# Outcomes (? stating the obvious)

- **1) Long term outcomes (LTOs) account for main social, medical & economic impact of MS, exponentially w T**
- **2) SP- main determinant LTO, progressive cane, bed, dead**
- **3) Development of SP matters most to patients, families, 3rd party payers - predictable, irreversible**
- **4) SP Rx Studies negative, 0 focus on SP devel In RR trials**
- **5) Relapse/MRI reduction - many Rx - none convincingly influence LTO, lengthen T to SP, nor SP probability**
- **6) Relapses not suitable outcomes if LTO is target and short term"disability" measures relapses not disability**
- **7) Nat Hist data on early relapses operate via SP so this is what should be measured if you insist on relapses**

SP is secondary progressve


Robert McNamara

"It is important to measure what matters most, not make what can most easily be measured matter."

Very a propos of MS clinical trials as this epitomises much of the last 25 years

So lets go back 25 years

# Jekyll Island referendum 1989 approx 60 MS trialists voting

**Table 1. Measures of response to experimental therapy**

| Outcome measure (ranked) | Responses: Probably significant n (%) | Responses: Most convincing n (%) | Total n (%) |
|---|---|---|---|
| 1. Change EDSS ≥1.0 on 2 consecutive exams | 29 (47) | 19 (30) | 48 (77) |
| 2. Change ambulation index ≥2 steps on 2 consecutive exams | 21 (34) | 24 (39) | 45 (73) |
| 3. Change mean EDSS between treatment groups | 34 (55) | 10 (16) | 44 (71) |
| 4. Change mean ambulation index between groups | 36 (58) | 7 (11) | 43 (69) |
| 5. Number MRI events | 27 (44) | 15 (24) | 42 (68) |
| 6. Opinion blinded MD | 29 (47) | 10 (16) | 39 (63) |
| 7. Change mean quantitative neurologic exam between groups | 25 (40) | 13 (21) | 38 (61) |
| 8. Estimated probability of no worsening | 25 (40) | 11 (18) | 36 (58) |
| 9. Number of treatment failures per group | 26 (42) | 7 (11) | 33 (53) |
| 10. Time to treatment failure | 24 (39) | 8 (13) | 32 (52) |
| 11. Relapse frequency | 24 (39) | 8 (13) | 32 (52) |

# London Ont. Natural History Study

1023 pts followed yearly (806 RR rest PP)

Population-based sample

"Full" ascertainment

concomitant prev. study Middlesex Cty core subcohort ( n= 300)

