSIS NOTE II

A NUMBER OF RESEARCH DEVELOPMENTS

BUT

FEW YET PROPERLY EVALUATED
IN ROUTINE CLINICAL SETTINGS

THE BEST STUDIED: CSF RT-QuIC in SPORADIC CJD

CSF using RT-QuIC

NOW A STANDARD CLINICAL TEST

In the UK*:
Sensitivity 95+%
Specificity ~100%

*Different centres use slightly different techniques

TESTS IN PRACTICE

NO MATTER HOW TECHNICALLY GOOD THEY ARE

THEY NEED TO BE USED
BY AN APPROPRIATE CLINICIAN
IN AN APPROPRIATE PERSON
AT AN APPROPRIATE TIME

THEY REMAIN *PART* OF THE CLINICAL PROCESS

They cannot REPLACE the whole clinical process

FOOTNOTE:
IF PrP^{Sc} IS DETECTABLE IN BLOOD, URINE & SKIN IS IT A RISK TO OTHERS ?

GENERALLY PRESENT AT LOW LEVELS

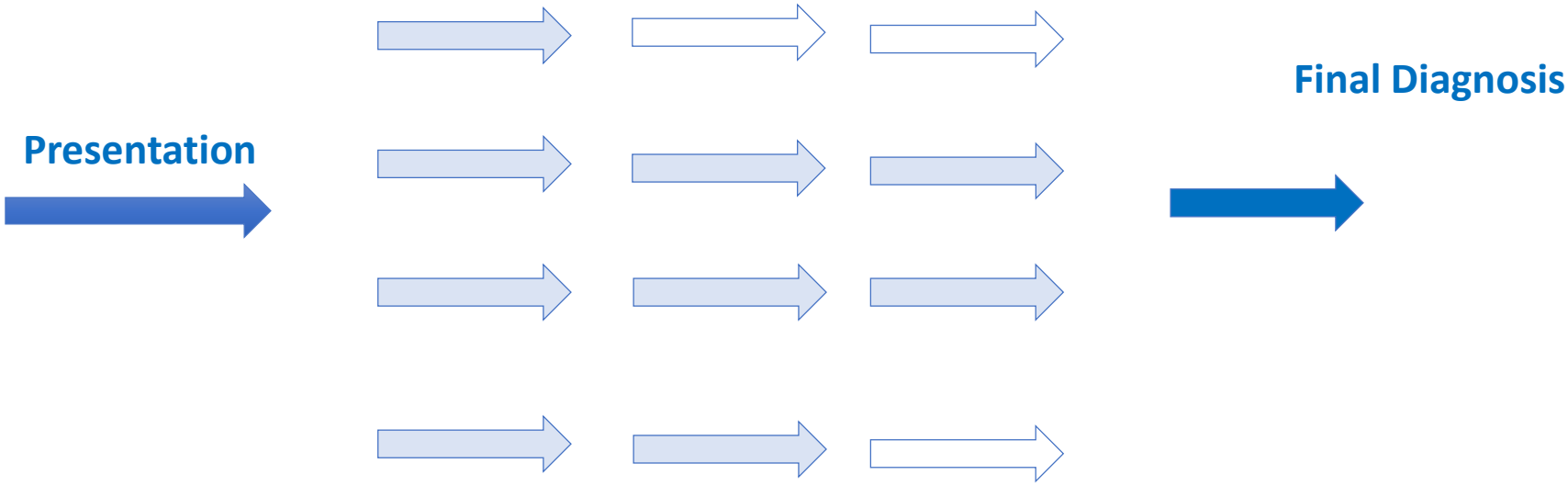
DETECTING ABNORMAL PrP IS NOT NECESSARILY DETECTING INFECTIVITY

INFECTION REQUIRES INFECTIVITY *AND* AN EFFECTIVE MEANS OF TRANSMISSION

INFECTIVITY IN EXPERIMENTS IS NOT NECESSARILY NATURAL INFECTION RISK

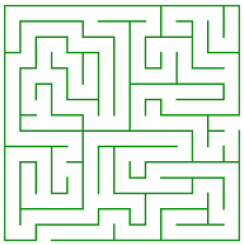
NO EVIDENCE OF 'ORDINARY' INFECTION WITH HUMAN PRION DISEASES EVEN WITH INTIMATE PERSONAL CONTACT

