

Intrathecal oligoclonal IgG in MS

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SKML – sectie HIM
13-DEC 2012, 13:30-14:15



Overview

- Are OCB in MS dead?
- *Vote #1*
- A brief history of OCB in MS
- UK NEQAS: 16 years OCB QC experience
- *Intermezzo*
- A meta-analysis
- *Vote #2*
- Conclusion



The new diagnostic criteria in MS

TABLE 4: The 2010 McDonald Criteria for Diagnosis of MS

Clinical Presentation	Additional Data Needed for MS Diagnosis
≥2 attacks ^a ; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack ^b	None ^c
≥2 attacks ^a ; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) ^d ; or Await a further clinical attack ^a implicating a different CNS site
1 attack ^a ; objective clinical evidence of ≥2 lesions	Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack ^a
1 attack ^a ; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For DIS: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) ^d ; or Await a second clinical attack ^a implicating a different CNS site; and For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack ^a
Insidious neurological progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria ^d : 1. Evidence for DIS in the brain based on ≥1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions 2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

Omission of OCB provokes protest

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Ann Neurol. 2011 Jul;70(1):183; author reply 183-4. doi: 10.1002/ana.22466.

Cerebrospinal fluid analysis in the 2010 revised McDonald's multiple sclerosis diagnostic criteria.

[Galea I.](#) [Freedman MS.](#) [Thompson EJ.](#)

Comment on
Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. [*Ann Neurol.* 2011]

PMID: 21786311 [PubMed - indexed for MEDLINE]

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Ann Neurol. 2011 Sep;70(3):520; author reply 521. doi: 10.1002/ana.22508. Epub 2011 Jun 27.

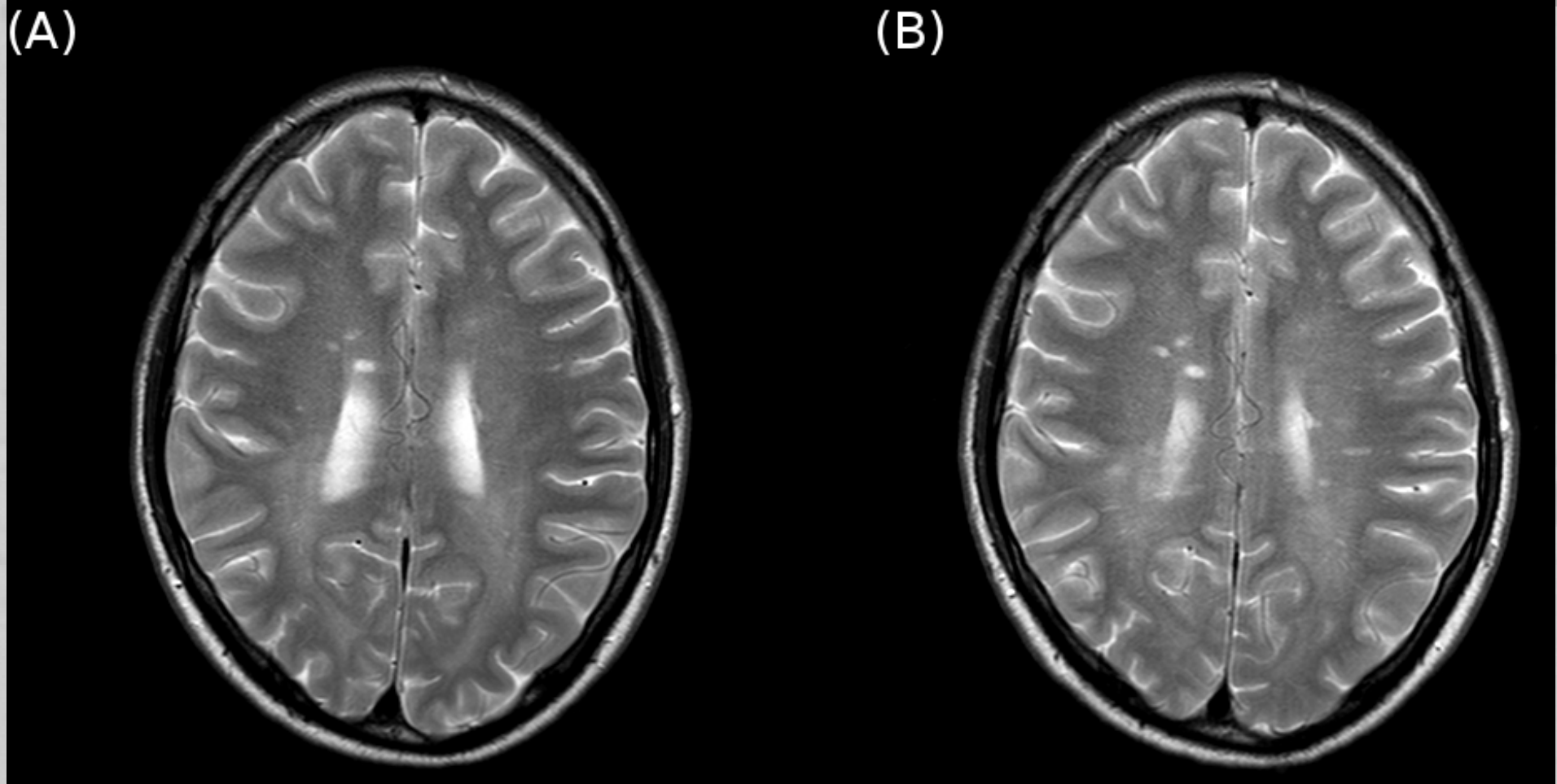
Revised McDonald criteria: the persisting importance of cerebrospinal fluid analysis.

