SEP & TROUBLES NEUROENDOCRINIENS

« Une leçon clinique à la Salpêtrière »
André Brouillet 1887
(Couloirs de l'Université Paris V)

H. VALDES-SOCIN
Chef de Clinique.
Service d'Endocrinologie
Clinicien-Chercheur.FNRS

UNIVERSITÉ DE LIÈGE

CHU de Liège

fnrs LA LIBERTÉ DE CHERCHER

A LA CARTE

CEPE A L'HONNEUR:
Une façon de la cuisiner…

- SEP & AXE du STRESS
- SEP & METABOLISME PHOSPHOCALCIQUE
- SEP & FACTEURS DE CROISSANCE

Impaired hypothalamic-pituitary-adrenal axis activity in patients with multiple sclerosis

Ysrraelit MC, Gaitán MI, Lopez AS, Correale J

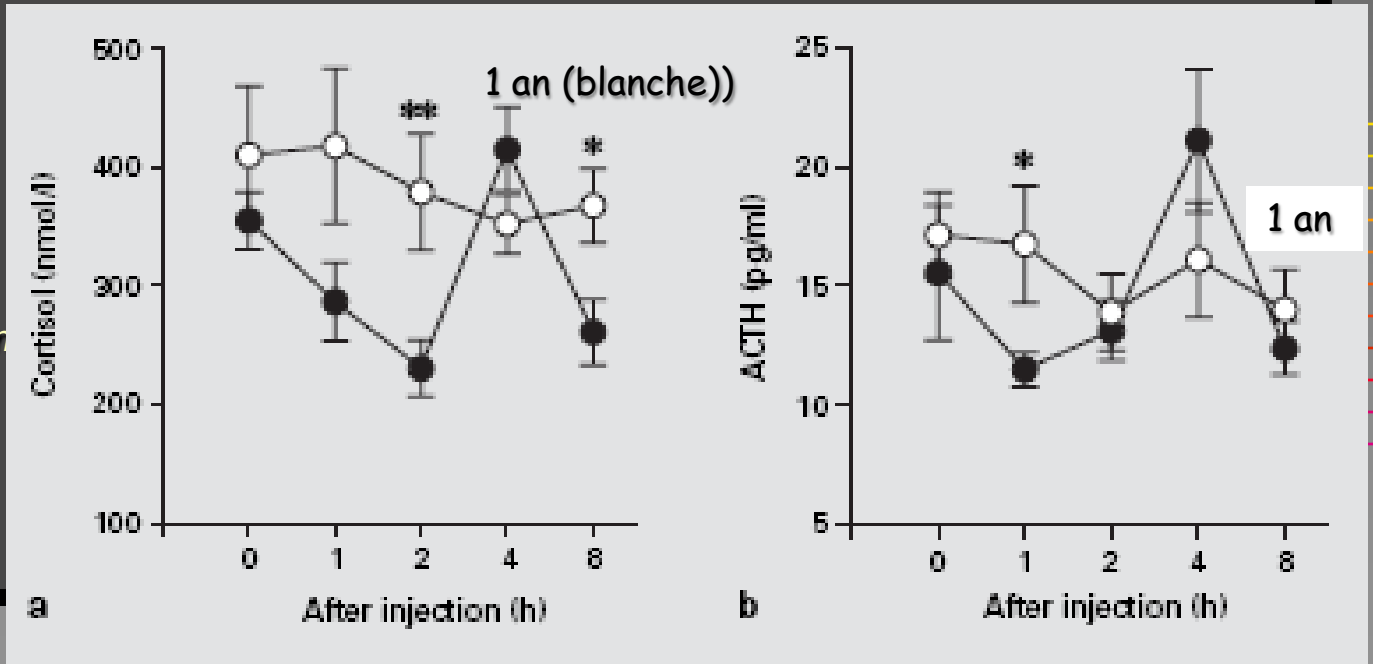
Neurology 2008

- 173 patients avec SEP
  - 40 primaire progressive
  - 41 secondairement progressive
  - 58 rémission-recidive
  - 60 contrôles

- All four groups of patients displayed significantly higher cortisol, ACTH, and DHEAS plasma concentrations and urine cortisol values than controls
- Although 62% of MS patients did not suppress Dex, suppression test results did not correlate with IL-1beta, IL-6, IFN-gamma, or TNF-alpha production

Acute interferon β-1b administration alters hypothalamic-pituitary-adrenal axis activity, plasma cytokines and leukocyte distribution in healthy subjects

- ACUTE
  - IFNβ-1b led to an increase in body temperature and heart rate, and in parallel, elevated cortisol, prolactin and GH plasma levels at 4 and 8 h after IFNβ-1b injection. There were no significant alterations in blood pressure, norepinephrine or epinephrine plasma levels.
- CHRONIC
- *Goebel & al Eur Neurol 2005*
  - *Rebif, n=13, 1 an traitement*
  - *Abolition réponse ACTH a un an*



A LA CARTE

CEPE A L'HONNEUR:
Une façon de la cuisiner…

- SEP & AXE DU STRESS
- SEP & METABOLISME PHOSPHOCALCIQUE
- SEP & FACTEURS DE CROISSANCE

En quête de soleil: VENCE

Jacques RAVERAT 1885-1925

My dearest, I know I love you and think you love me. Anyhow your love has been the best thing in my life. I send you this for you to keep and remember if you get morbid"

