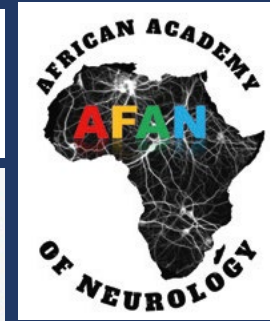


EAN/AFAN Regional Teaching Course

Douala, Cameroon, October 20, 2022

15:40 – 16:00 hrs



Environmental & Nutritional Risk Factors for Atherosclerosis, Stroke and Vascular Dementia

Gustavo C. Román MD, DrHC

Blanton Presidential Distinguished Chair

Methodist Neurological Institute, Houston, Texas, USA

Professor of Neurology

Weill Cornell Medical College, New York, USA

GCRoman@HoustonMethodist.org

Malnutrition

- 1/4 of the 1.2 billion inhabitants of Africa suffer from poor nutrition or malnutrition
- 300 million people
- Causative factors:
 - Poverty
 - Overpopulation
 - Illiteracy

Dietary constituents and energy requirements

- Proteins, carbohydrates and lipids
- Vitamins and minerals
- These allowances should be multiplied by 110 to 222% during pregnancy
- Nutritional deficiencies including vitamins, proteins, glucids, lipids and oligoelements, lead to deleterious various biological and clinical disturbances



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Environmental Research

journal homepage: www.elsevier.com/locate/envres



In utero exposure to endocrine disruptors and developmental neurotoxicity: Implications for behavioural and neurological disorders in adult life

Glancis Luzeena Raja^{a,*}, K. Divya Subhashree^b, Kamalini Esther Kantayya^b

^a Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic Graduate School of Biomedical Sciences, Rochester, MN, 55902, USA

^b Department of Biotechnology, SRM Institute of Science and Technology, Chennai, 603203, India



Iodine supplementation during pregnancy: a public health challenge

Pere Berbel¹, María Jesús Obregón², Juan Bernal^{2,3}, Francisco Escobar del Rey² and Gabriella Morreale de Escobar^{2,3}

Iodine deficiency causes maternal hypothyroxinemia, which affects pregnant women even in apparently iodine-sufficient areas, and often goes unnoticed because L-thyroxine (T4) levels remain within the normal range, and thyroid-stimulating hormone (TSH) is not increased. Even a mild hypothyroxinemia during pregnancy increases the risk of neurodevelopmental abnormalities, and experimental data clearly demonstrate that it damages the cortical cytoarchitecture of the fetal brain. The American Thyroid Association (ATA) recommends a supplement of 150 mg iodine/day during pregnancy and lactation, in addition to the use of iodized salt.