[Tumani H.](#) [Deisenhammer F.](#) [Giovannoni G.](#) [Gold R.](#) [Hartung HP.](#) [Hemmer B.](#) [Hohlfeld R.](#) [Otto M.](#) [Stangel M.](#) [Wildemann B.](#) [Zettl UK.](#)

Comment on
Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. [*Ann Neurol.* 2011]

PMID: 21710627 [PubMed - indexed for MEDLINE]

A own case – VUmc – July 2011



41 yrs, male patient:

Feb-2011 vertigo+nystagmus, MRI (A): exclusively PV located lesions

Jul-2011 ON OD (VEP P100 125 ms), MRI (B): unchanged lesions

CSF: IEF shows OCB



Before 2011: CSF OCB could substitute for radiological DIS in RRMS

Since 2011: CSF OCB cannot substitute for radiological DIS in RRMS



Vote #1

Who thinks CSF OCB should still be allowed to substitute for radiological DIS in MS?



The origin of CSF in MS

1925-1930 Arne Tiselius (Uppsala).

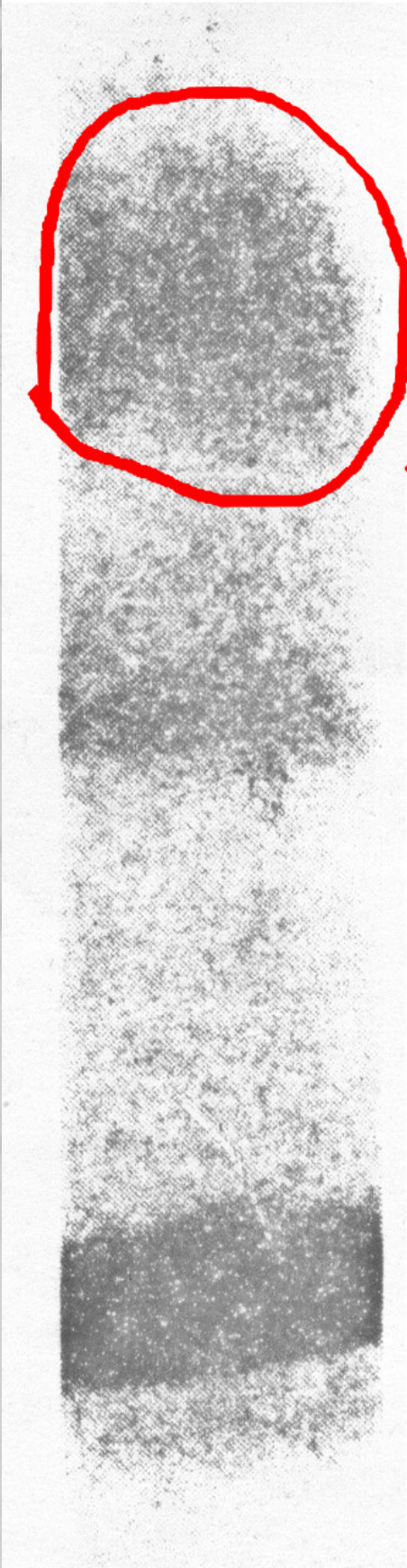
Discovers electrophoresis - 1948 Noble prize