Jacques RAVERAT, 9 février 1925

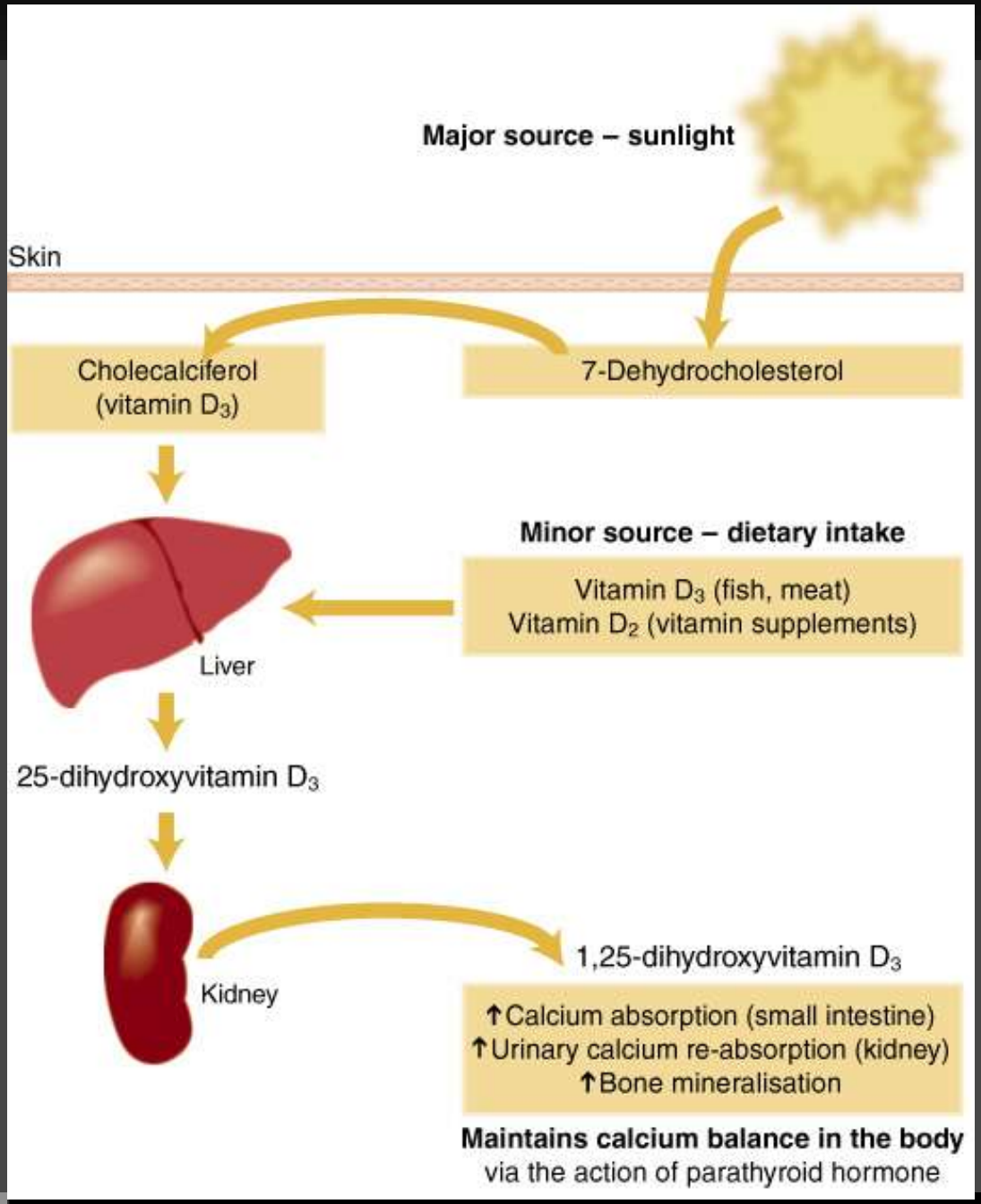
L'HERITIERE DE DARWIN

Gwen RAVERAT, autoportrait

Jacques, dying
(pencil, Gwen Raverat, 1925)

SEP ET CALCIUM

- Physiologie vitD.
- Vitamine D-immuno modulation.
- Exposition soleil-risque SEP.
- Variations saisonnières vit D-SEP.
- Vitamine D-activité SEP.



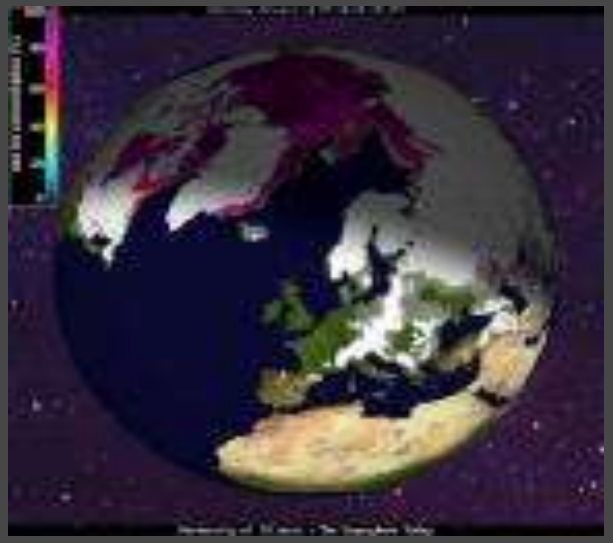
25 OH VITAMINE D

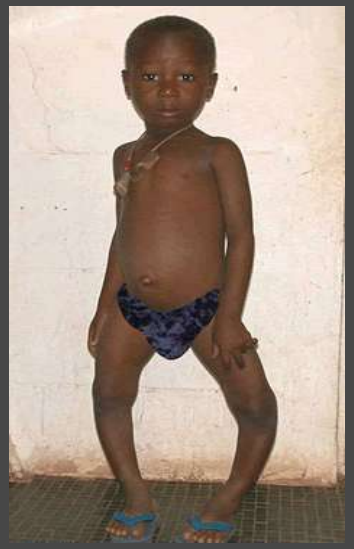
SUFFISANCE >32 ng/ml

DEFICIENCE SEV<20 ng/ml

Carence en vit D: facteurs de risque

- Latitude
- Pigmentation de la peau
- Exposition à la lumière
- L'âge; **phénytoïne, carbamazépine !!**