Stable population little outmigration,

NH 1-10, Weinshenker et , Cottrell et, Kremenchutzky et, Scalfari et

i saw 20-30 MS patients for almost 25y to collect plus many colleagues

# Reanalysis 28,000 patient-yrs.

**shortest followup in the sample was 16 years**

**and the only nat hist study giving an accounting of loss/retention**

95% followup 806 RR

97% diagn. accuracy

clin criteria preMR no treatable missed

> 40% dead , > 40% Dss 6+

>75% of lifetime, >90% ambulatory course

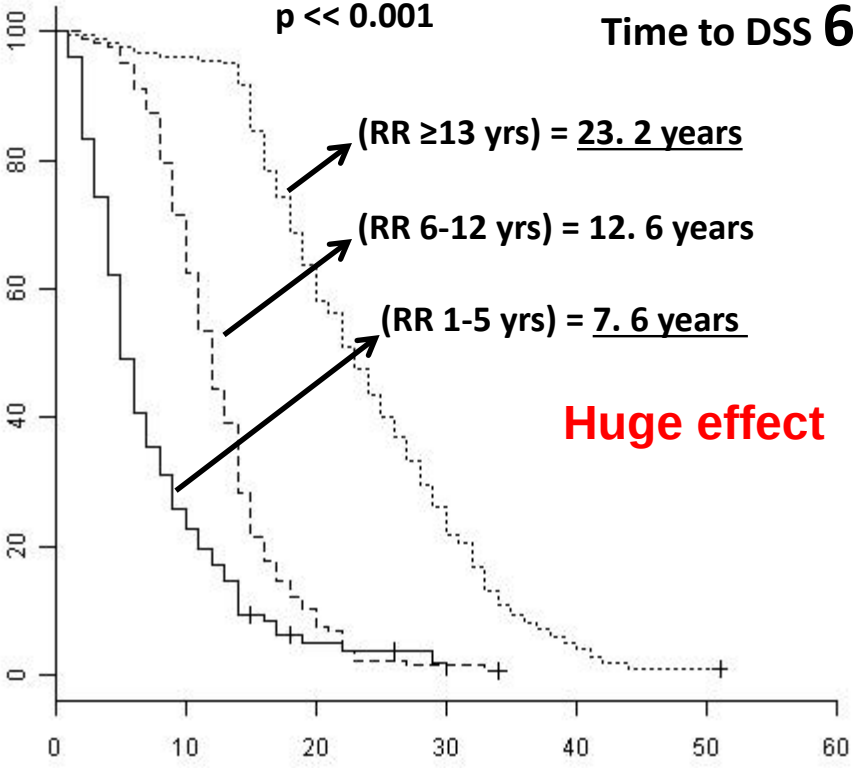
Focus – preSP i.e. from onset

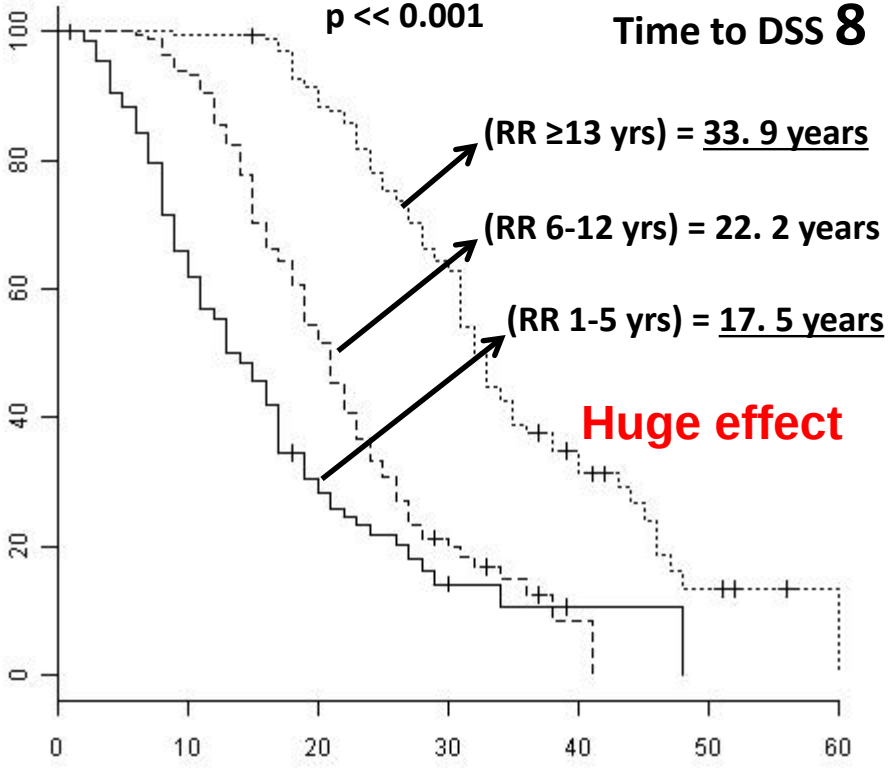
# Predictive effect of latency to progression

## Duration of RR phase= latency of SP

- **Short (continuous line) = 1-5 years**
- **Int. (dashed line) = 6-12 years**
- **Long (dotted line) ≥ 13 years**

**Survival analysis from disease onset**



# Relapses and progression

DSS 6,8,10 i.e. cane, bed, and dead **(no sissy outcomes)**

**Site of first attack ? cf. compartmentalisation theory Lassmann**

Recovery from first attack complete vs. partial

Polysymptomatic/disseminated onset vs. unifocal

PPMS primary progressive disease +/- relapses ?

Age onset progressive course (none vs one vs many preceding)

PPMS/SAPMS/SPMS - survival (none vs one vs many)

Progression and relapses ? y1-y2 vs. y3-SP vs all

Suppression of relapses and progression LTF data

Suppression of mri and progression LTF data

SAP is single attack followed by progression

# Site of first attack ~ irrelevant for long term outcomes

<u>No significant difference among common sites</u>

(there might be for low levels but certainly not for 6,8,10)

Brain stem only marginally worse $p<0.02$ not sig after bonferroni ON better and motor cord worse? **No**

Preferential progress site of initial attacks? **No**

So much for onset-specific compartmentalisation predicting progression to begin and be worse at sites of previous attacks

# Relapses and progression

DSS 6,8,10 i.e. cane, bed, and dead (no sissy outcomes here)

Site of first attack ?

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# Complete recovery vs. partial vs. none

No difference - lack of recovery not an intrinsic feature of individual disease

(determined by random factors, evident to experienced clinicians following individual patients and in studies of CIS)

# Relapses and progression

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# Polysymptomatic vs. unifocal onset ~Severe vs. mild onset