1942 Elvin Kabat (New York)

first to use electrophoresis for CSF (70 mL !)

describes an increase of gamma globulin in the CSF not seen in the serum

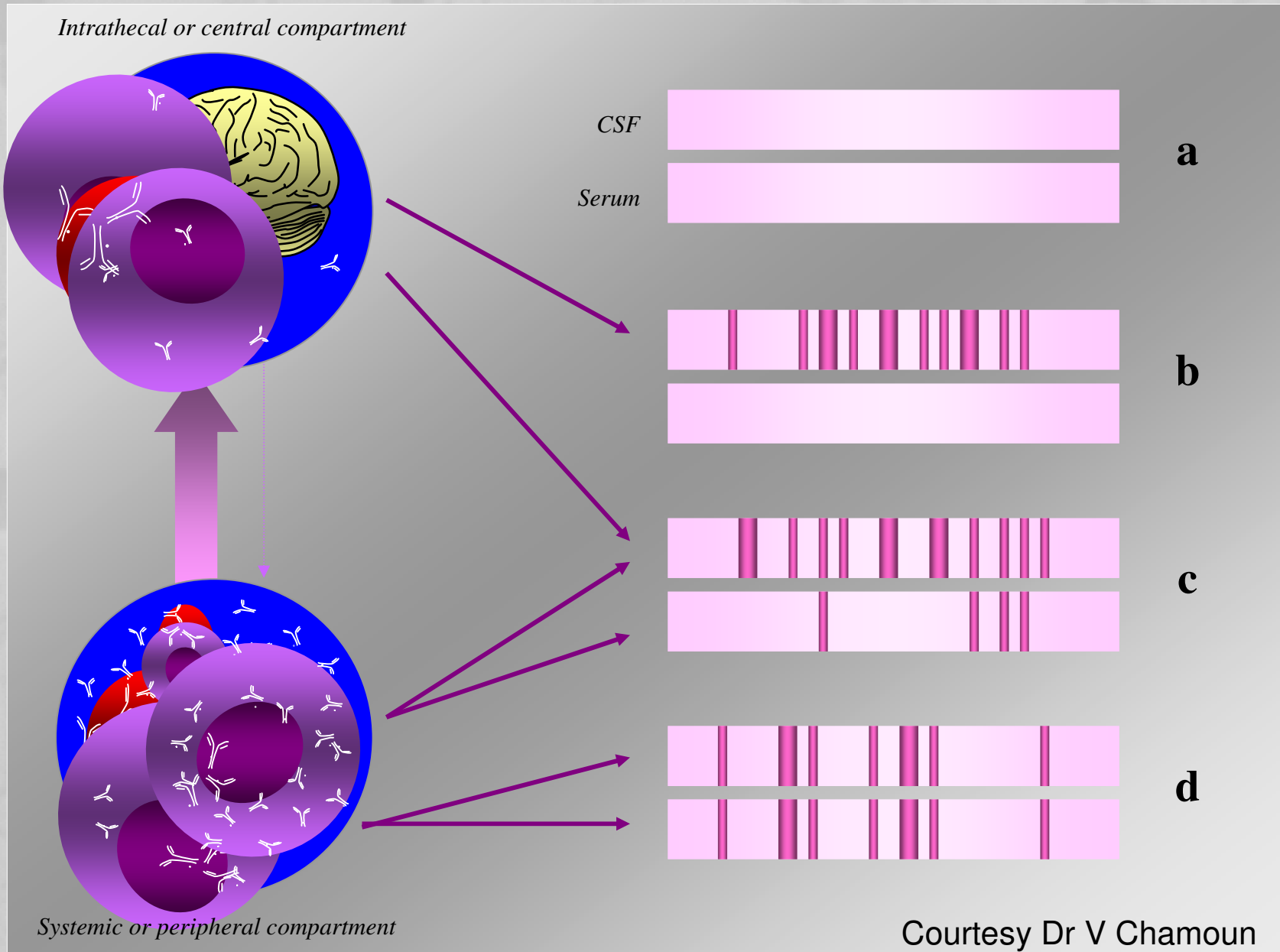




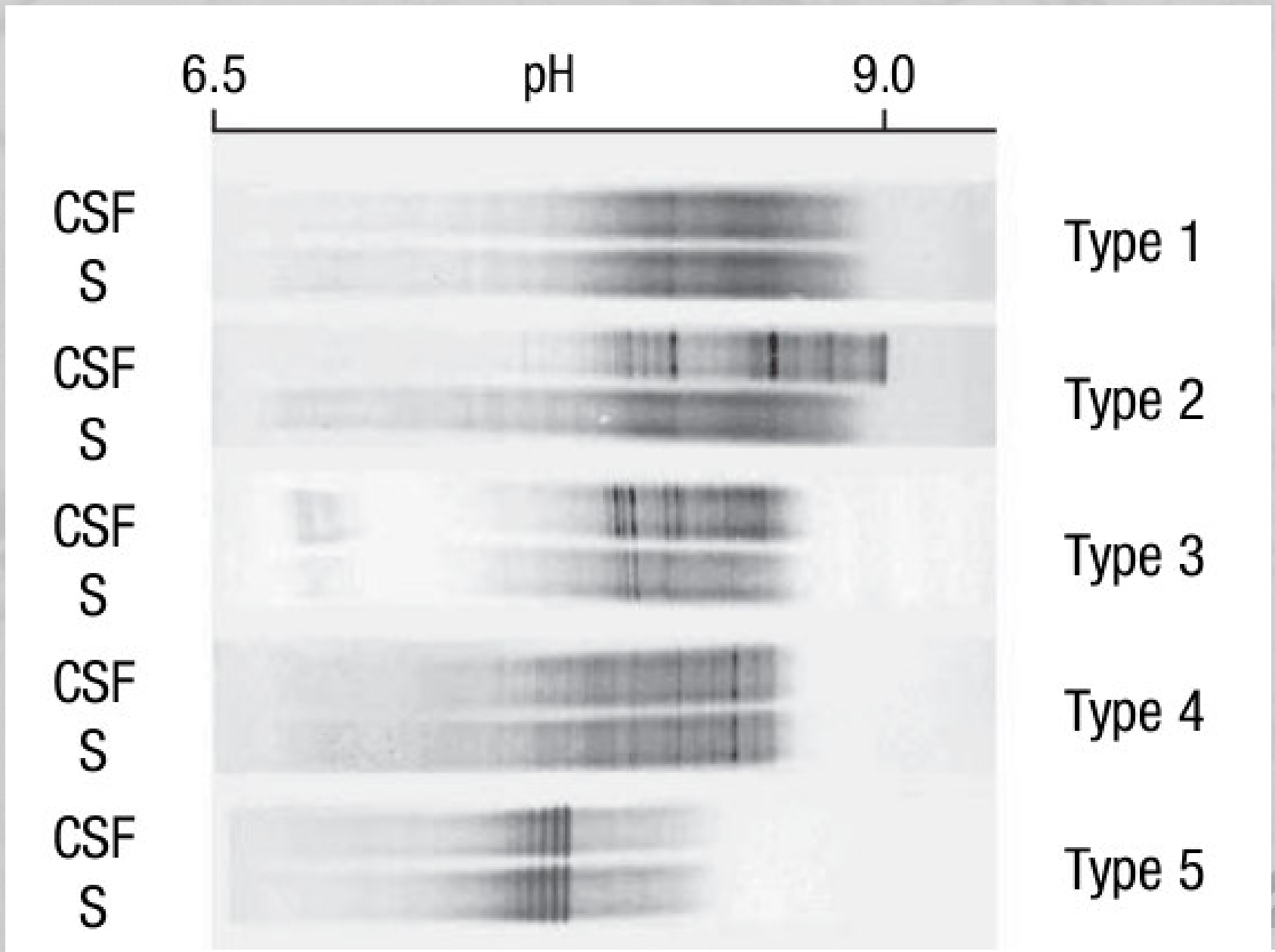
CSF

Serum

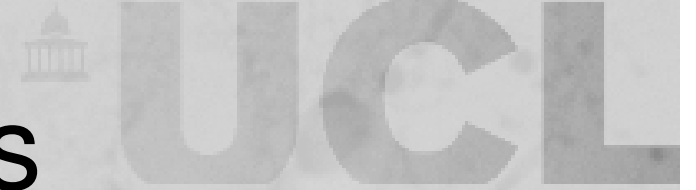
OCB sources



The 5 OCB pattern



OCB consensus guidelines



A pre-2005 literature review reveals a low diagnostic sensitivity for OCB in MS (45%-77%)