Through the diagnostic maze

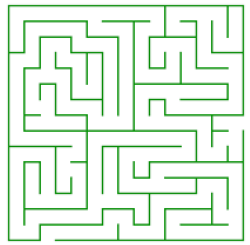


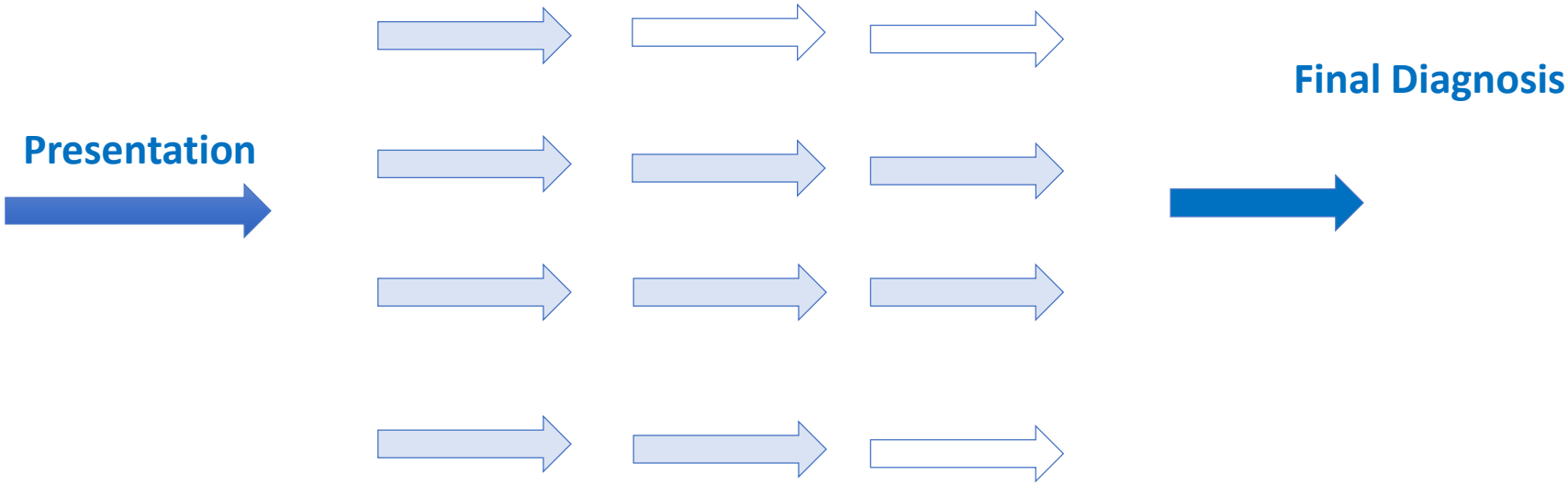
Patient/Family View

Looks Obvious
Presentation was Typical of CJD



Through the diagnostic maze