No difference in T to 6, 8, or 10

# Relapses and progression

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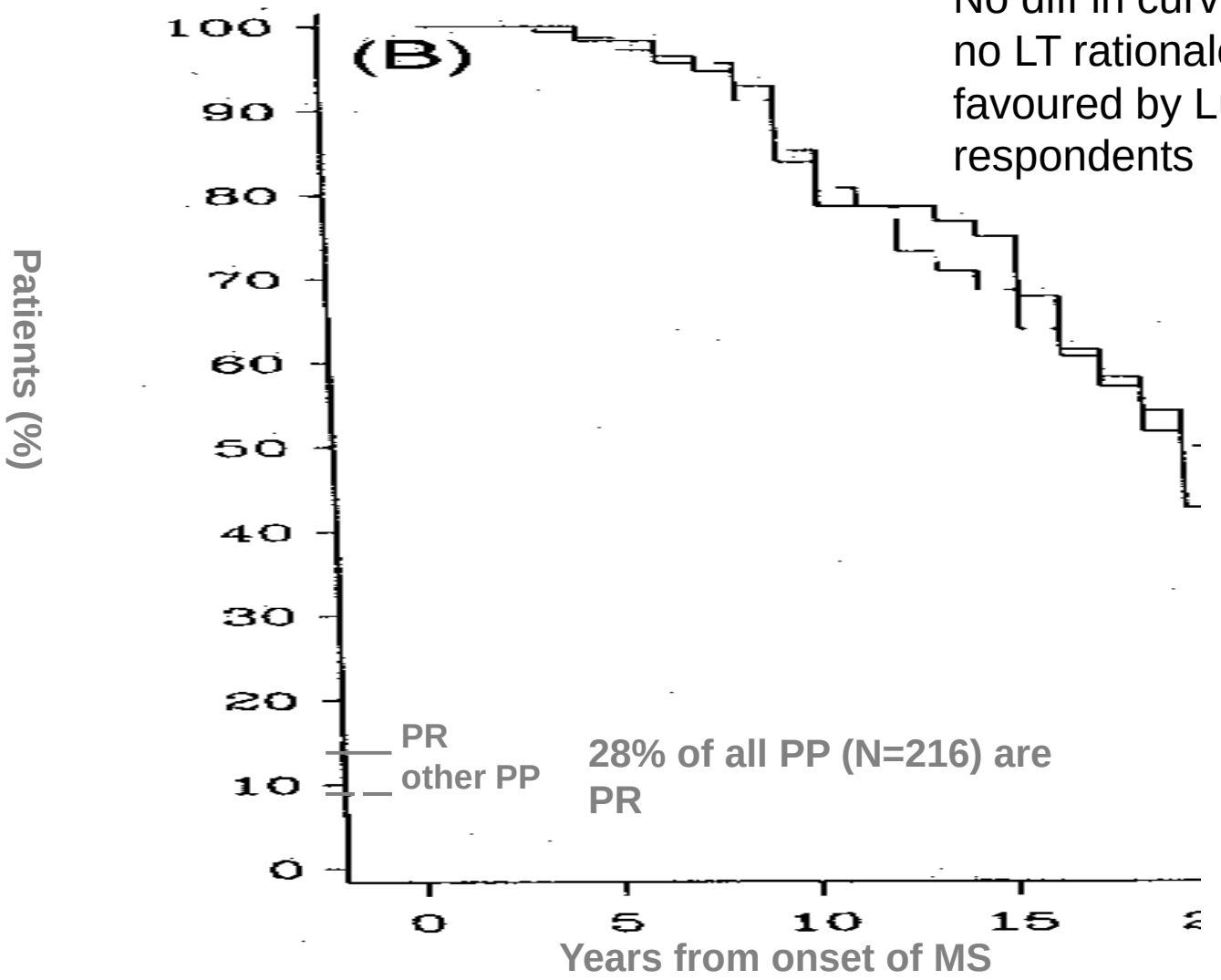
PPMS *with* relapses (28%) = PPMS *without* for times to DSS 6, 8, 10

Survival distribution of PP MS with (PR) & without ('pure' PP) superimposed relapses
Time to **DSS8**

No diff in curves to DSS8, no LT rationale for RP MS favoured by Lublin respondents




Kremenchutzky et al, Brain 1999

# Relapses and progression

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# Do relapses shorten SP latency? main outcome determinant

## Mean ages of onset of progressive deficit (DSS≤2)

| Progressive MS types Total N = 759 | | Onset progression Mean (years) |
|---|---|---|
| SPMS - all | N=270 | 39.4 |
| SPMS (-SAP) | N=130 | 39.2 |
| *SAPMS | N=140 | 40.9 |
| PPMS | N=219 | 38.6 |

**Many relapses preSP vs. none?**

**onset not sooner but slightly later**

**NO INDICATION THAT RELAPSES INFLUENCE AGE OF ONSET OF SP**

* includes second series of SAPMS

# Causality Predictions (widely believed)

(if relapses and late disability were *causally* related)