D.F. Keren *Am J Clin Pathol* 2003;120:649-651

This contrasts with the experience of pioneering experts in the field

Updated consensus guidelines are published

M.S. Freedman *et al. Arch Neurol* 2005;62:865-870



Sensitivity of CSF OCB for MS

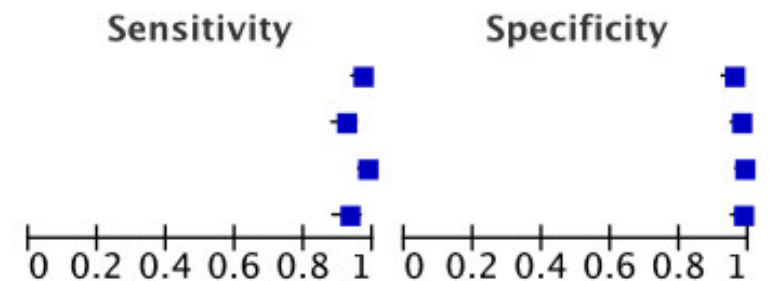
Reference	Patients (n)	MS (n)	Sensitivity (%)
Kostulas 1987	1114	58	100
McLean 1990	1007	82	95
Ohman 1992	558	112	96

M.S. Freedman *et al.* Arch Neurol 2005;62:865-870



UK NEQAS 2008-2011

Study	TP	FP	FN	TN	Sensitivity	Specificity
UK NEQAS 2008	245	12	9	241	0.96 [0.93, 0.98]	0.95 [0.92, 0.98]
UK NEQAS 2009	243	7	22	254	0.92 [0.88, 0.95]	0.97 [0.95, 0.99]
UK NEQAS 2010	271	5	6	275	0.98 [0.95, 0.99]	0.98 [0.96, 0.99]
UK NEQAS 2011	177	4	14	182	0.93 [0.88, 0.96]	0.98 [0.95, 0.99]