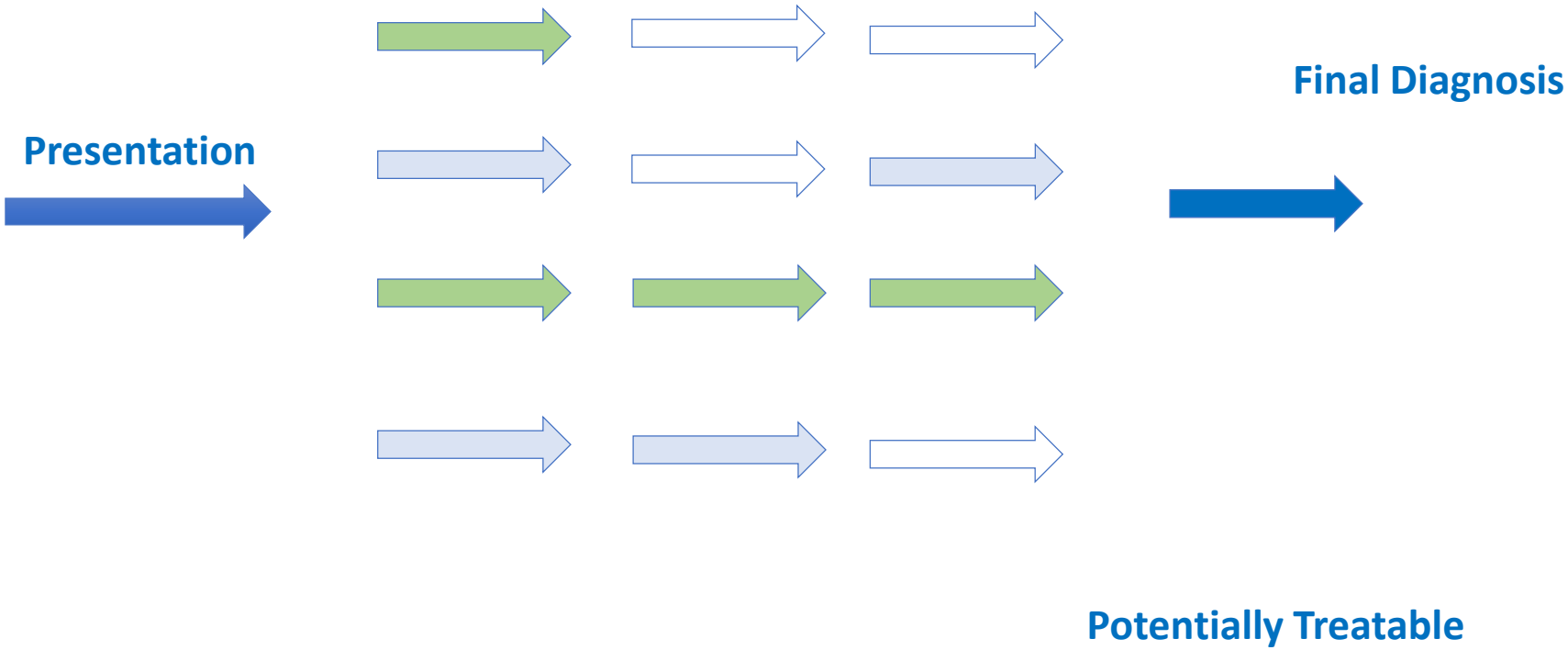


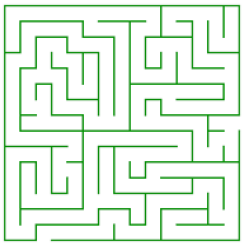


Medical View

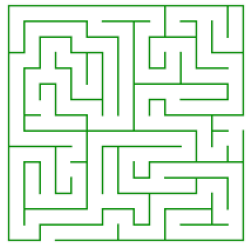
Not Obvious
Presentation Typical of many things