Relapse freq influences onset age of SP

as main outcome determinant dwarfing all others

**No, none vs. many - sl. *earlier* onset PP vs SP 38y**

**SP40y** ↑Total attacks relate to worse outcome

**No , (actually y3+ assoc. (trials) with <u>better</u>**

**outcome)** Attacks during pivotal trials more

NB **important and no**

**No they aren't, they are clearly <u>less</u> rationale for suppressing them as a primary target**

<u>Poss</u>. rationale for v. early attacks

# Effect of latency to progression on SP course itself

**v. Little effect on times to DSS6 or 8 from SP onset (most SP onset at DSS3)**

Duration of RR phase

- **Short (continuous line) = 1-5 years**
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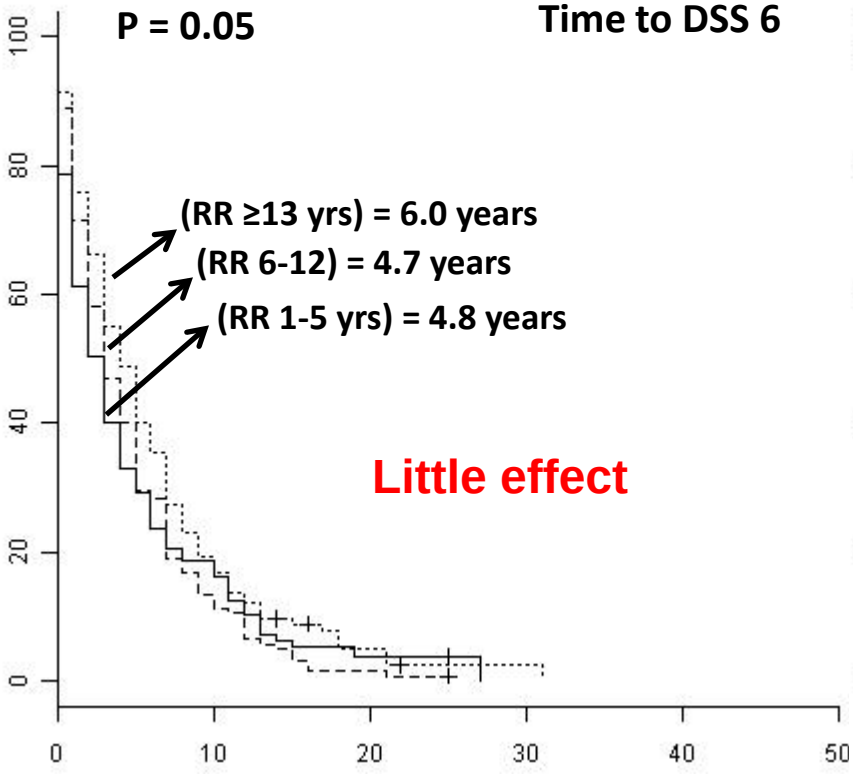
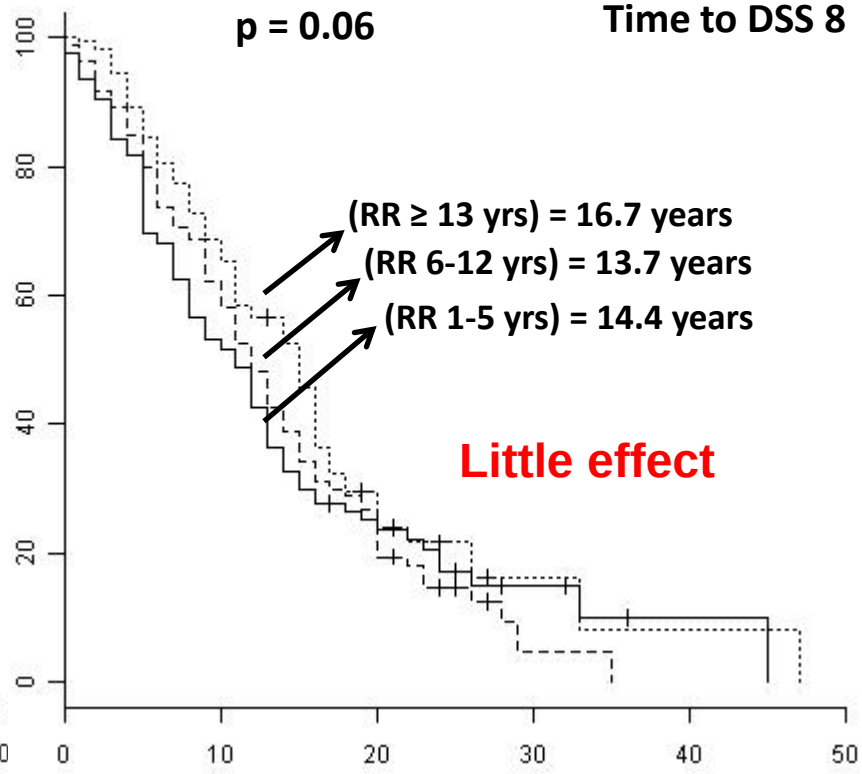
**Survival analysis from onset of secondary progression**



# Relapses and progression

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Age onset progressive course