PREVENIR LA CARENCE en VIT D

- Exposition soleil mais intensité lumière insuffisante automne-hiver

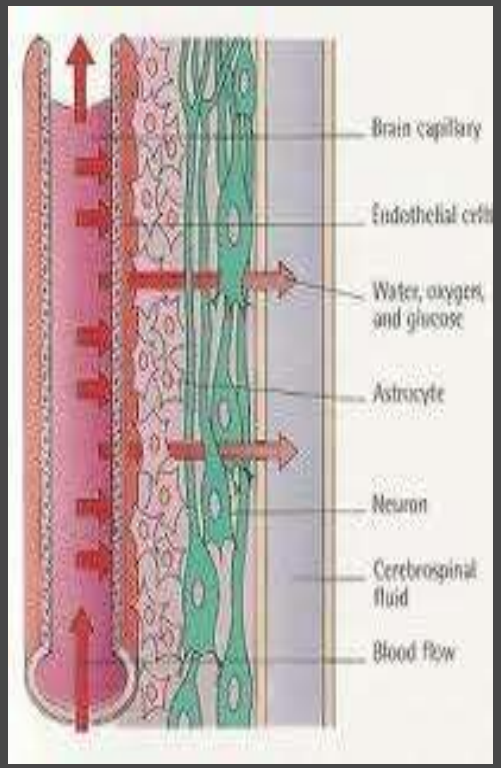
- Supplémentation vitamine D (cholécalciférol) 600 UI /j +1g de calcium
  - Aliments: foie, poissons + laitages
  - D vital® 440, Stéovit D3 ® 400, cacit vit D ® 880: insuffisant…
  - Ou Vitamine D Cure ® 25000x2 /mois +1 g de calcium/J.

- SEP et VitD . Steffensen & al . Abstract. ECTRIMS 2009
  - 20 000 UI D/semaine + 500 mg Ca/J, 48 semaines, n=69
  - 17% ------61 % vit D normale.

Vit D et fonction cérébrale

↓ *Tests activité , cognitive ;comportement*
vitamin D-restricted rats ou VDR ko mice

D3



VDR: **microglia, astrocytes, oligodendrocytes & Schwann**

D3

D3

VDR

VDR:gpr

NGF
NT-3,
NT4/5
GDNF

Plasticité Neuronale
Memoire

Survie cellules DA

calcium-binding proteins
calbindin-D28k,
parvalbumin,
calretinin,
calmodulin

→ Ca2+ L Channel

D'après McCann and Ames. Vit D and Brain function. FASEB 2008

Traiter? Pourquoi?

- Multiple Sclerosis & Vit D deficiency= 127 articles
  - Déficience fréquente.
  - Facteur de risque reconnu.
  - Facteur de risque récidive.
  - 1 seul article phase I/II intervention.

VARIATIONS SAISONNIERES/SEP

- Maghzi & al Mult Sler 2010
  - Izfahan (IRAN)
  - 1584 patients,
  - augmentation de prévalence 48/100000
  - Sex ratio F>M

- Salzer & al Acta Scandinava 2010
  - Suède
  - 9361 patients
  - Plus de cas nés en juin (11%) et moins en décembre (8%)

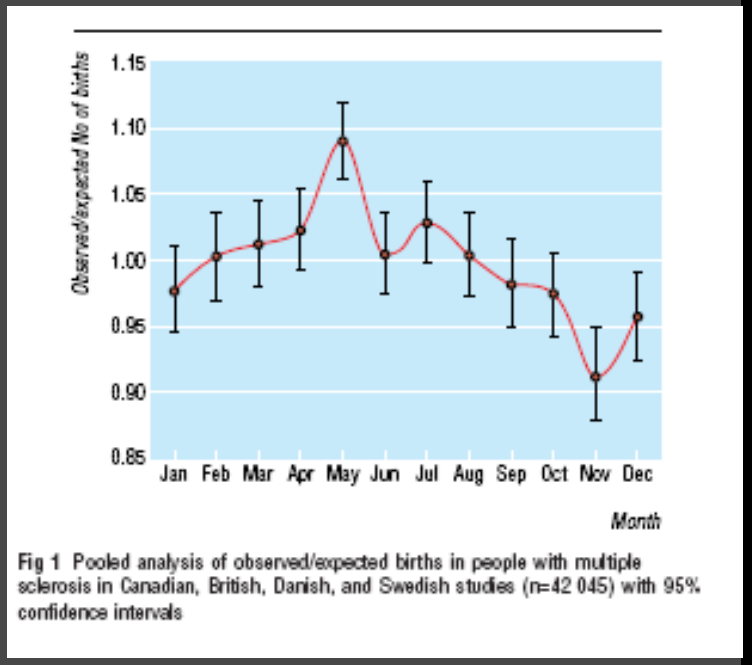


Fig 1 Pooled analysis of observed/expected births in people with multiple sclerosis in Canadian, British, Danish, and Swedish studies (n=42 045) with 95% confidence intervals

- Willer & al BMJ 2005
  - Canada (n=17000) vs UK (n=11 000),
  - Plus de cas SEP nés May>Nov