Acknowledgement: Mrs D Patel & Dr W Egner, UK NEQAS

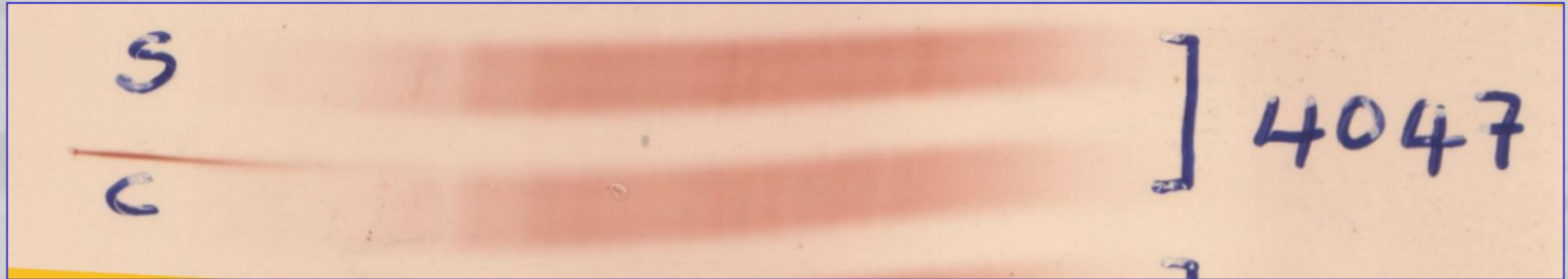


Intermezzo

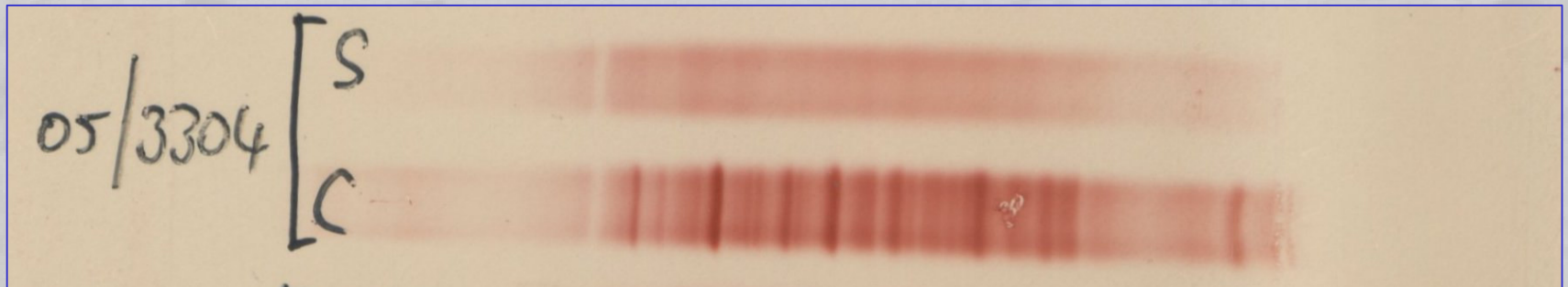


Pattern training

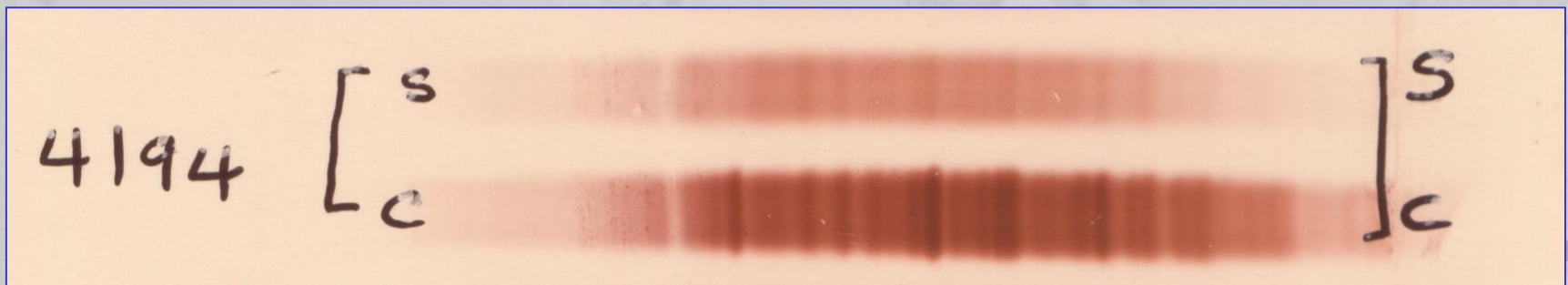
“normal”