**PPMS/SAPMS/SPMS - survival (none vs one vs many) 6,8,10**

**P**rogression and total relapses ? y1-y2 vs. y3-SP

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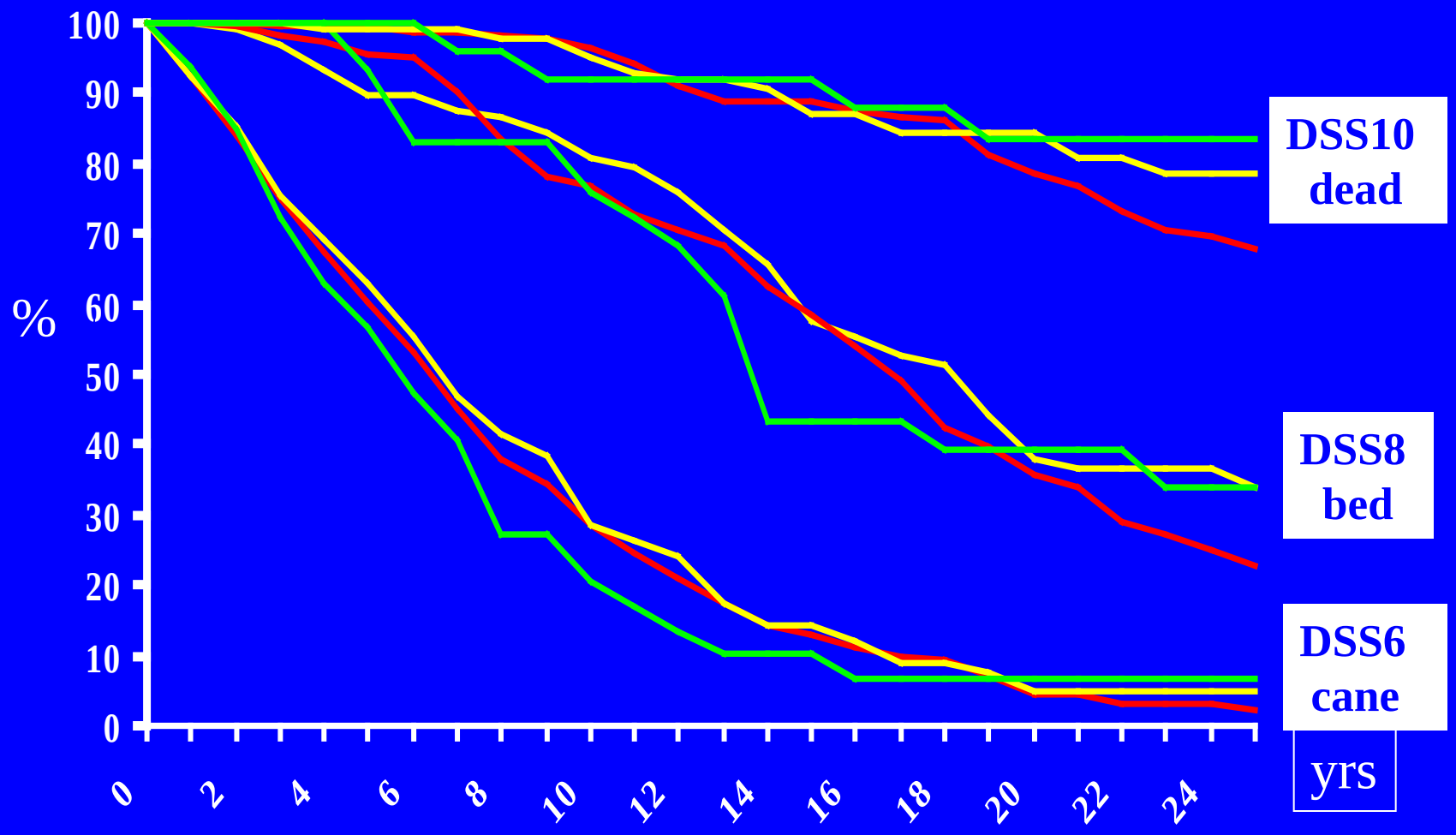
# Time to DSS 6/8/10 - years from onset of progressive MS