BRAIN
A JOURNAL OF NEUROLOGY

Immunomodulatory effects of Vitamin D in multiple sclerosis

Jorge Correale, María Célica Ysrraelit and María Inés Gaitán

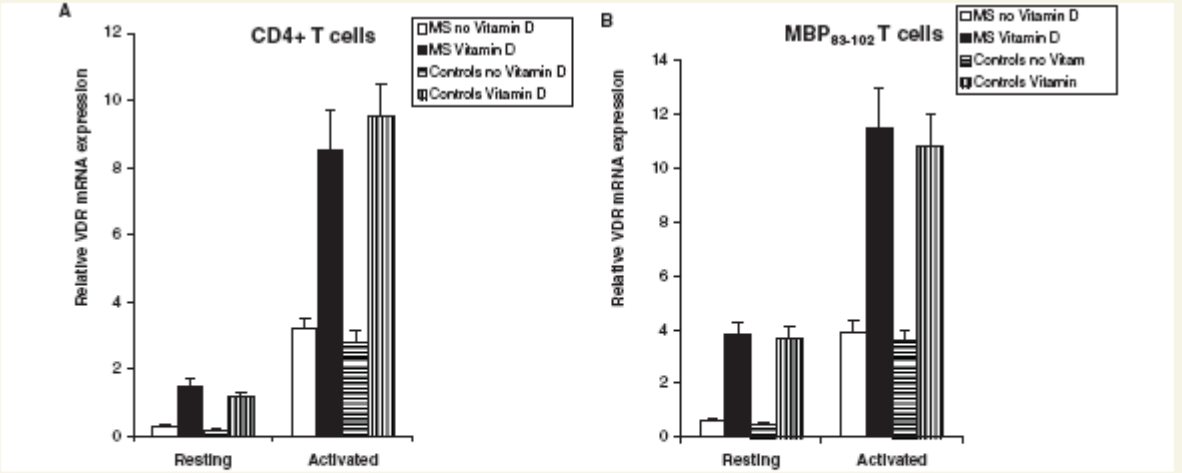
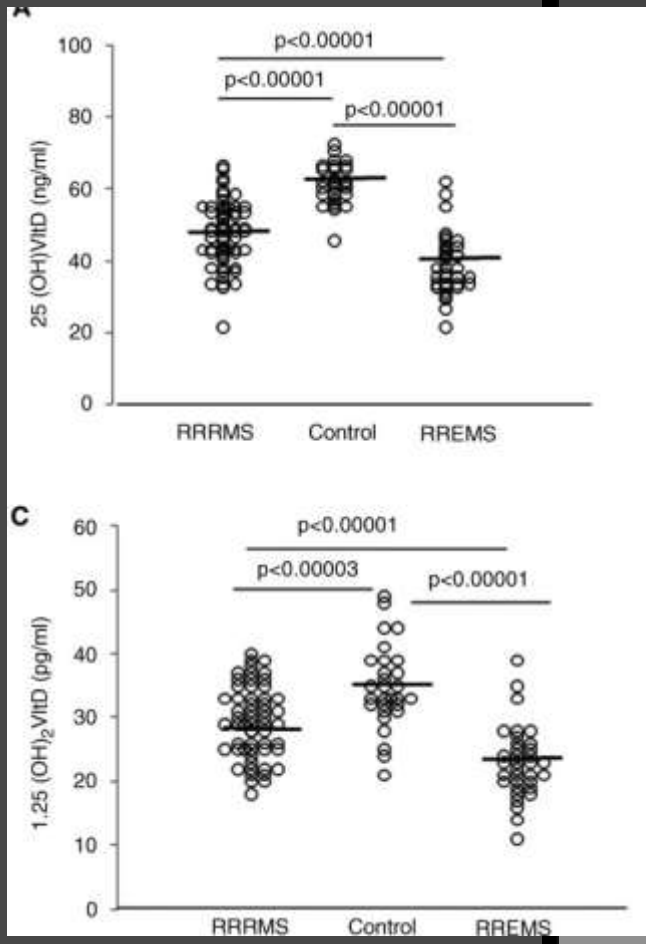


Figure 3 VDR is upregulated on activated T cells, and after exposure to 1,25 $(OH)_2$ Vitamin D. Purified CD4+ T cells and MBP peptide-specific T-cell lines were cultured in resting state and after activation in the presence or in the absence of 1,25 $(OH)_2$ Vitamin D (10 nM). Total RNA was extracted after 3 days in culture, and gene expression was detected by quantitative RT-PCR. Data are expressed as VDR mRNA relative to GAPDH, mean values ± SEM of mRNA expression in *ex vivo* CD4+ T cells isolated from 25 relapsing remitting multiple sclerosis patients, and 20 healthy controls (A), as well as from 35 myelin peptide-specific T-cell lines isolated from 20 relapsing remitting patients, and 30 myelin peptide-specific T-cell lines isolated from 20 healthy subjects (B). No significant differences were observed between relapsing remitting patients and healthy controls.



Etudes d'intervention chez les animaux

- PTH-hypercalcémie-Vit D stable
  - Protection femelle>male.

  Meehan TF& al...Arch Biochem Biophys. 2005
- Vit D3
  - Protection femelle>male.

  Spach & alJ Immunol. 2005
- VDR-KO model
- CA2+
  - *Cantorna & al. J Nutr. 1999*

