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
DETECTION OF GENETIC MUTATION IN GENETIC PRION DISEASES
II

DETECTION OF PrP$^{Sc}$

BRAIN
ESSENTIALLY SPECIFIC TESTS

III

DETECTION OF PrP$^{Sc}$

BRAIN: BIOPSY or AUTOPSY
III

DETECTION OF PrP$_{Sc}$ ELSEWHERE IN BODY?

TONSIL: variant CJD
OUTLINE

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SUMMARY: A GUIDE TO LISTENING TO EXPERTS
TWO BROAD DEVELOPMENTS RELATED TO BASIC DISEASE MECHANISMS

IMPROVED DETECTION OF PrP$^{\text{Sc}}$

SIMPLER METHODS TO OBTAIN NEURAL TISSUE
ESSENTIALLY SPECIFIC TESTS RELATED TO BASIC DISEASE MECHANISMS

\[ \text{PrP}^{\text{Sc}} \ \text{CAN BE FOUND OUTSIDE OF BRAIN} \]

IN SPORADIC CJD

BUT AT LOW LEVELS
ESSENTIALLY SPECIFIC TESTS
RELATED TO BASIC DISEASE MECHANISMS

PrP$^\text{Sc}$ DETECTABLE

IF LOW LEVELS INCREASED
USING
AMPLIFICATION TECHNIQUES
AMPLIFICATION

SAMPLE

PrP<sub>Sc</sub>

AMPLIFY THE AMOUNT SO BECOMES DETECTABLE BY AVAILABLE METHODS
ESSENTIALLY BASED ON AUTO-CATALYTIC CONVERSION OF PRION PROTEIN

PrP<sup>C</sup>  ➔  PrP<sup>Sc</sup>
TWO BASIC PrP\textsuperscript{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 PrPSc

SIMPLER METHODS TO OBTAIN NEURAL TISSUE
BRUSHING TO OBTAIN OLFACTORY NEURONES USING AMPLIFICATION METHODS TO AID PrP<sup>Sc</sup> 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\textsuperscript{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

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TREATMENT POSSIBILITIES

SUMMARY: A GUIDE TO LISTENING TO EXPERTS
WE ALL WANT SUCCESSFUL TREATMENT

SUPERFICIALY STRAIGHTFORWARD:

GIVE A TREATMENT

DO THEY GET BETTER OR NOT?
TWO TREATMENT SITUATIONS

CLINICAL ILLNESS

PREVENTION

GENETIC MUTATION CARRIERS
TWO TREATMENT SITUATIONS

A TREATMENT MAY BE EFFECTIVE IN ONE ROLE BUT NOT THE OTHER
WHAT DO TREATMENTS DO?

NOT ALWAYS EASY TO TELL THE DIFFERENCE
WHAT DO TREATMENTS DO?

DISEASE PROCESS

CURE

MAJOR

MINOR

POTENTIALLY DIFFICULT TO DETECT
WHAT DO TREATMENTS DO?
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]
TREATNG 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
DISEASE

VARIABLE

VARIABLE

VARIABLE

TREATMENT
VARIABILITY IN DISEASE TYPES
- Sporadic
- Genetic
- Iatrogenic
- Zoonotic

PERSON

TREATMENT
PERSON

COMMONEST FORM
SPORADIC CJD

TREATMENT
USING SURVIVAL AS A END-POINT?

Pocchiari et al. BRAIN 2004

Kaplan-Meier survival curves

Sporadic CJ D

Gender

Age at onset

Cumulative survival (%) vs. Disease duration (months)

$F, M$

$p < 0.0001$

USING SURVIVAL AS A END-POINT?

Pocchiari et al. BRAIN 2004

Kaplan-Meier survival curves

Sporadic CJ D

Cumulative survival (%) vs. Disease duration (months)

$F, M$

$p < 0.0001$
USING SURVIVAL AS A END-POINT?

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Kaplan-Meier survival curves

Sporadic CJ D

\[ p < 0.0001 \]

\[ p < 0.0001 \]

PRNP 129

PrP Type

\[ p < 0.0001 \]
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
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SUMMARY: A GUIDE TO LISTENING TO EXPERTS
INTERMEDIATE FORMS

PROCESS OF NEURONAL DEATH

PrP<sub>C</sub>

PrP<sub>Sc</sub>
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

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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
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