PP-MS dss2

SP-MS dss2

SAP-MS dss2

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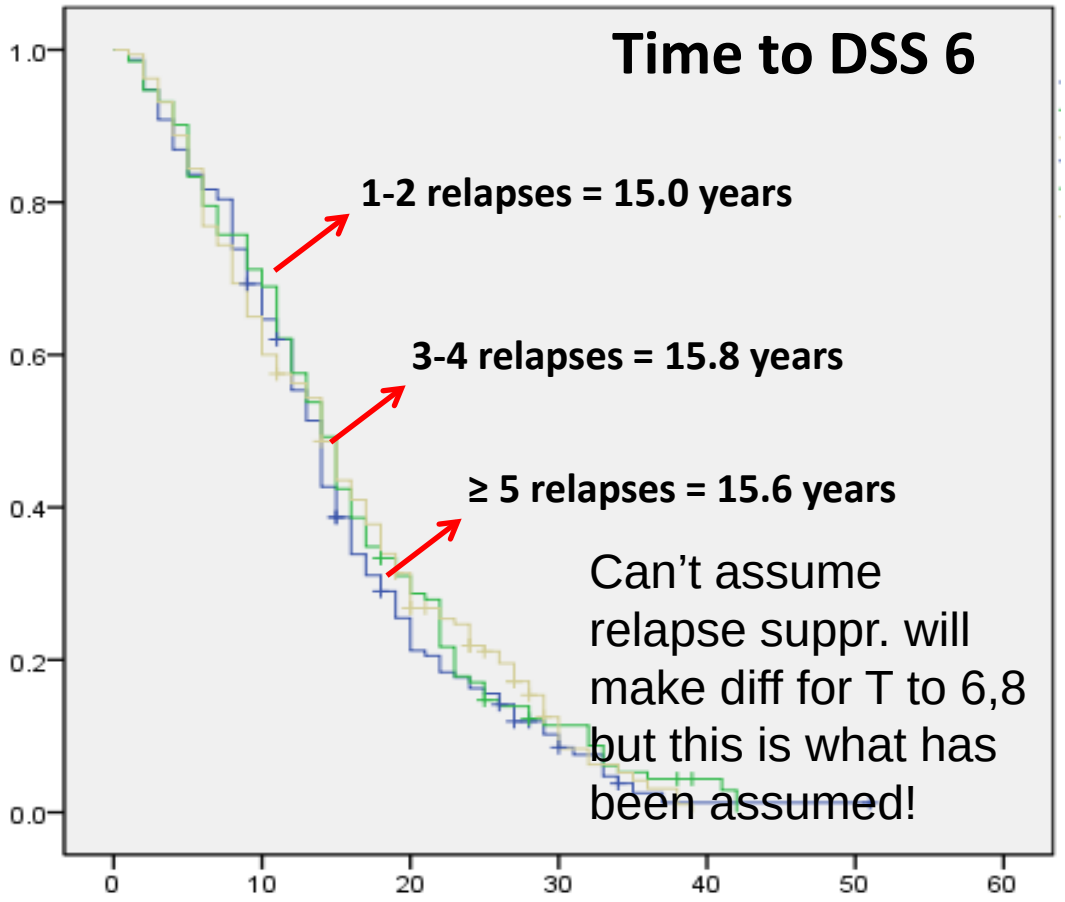
# Total Relapses during RR phase



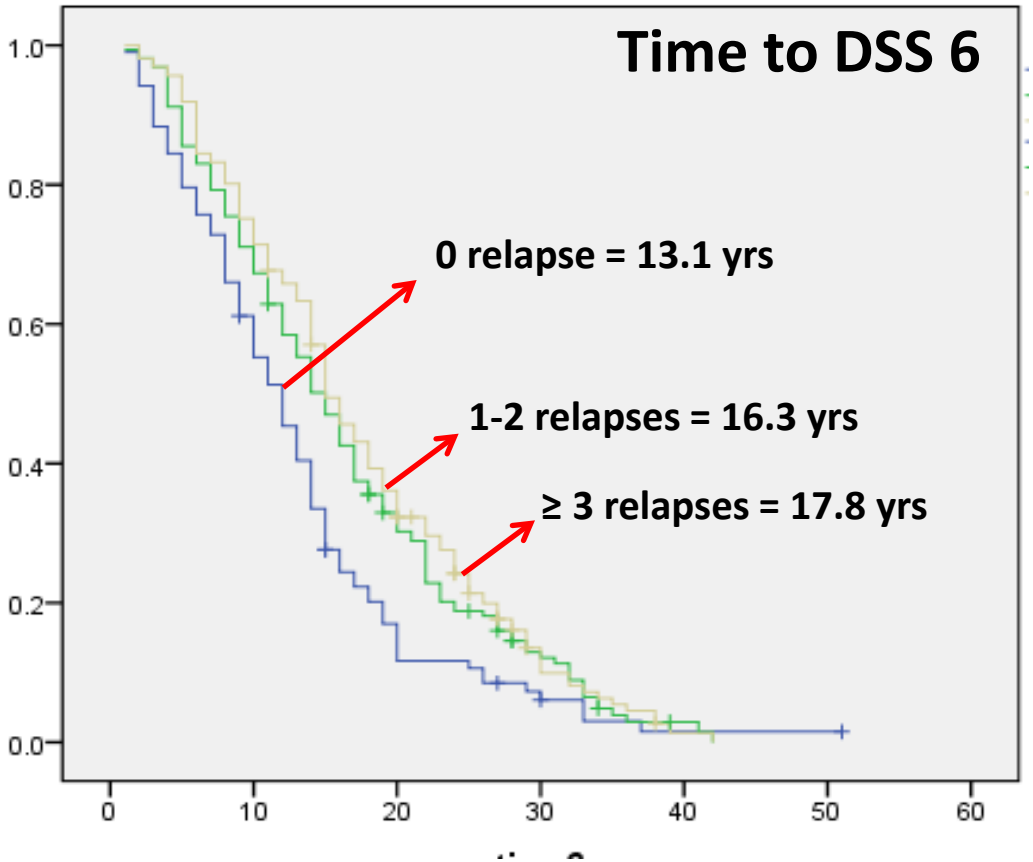

| Num of relapses | HR (p = 0.76) |
|---|---|
| 1 | 0.99 |
| 2 | 0.98 |
| 3 | 0.98 |
| 4 | 0.97 |
| 5 | 0.97 |