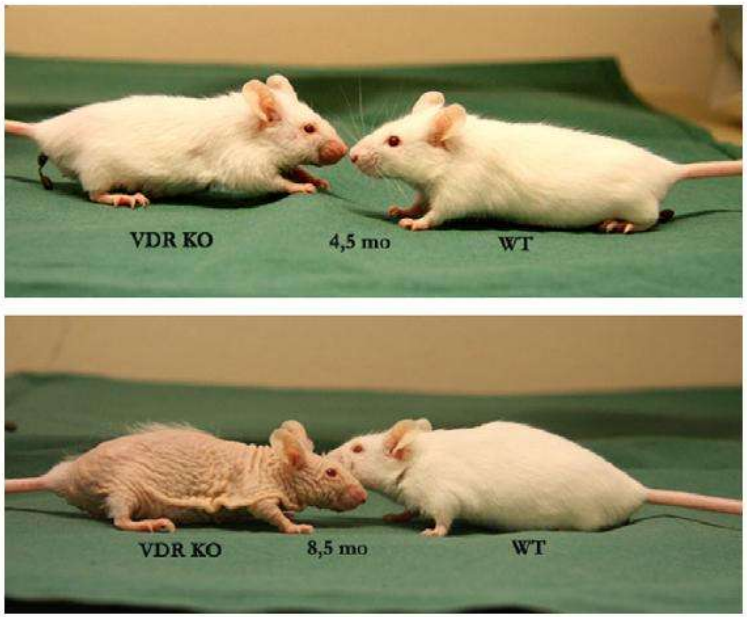


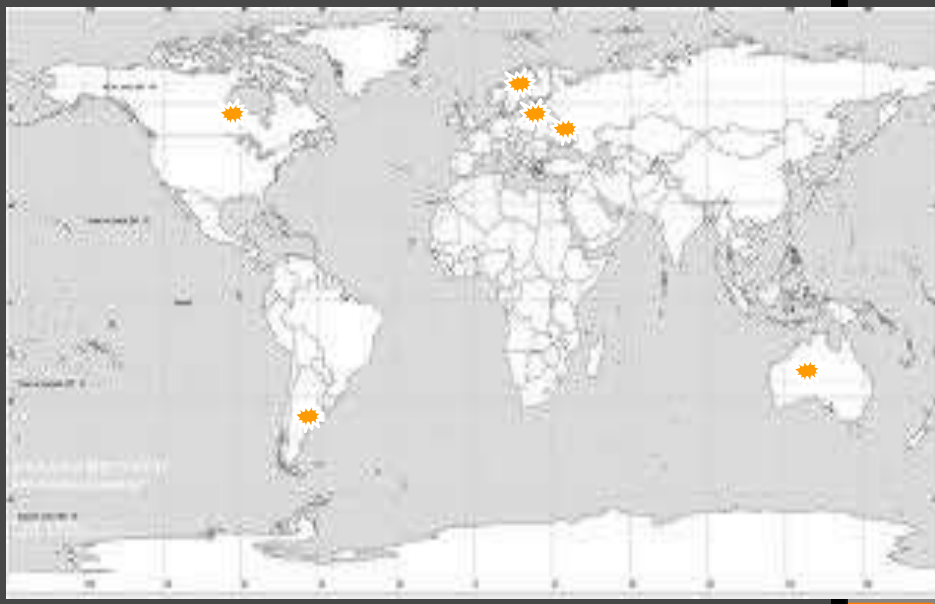
Fig. 2. Phenotype of VDR knockout mouse (KO) compared to wildtype littermate (WT; NMRI background strain) at the age of 4.5 (top) and 8.5 (bottom) months.

Keisala T & al.
J Steroid Biochem Mol Biol. 2009

Higher 25-hydroxyvitamin D is associated with lower relapse risk in multiple sclerosis

- ***Retrospective association documented I***

n the USA,
Argentina,
Australia,
Canada,
Finland,
Germany, and
the Netherlands (7).



- N=145, cohort largely on immunomodulatory therapy, higher 25-OH-D levels were associated with a reduced hazard of relapse. Dose-dependent linear fashion, with each 10 nmol/l increase in 25-OH-D resulting in up to a 12% reduction in risk of relapse

Simson & al. Ann Neurol. 2010 Aug;68(2):193-203

Etudes Pilotes d'Intervention

Auteurs	Patients	Supplément	Effets
Goldberg & al 1986	N=10	Vit D 5000/J	Less relapses
Wingerschuk & al 2005	N=15 1 an	Calcitriol 2.5µg/J	27 % relapse
Kimball& al 2007	N=12	Vit D 28000-280000/ week	Less MRI lesions

PERSPECTIVES-CLINICAL TRIALS NIH

1_The Effects of Interferon Beta Combined With Vitamin D on Relapsing Remitting Multiple Sclerosis Patients
This study is currently recruiting participants. Verified by Carmel Medical Center, November 2010

Phase I trial vit D3-SEP

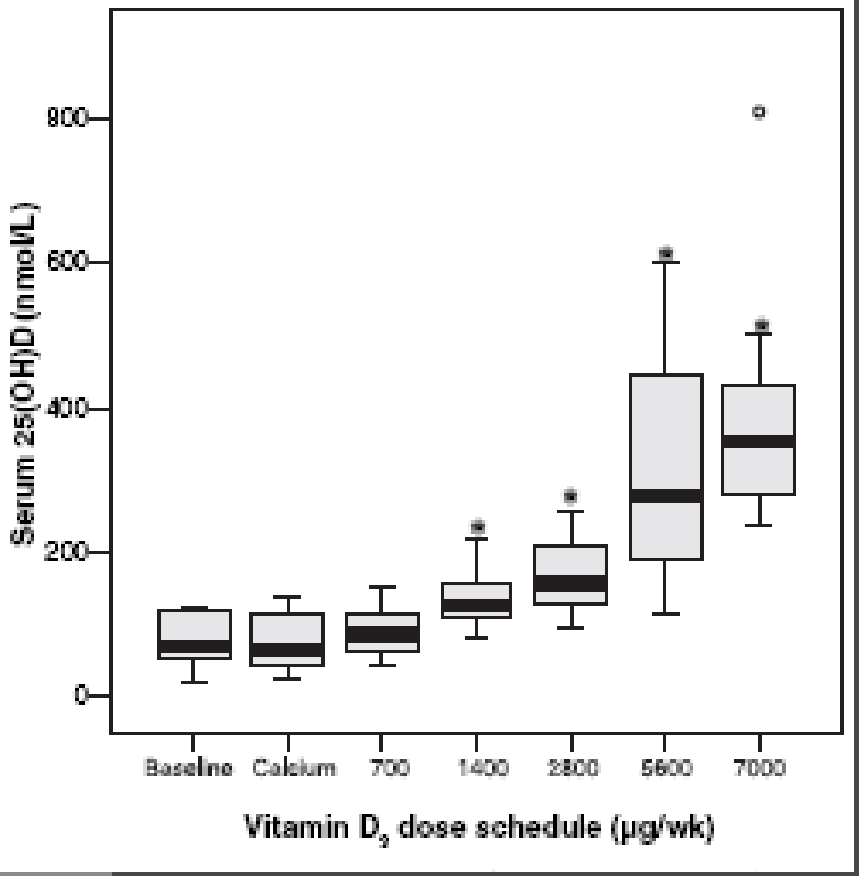


TABLE 3
Effect of the full protocol of vitamin D_3 supplementation on biochemical measures: comparison of baseline values and values after a 28-wk vitamin D_3 treatment (100–1000 μg/d)[1]