“MS”



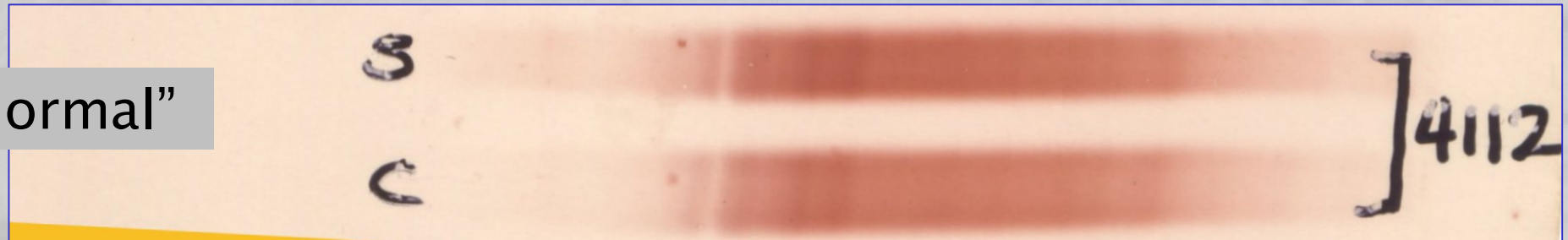
“MS”



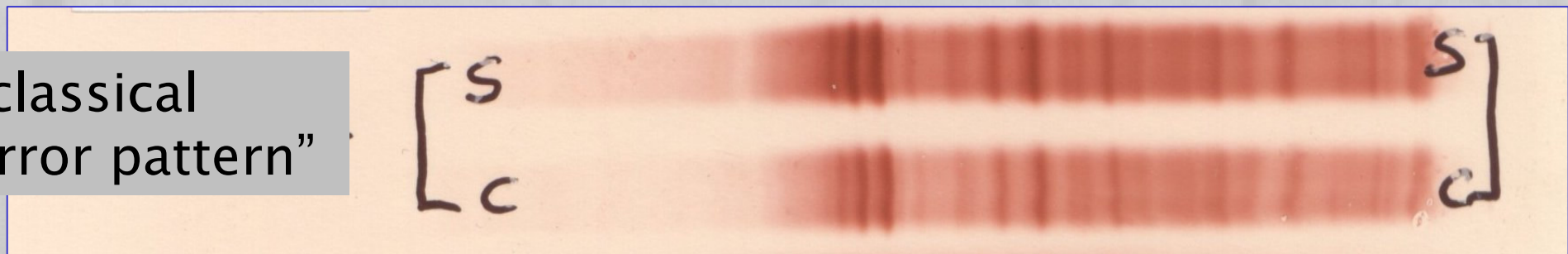
CSF Isoelectric focusing requires only 2.5 microlitres CSF!

Pattern training

“normal”



“A classical mirror pattern”



Pattern training

“contaminated”

Serum

CSF



Courtesy of Dr A Bartos, Prague

IEF+

Silverstain

LHON, G3460A mutation

- 18 year old male
- Loss of vision in L eye followed by R eye 2/12 later
- No pain
- Progressive
- No other symptoms
- MRI (STIR): chiasmal hyperintensity
- CSF: ... pattern?