HR =Hazard ratio

**Relapses** ← **? Causal or concomitant ?** → **Late outcome**

# Relapses Y3 - onset SP assoc. with *better* outcome

## These are the relapses enumerated in most trials

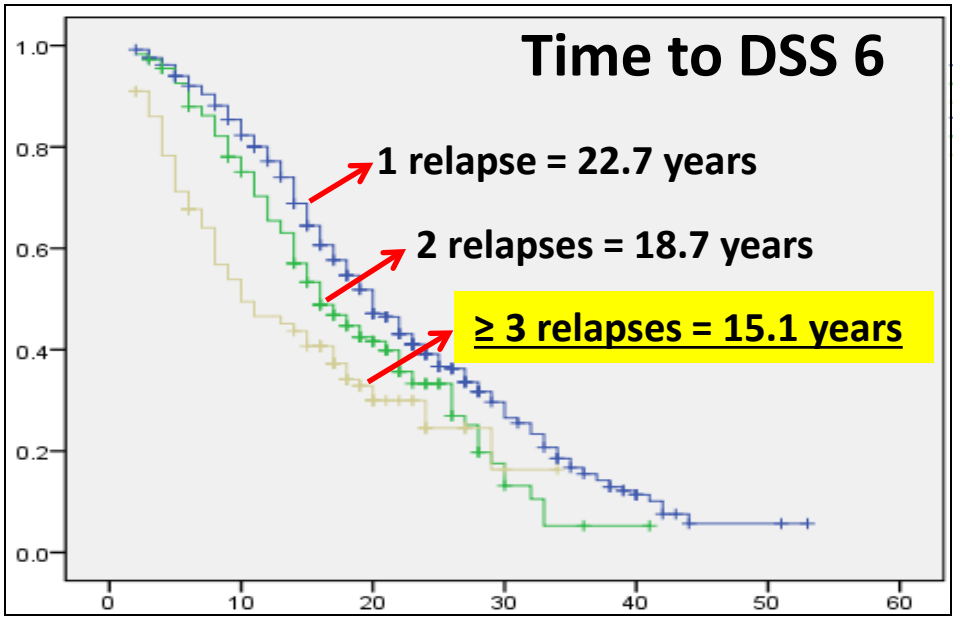



| Num of relapses | HR (p = 0.01) |
|---|---|
| 1 | 0.94 |
| 2 | 0.89 |
| 3 | 0.85 |
| 4 | 0.80 |
| 5 | 0.76 |

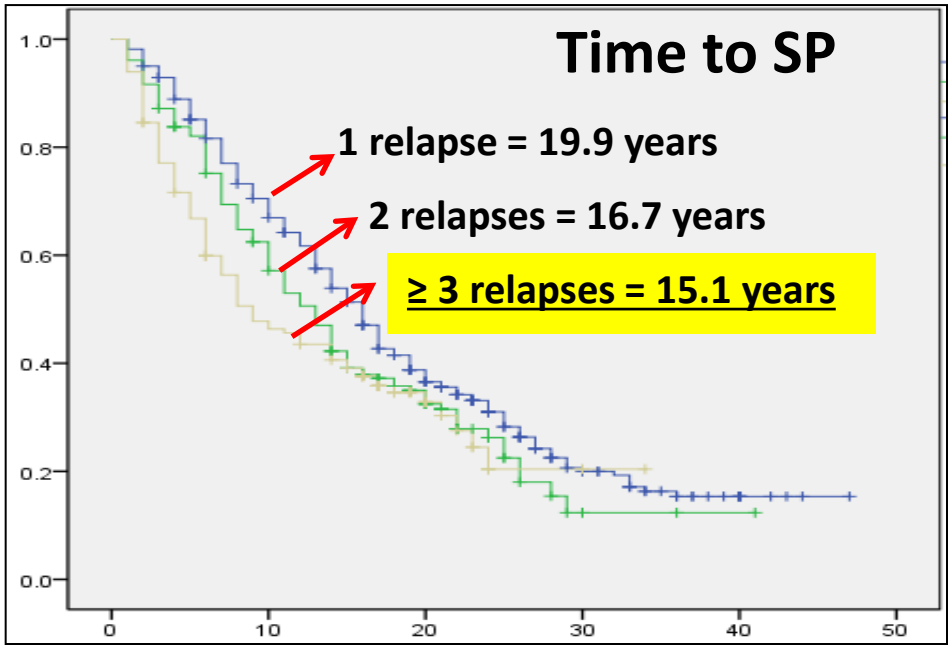
**Scalfari et al. 2010**

This is a slightly bigger effect than y1y2 associating with more rapid disability