	Subjects	Serum 25(OH)D	Serum calcium	Urinary calcium: creatinine	PTH	Creatinine
	n	*nmol/L*	*mmol/L*		*pmol/L*	*μmol/L*
Baseline	12	78.2 ± 35.3[a,2]	2.36 ± 0.09[a]	0.42 ± 0.31[a]	2.75 ± 1.54[a]	69.08 ± 22.75[a]
Trial completion	12	385.5 ± 157.0[b]	2.23 ± 0.43[a]	0.47 ± 0.28[a]	1.81 ± 1.15[a]	70.42 ± 15.23[a]
Reference values[3]		<250	2.1–2.6	<1.0	1.3–5.4	50–110

[1] 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone. Values in a column with different superscript letters are significantly different, $P < 0.001$ (paired *t* test with Holm's adjusted Bonferroni correction).
[2] $\bar{x}$ ± SD (all such values).
[3] The normal distribution as obtained in the clinical laboratory at St Michael's Hospital (Toronto, Canada).

TABLE 1
Vitamin D_3 dose-escalation schedule

		Supplementation		
		Vitamin D_3		
Study visit[1]	Stage of the study	μg/wk	IU/wk	Calcium (mg/d)
1	1–2 wk	0	0	1200
2	3–4 wk	700	28 000	1200
3	5–10 wk	1400	56 000	1200
4	11–16 wk	2800	112 000	1200
5	17–22 wk	5600	224 000	1200
6	23–28 wk	7000	280 000	1200
7[2]	≈3 mo later	—	—	—

[1] Each study visit occurred on the first day of the week.
[2] Vitamin D_3 and calcium supplementation were discontinued after 28 wk.

Kimball SM, & al. Am J Clin Nutr. 2007 Sep;86(3):645-51

A phase I/II dose escalation trial of vitamin D3 and calcium in multiple sclerosis

- N=49 (25 MS vs 24 contrôles), 52 semaines. CLASS I/II

  Titration vit D 10000 UI/J, safe, moins de récidive, moins de prolifération de cellules T .

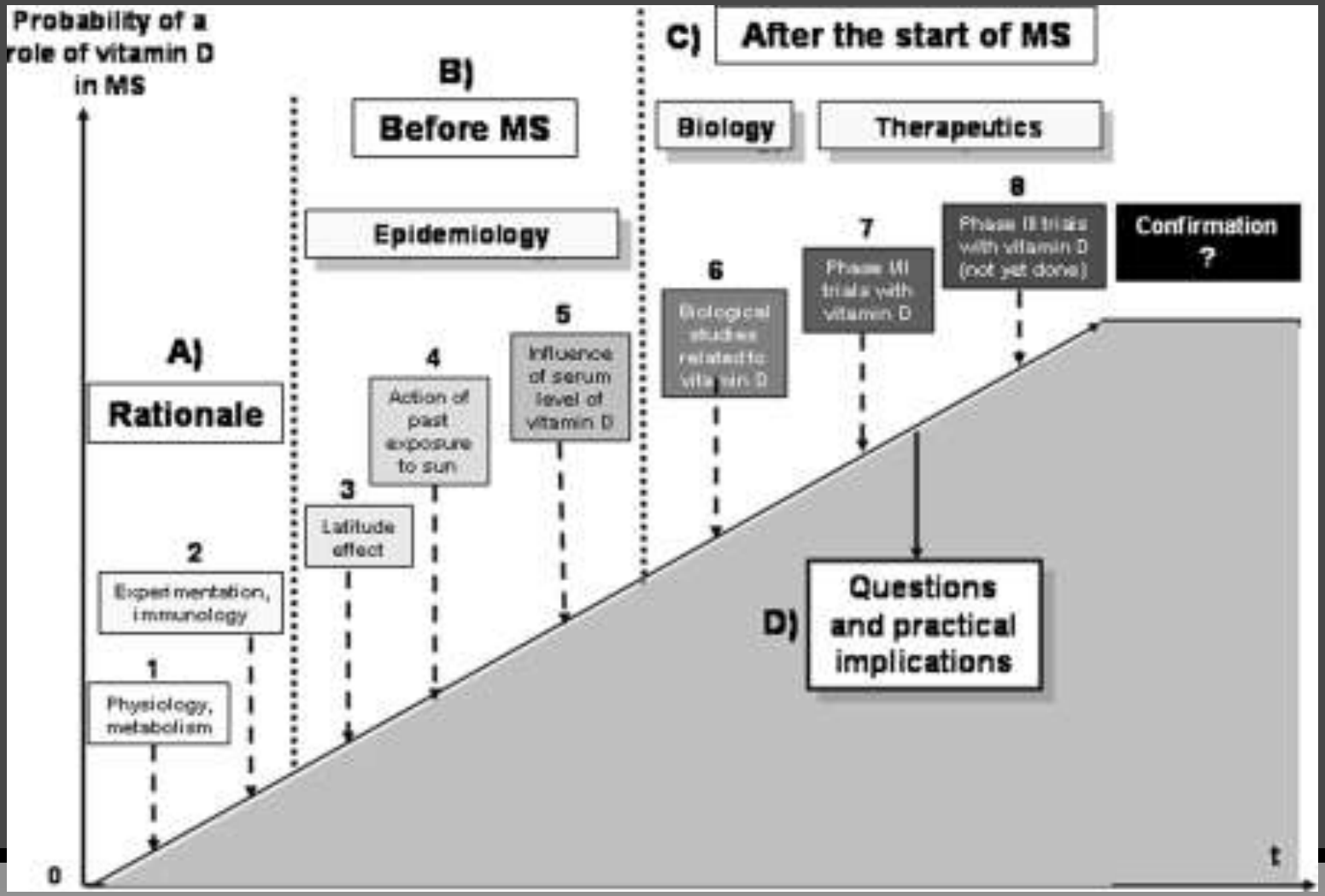
Burton, J. M, Kimball & al. Neurology. 2010 Jun 8;74(23):1852-9. Epub 2010 Apr

The control patients were allowed to take up to 4000 IU/d of vitamin D3 and calcium at their discretion. The treatment group was given an escalating dose of vitamin D3 that began at 4000 IU/d, escalated to 40,000 IU/d, and decreased back to 10,000 IU/d for an average of ~10,000 IU/d over the course of a year.