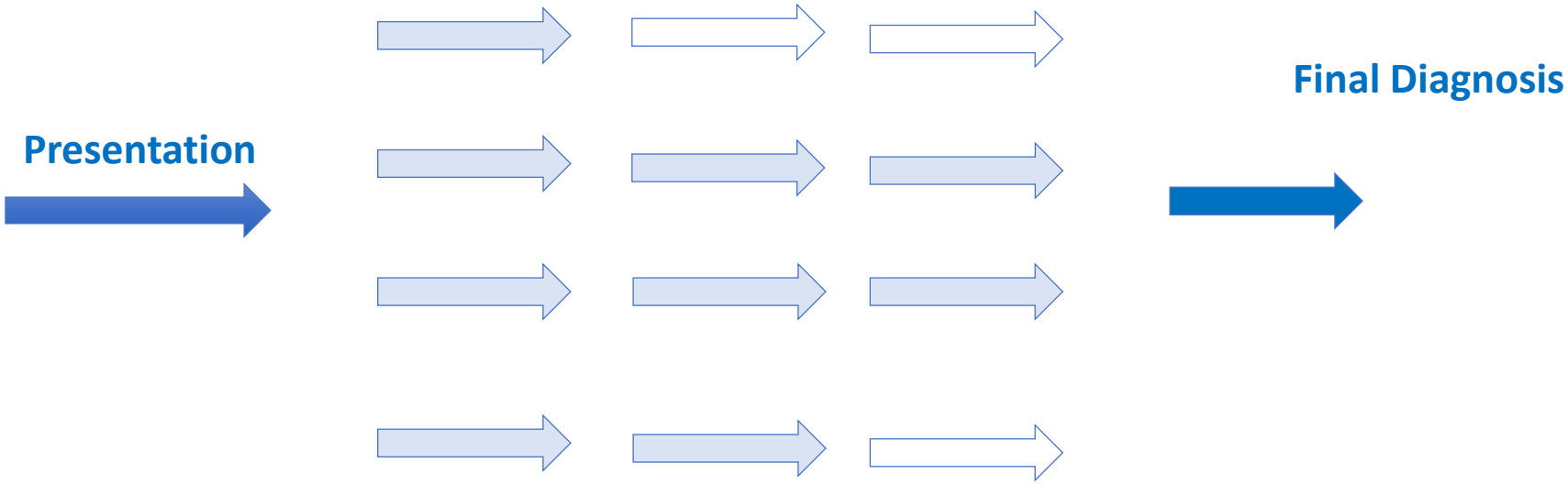
Through the diagnostic maze





Through the diagnostic maze





Frustratingly & agonisingly:
This process takes time…..but time is sometimes a *necessary* part of the process

DIAGNOSIS OF HUMAN PRION DISEASE

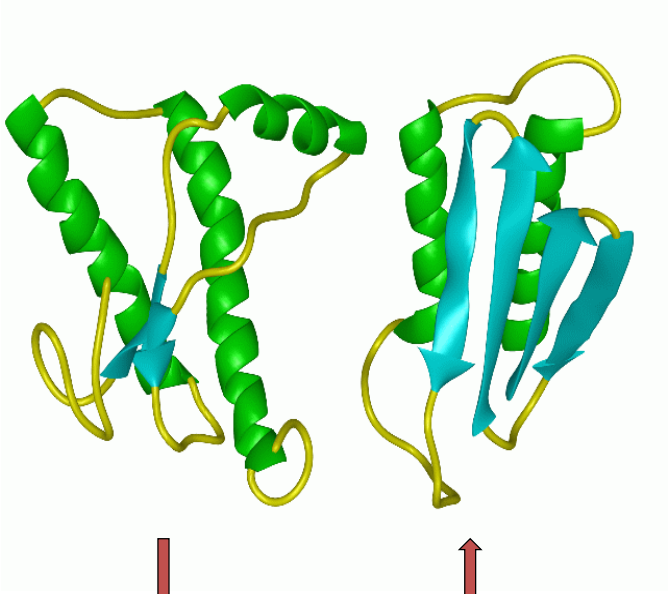
PATHOLOGY IS THE FINAL DEFINITIVE TEST

BUT

A VERY CONFIDENT CLINICAL DIAGNOSIS IS POSSIBLE IN MANY CASES

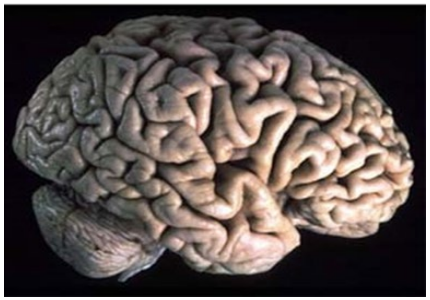
For example:
Antibody against PrP^C
to deplete it