S C

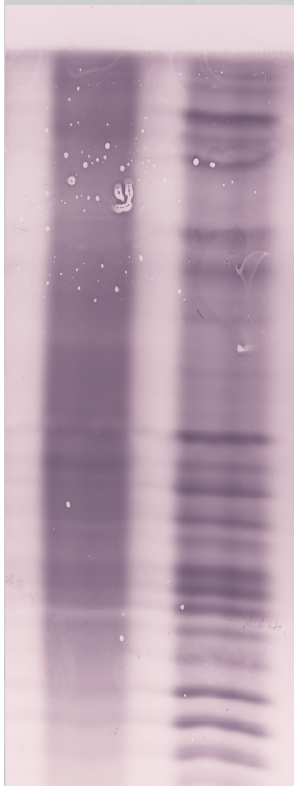


Courtesy of Prof Brassat, Toulouse

IEF +
immunoblot

Wolfram's Syndrom (DIDMOAD)

- 19 year old Female
- Hx of optic atrophy & ataxia (cerebellar), deafness
- PmHx: Type I Diabetes, meningitis as child
- FHx: NIL
- Died aged 21 (suicide)
- CSF: no cells, normal proteins, ... pattern?



S C

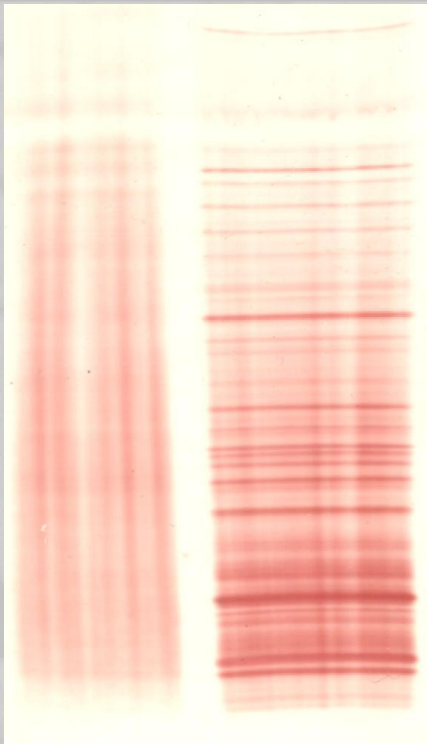
Positive for wolframin mutation (AR)
diabetes, deafness, optic atrophy



Courtesy of Prof F Deisenhammer

Morvan's Syndrom

IEF+
immunoblot



S

C

- 18 year old male
- PmHx: Gilbert's syndrome
- 1 year Hx of fatigue, disrupted sleep pattern, constipation, hypersalivation & hyperhidrosis, painful cramps, myotonia, fasciculations
- CSF: ... pattern ?

Loscher et al. Muscle & Nerve 2004;30:157-163

- CK 600 U/L (n < 80 U/L)

- EMG: myokymic & neuromyotonic discharges

- No antibodies to AchR, P/Q or VGKC, Hu,

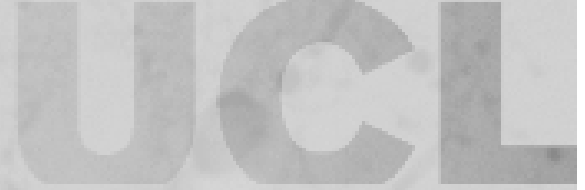
Ma2

The last 5 minutes...

- Are OCB in MS dead?
- *Vote #1*
- A brief history of OCB in MS
- UK NEQAS: 16 years OCB QC experience
- *Intermezzo*
- **A meta-analysis**
- *Vote #2*
- Conclusion



Conclusion: CSF OCB in MS



Excellent GLP can be achieved (UK NEQAS)

Diagnostic sensitivity > 90%

Diagnostic specificity ~ 60% were it matters

OCB a substitute for radiological DIS?

“No, one unspecific test should not be replaced by another.”



... the end

Thank you for your attention !