There were no adverse events in either group. Most importantly, 38% of the control group but only 8% of the treatment group hadan increase in disability at the end of one year (p=0.019). For the first time, an intervention may have allowed the progression of MS disability.

Vit D/SEP: état des lieux

- *Pierrot-Deseilliany J Neurol. 2009 Sep;256(9):1468-79. Epub 2009 Apr 28*

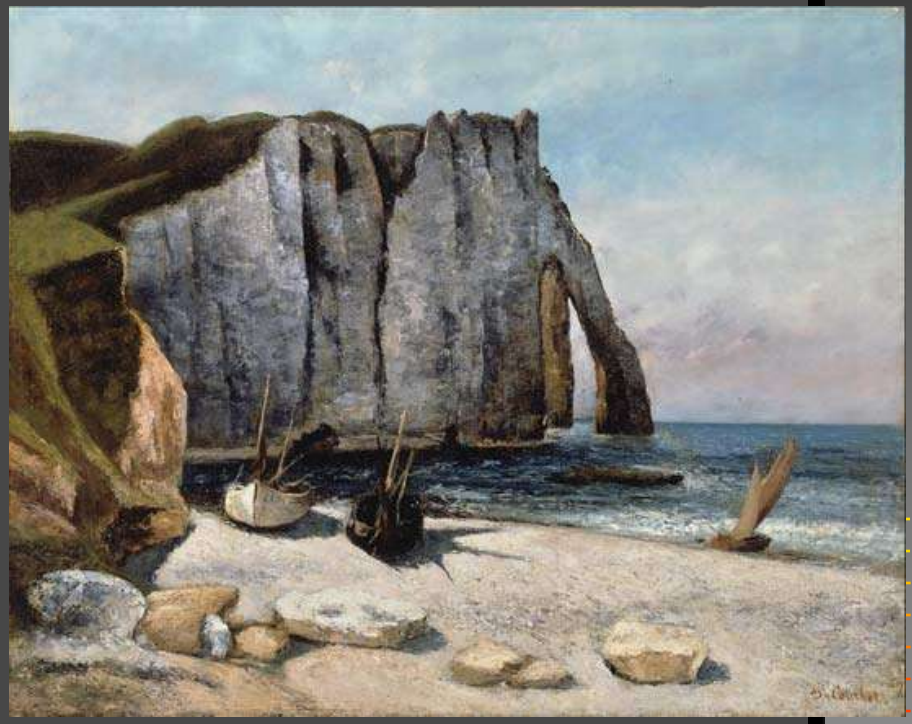


Déficience vit D, mais quels autres enjeux?

- Pathologie osseuse et SEP++.

  Marrie & al. Neurology 2009

  - Excluding age:
  - 1,413 (15.1%) participants had 1 clinical risk factor for fracture,
  - 2,341 (25.0%) had 2, and 5,393 (57.7%) had 3 or more.
  - Among participants with a history of fracture, 746 (55%) reported taking calcium supplements, 858 (68.8%) reported vitamin D supplements or a multivitamin with vitamin D, and 334 (22.5%) reported taking a bisphosphonate.



Les falaises d' Etrétat après l'orage.
Gustave Courbet 1819-1877

A LA CARTE

CEPE A L'HONNEUR:
Une façon de la cuisiner…

- SEP & AXE STRESS
- SEP & METABOLISME PHOSPHOCALCIQUE
- SEP & FACTEURS DE CROISSANCE

HISTOIRE des FACTEURS DE CROISSANCE du SNC

Prix Nobel Médecine 1986
Découverte du NGF

- Rita Levi Montalcini 1909-
  - Découverte NGF
  - NGF > dans le LCR des patients avec SEP *(Neuroscience Lett 1992)*
  - Hormones thyroïdiennes/remyélinisation SEP *(PNAS 2004)*

Axe GH/IGF-1 (somatomédine C)

- Salmon and Daughaday (1957) hypothesized that ST stimulated somatic growth indirectly via circulating sulfation factors.

- SEP & IGF1: 57 articles
  - 1 article d'intervention

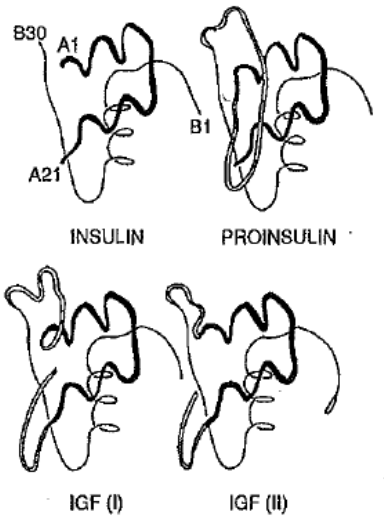
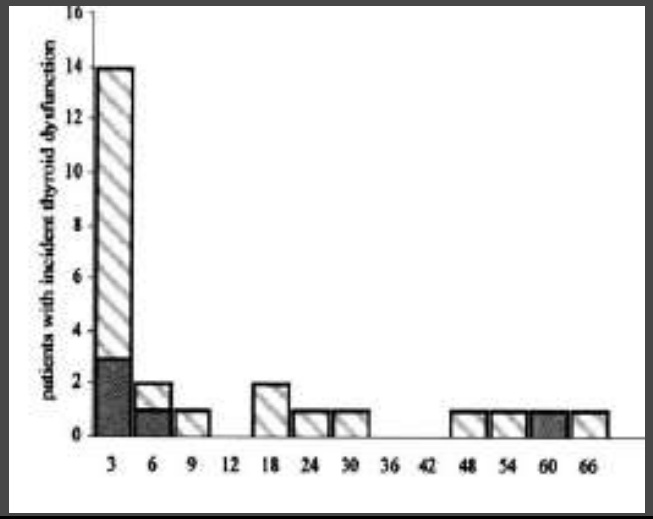