PrP^C

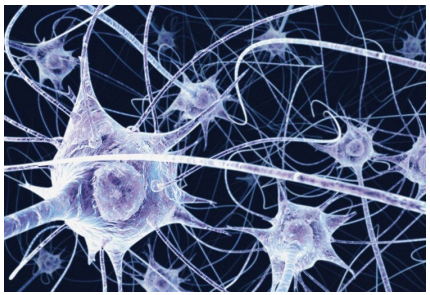


PrP^{Sc}

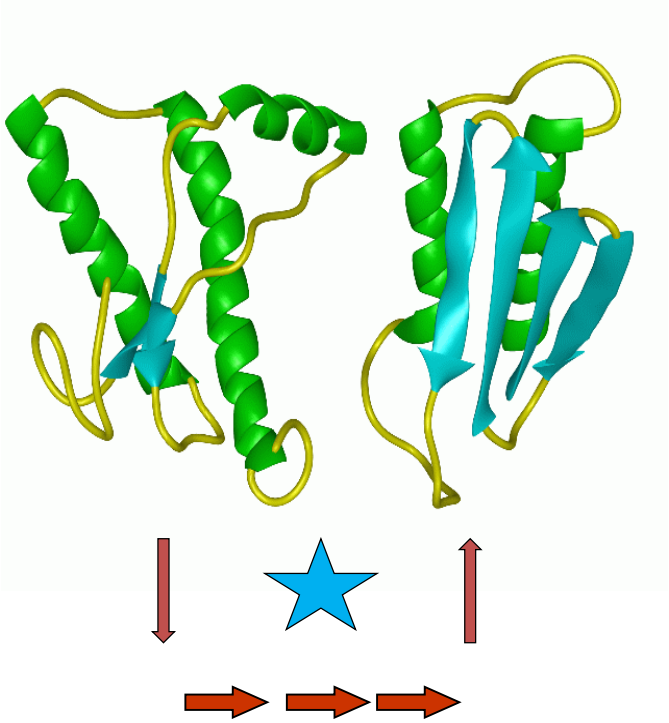
INTERMEDIATE FORMS



PROCESS OF NEURONAL DEATH



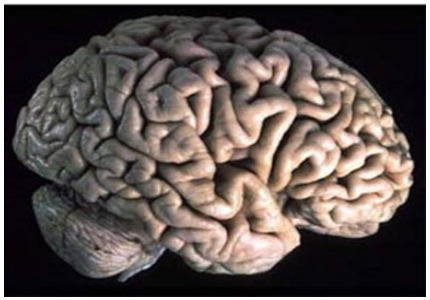
PrP^{C}

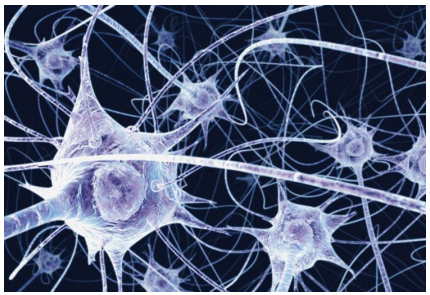


PrP^{Sc}

INTERMEDIATE FORMS

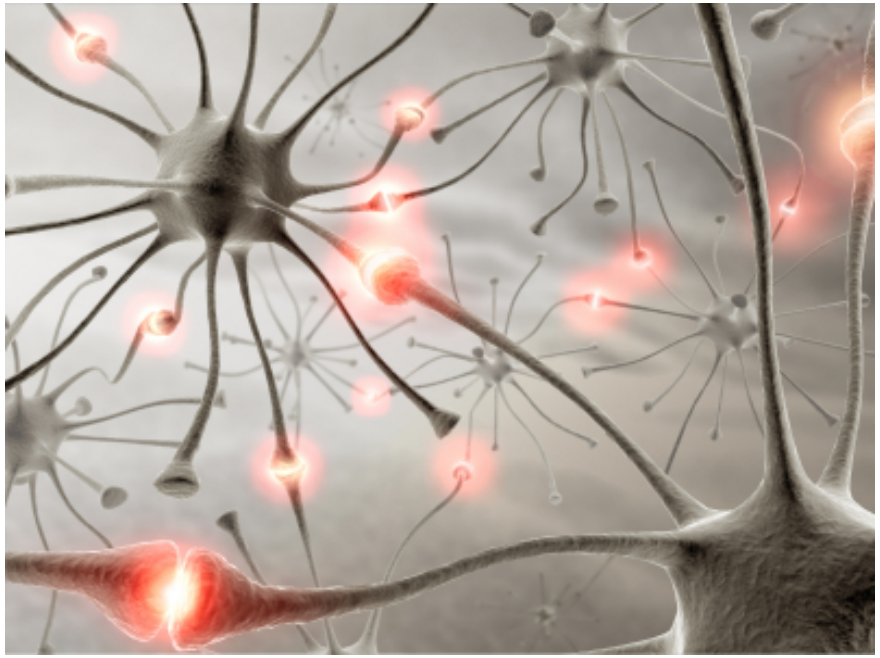
For example:
Small molecules
That interfere with this process





PROCESS OF NEURONAL DEATH

UNDERSTANDING PROCESSES OF NEURONAL DEATH



PROBABLE EARLIEST CHANGES IN SYNAPSES

EXPERIMENTAL EVIDENCE THAT THESE EARLY CHANGES ARE REVERSIBLE

A NOTE OF CAUTION:
TWO TREATMENT SITUATIONS

CLINICAL ILLNESS	PREVENTION
TREATMENT FOR PEOPLE ALREADY ILL	TREATMENT BEFORE ILL Eg GENETIC MUTATION CARRIERS
MAY WELL BE TOO LATE	
Eg of AD TRIALS	

RETURN TO THE FOLD
BACK TO THE FUTURE

ALZHEIMER'S

MOTOR NEURONE DISEASE

PARKINSON'S

COULD THEY BE TRANSMISSIBLE TOO ?