# Early relapses (Y1+Y2) show meaningful association




| Num of relapses | HR (p < 0.001) |
|---|---|
| 1 | 1.23 |
| 2 | 1.51 |
| 3 | 1.85 |
| 4 | 2.27 |
| 5 | 2.79 |




| Num of relapses | HR (p < 0.001) |
|---|---|
| 1 | 1.25 |
| 2 | 1.56 |
| 3 | 1.94 |
| 4 | 2.42 |
| 5 | 3.02 |

# Early relapse association via?

extremes approach - frequent y1y2 relapsers

- **1) relapses leave successive cumulative unremitting disability at relapse time?**

Answer: it does to a degree in minority so 1/5 get to DSS3 via relapse and stay there but

no impact on 6,8,10 for total relapse frequency

- **2) increased probability of progression?**

Answer: marginally

**3) shortened latency to SP?**

Answer: yes big effect, nearly all of it, so freq early relapse hasten SP onset

- **4) faster slope of worsening?**

Answer: slight

# Relapses and progression

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Progression and total relapses ? (y1-y2 vs. y3-SP)

**Suppression of relapses and progression - LTF data**

**Suppression of mri and progression - LTF data**

# Univariate regressions of relationship between 2-year outcome measured in the original IFNβ-1b study and the 16-year outcome for physical and cognitive abilities *

| | Physical Outcome (logistic regression) | | Cognitive Outcome (linear regression) | |
|---|---|---|---|---|
| | $R^2$ | *p*-value** | $R^2$ | *p*-value** |
| **Baseline Variables** | | | | |
| **Baseline EDSS** | 0.22 | <0.0001 | 0.12 | <0.0001 |
| MSSS at Trial Onset | 0.07 | 0.0004 | 0.02 | 0.09 |
| Baseline MRI T2 BOD ($mm^2$) | 0.07 | 0.001 | 0.21 | <0.0001 |
| Duration of MS (y) | 0.05 | 0.003 | 0.05 | 0.004 |
| 3rd Ventricular Width (mm) | 0.04 | 0.011 | 0.21 | <0.0001 |
| Age at Trial-start | 0.01 | ns | 0.00 | ns |
| Age at MS-onset | 0.01 | ns | 0.04 | 0.02 |
| Annual relapse rate prior to Trial (2y) | 0.00 | ns | 0.00 | ns |
| Pre-Morbid IQ | 0.00 | ns | 0.14 | <0.0001 |
| Gender | 0.00 | ns | 0.00 | ns |

Rsq is percent of variance explained by factor

| ***On-Study* Variables** | physical | | cognitive | |
|---|---|---|---|---|
| **Annual relapse rate But these are treatment resistant relapses ? sig** | 0.12 | <0.0001 | 0.02 | ns |
| **EDSS change from baseline shows little meaning for the trial defns of disability** | 0.11 | <0.0001 | 0.01 | ns |
| Categorical EDSS change (≥1 point) | 0.06 | 0.002 | 0.02 | 0.05 |
| **Confirmed 1-point EDSS progression The trial outcomes** | 0.02 | 0.05 | 0.00 | ns |
| Change, 3rd Ventricular Width (mm) | 0.00 | ns | 0.07 | 0.003 |
| Treatment Group during RCT | 0.01 | ns | 0.02 | 0.09 |
| **Total IFNβ-1b Exposure (y) (on LTF)** | 0.00 | ns | 0.01 | ns |
| **Number of New T2 Lesions** | 0.01 | ns | 0.01 | ns |
| NAbs (≥ 20 NU/ml) | 0.00 | ns | 0.00 | ns |
| **Change, MRI T2 BOD ($mm^2$)** | 0.00 | ns | 0.01 | ns |

Rsq - % of variance explained by factor, 1result near sig for cognitive 3rd ventric. Width, 2 for physical

# What to do?

All suggested to P. Leber FDA in 1993, they asked for 4) but did not enforce

- 1) Stop marketers from misleading patients & families that RR drugs prevent disability*
- 2) For trials to be ethical, outcomes must be validated, primary data with the investigators
- 3) Aim for LTOs and the most accessible is SP development, and would take less than 5y
- 4) Any lesser outcome should require obligatory LTF, drug licence pulled for non-compliance

*or tell patients that" disability" does not mean what they think it means

# Many contributors

- Especially colleagues in London Ontario for the nat hist studies, recent relapse analyses Antonio Scalfari
- LTF studies made possible by Bayer esp V Knappertz
- Sylvia Lawry Centre esp. Martin Daumer

# finis

- Let the wild rumpus start
  Maurice Sendak