Figure 1

Predicted structure of the insulin-like growth factor family of peptides. The heavy line represents the A chain, double lines represent a D extension to the A chain or the C chain joining the A and B chains (from: LeRoith D. Insulin-like growth factors in health and disease. Ann Intern Med 1992; 116: 855; with permission from the American College of Physicians)

Interféron β: thyroïde et GH?

- IFNβ (1a Avonex, 1b Betaferon) /dysthyroïdie
  - N=106 SEP (76F/40H)
  - Avant tt: 8.5% ATPO, 2.5% HYPO
  - Après 1 an tt: 24% (hypo, hyper, TPO)



Caraccio & al. JCEM 2005

- IFNβ / IGF1
  - N=23 SEP
  - IGF-I 38% (p = 0.018), acid-labile subunit 17% (p = 0.044) and IGFBP-2 43% (p = 0.035) > in MS patients/ controls.
  - When stratified for interferon-beta (IFN-β) use: increase in [IGF-I] 52% (p = 0.013) and [IGF_{TOTAL}] 19% (p = 0.043) in MS patients with IFN-β treatment,
  - but MS patients not undergoing IFN-β treatment had similar IGF and IGFBP concentration to controls.

Interferon-β treatment associated with a biochemical profile suggestive of acromegaly.

	Initial results		5-days profile, INF-β treatment					No INF-β treatment
GH, µg/L			20.7	0.83	3.3	2.51	6.0	5.7
Total IGF-I, µg/L, in-house RIA	664	757						
Z-score	+5.40	+6.38						
Total IGF-I, µg/L, Immulite, Siemens			408	459	420	451	402	436
Z-score			+3.16	+3.70	+3.29	+3.62	+3.10	+3.46
Total IGF-I, µg/L, in-house TR-IFMA			426	418	416	457	458	457
Z-score			+5.84	+5.66	+5.61	+6.55	+6.57	+6.55
IGFBP-3, µg/L, Immulite, Siemens			5670	5520	5540	5650	5470	5030
Z-score			+1.27	+1.09	+1.11	+1.25	+1.02	+0.47
IGF-I bioactivity, µg/L, in-house KIRA			4.9	5.7	5.4	4.7	3.8	5.1
Z-score			+13.3	+15.8	+14.8	+12.5	+9.5	+13.8
Prolactin, mIU/L (<600 mIU/L)	76	73	176	99	144	103	140	106
FSH, U/L	41	57	57	49	51	51	52	56
LH, U/L	32	41	49	38	43	41	42	42
Estradiol, nmol/L	0.06	0.04	<0.026	<0.026	<0.026	<0.026	<0.026	<0.026
ACTH, ng/L (0–46 ng/L)	14							
Cortisol, nmol/L (200–600 nmol/L)	309							
TSH, mIU/L (0.5–4.0 mIU/L)	7.1	4.1	9.3	5.0	6.4	5.5	5.2	4.6
Free T3, pmol/L (4.0–6.8 pmol/L)	5.1	4.9						
Free T4, pmol/L (12.8–20.4 pmol/L)	13.0	12.0						
Total T3, nmol/L (1.0–2.6 nmol/L)			2.2	2.0	2.4	2.3	2.2	2.5
Total T4, nmol/L (60–140 nmol/L)			90	96	91	84	83	82

Andreassen & al. Scand J Clin Lab Invest. 2010 Nov;70(7):519-22. Epub 2010 Sep 27

GH, IGF-1 & LCR dans la SEP

Poljakovix et al. Clinical Neurol and Neurosugery 2006

N=46 patients/n=49 controls

	IGF1p		GHp		IGF1(LCR)		GH (LCR)	
N	46	49	46	49	49	46	49	46
ng/ml	31.6	35	0.8	0.65	3.4	3.1	0.45	0.85
P	0.109		0.365		0.174		p<0.001	

Traitement par IGF-1 & SEP

- Encéphalomyélite expérimentale chez la souris

1995 Liu & al	reduction lésions aigues
1998 Li W & al	réduction lésions aigues
2000 Cannella	oui aigu-NON CHRONIQUE

- SEP & IGF-1 rh chez l'homme (n=7)
  - Etude 6 mois, 50mg scx2/J
  - CEL, MRS cervical spine
  - Safe, but no alter the course of the disease
  - Frank & al. Mult Scler. 2002 Feb;8(1):24-9

Amyotrophic lateral sclerosis & IGF-1rh

- Cochrane Database Syst Rev. 2002;(3):CD002064- Metaanalyse
  - Européen, n=183, placebo(59)/control (124), 0.01 mg/kg sc IGF-1
  - USA, n=179, placebo90/control 89,), 0.05 mg/kg sc IGF-1
  - Effet modeste, plus d'études nécessaires

CONCLUSIONS

- 1- Je vous ai dit plus sur le sujet que ce que je sais moi-même.
- 2- Ce qui a été dit, peut changer par la suite.
- 3- J'espère avoir soulevé plus de questions que de réponses.
- 4- En tout cas, comme toujours, plus de recherches sont nécessaires.

Prof Stephen Hawking

Fuller Albright (1900-1969)