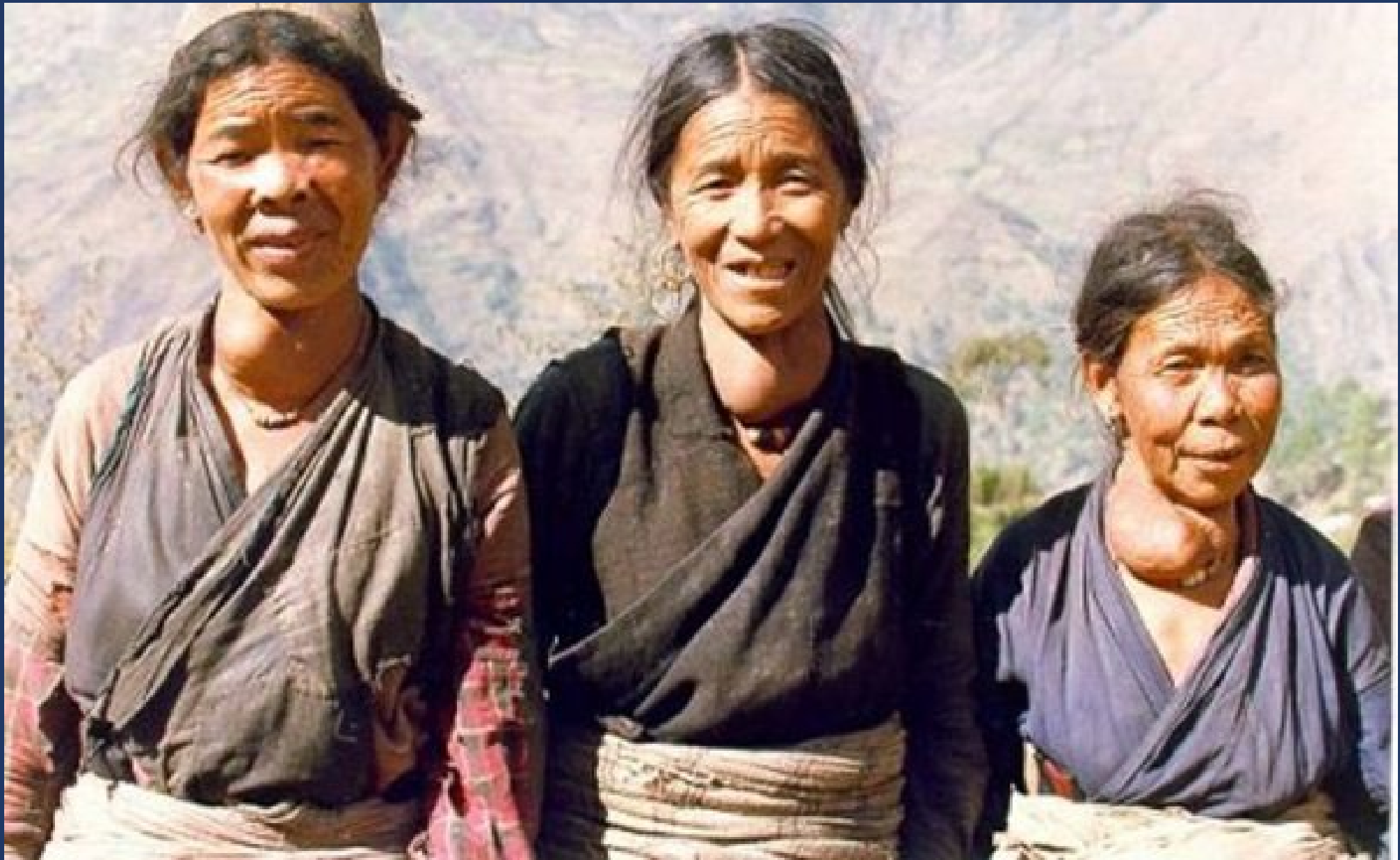
Table 1. Recommended minimum daily iodine intake

Group	Iodine requirements
Premature children ^a	>30 µg/kg/day
Children 0–6 years ^a	90 µg/day
Children 6–10 years ^a	120 µg/day
Adults ^a	150 µg/day
Pregnant women ^b	250–500 µg/day
Women during lactation ^b	250–500 µg/day

Iodine deficiency disorders

- Iodine deficiency occurs in areas of the earth where iodine was leached from the soil by the effects of rain, glaciations, and flooding waters. These areas typically include flood plains and mountainous regions such as the Alps, the Pyrenees, the Balkans, the Andes, the Himalayas, and the New Guinea Highlands.
- These populations suffer from high prevalence of goiter, short stature, deafness, mental retardation, spontaneous abortion, stillbirths, perinatal and infant mortality, as well as decreased fertility rate, all due to the effects of hypothyroidism.
- 1/3 of the population affected (128 countries) has no access to iodized salt. Other sources of iodine in the diet include dairy products, grains, cereals, and marine products (fish, seaweed, seafood).





Women with goiter in the Himalayas



**Male from Ecuador
about 40 years old,
deaf/mute, unable
to stand or walk.
Use of the hands
was strikingly
spared, despite
proximal upper-
extremity spasticity.**

DeLong GR, Stanbury JB, Fierro-Benitez R.
1985. Neurological signs in congenital
Iodine Deficiency Disorder (Endemic
cretinism). *Dev Med Child Neurol* 1985;27:
317-324



Endemic cretinism

- EC is the most severe degree of *in utero* brain damage from maternal hypothyroxinemia from dietary iodine deficiency.
- Clinical features: profound mental retardation, deaf-mutism, squint of eyes, signs of bulbar damage, spastic diplegia, pyramidal and extrapyramidal signs, and typical gait with laxity and deformities of the joints.
- EC is different from congenital hypothyroidism, which occurs in about 1 in 3500 newborns as a result of morphological or functional deficiencies of thyroid function in the fetus and the newborn unrelated to dietary iodine deficiency



Congo. Normal male and 3 females aged 15-20 years : severe longstanding hypothyroidism with dwarfism, retarded sexual development, puffy features, dry skin and severe mental retardation.

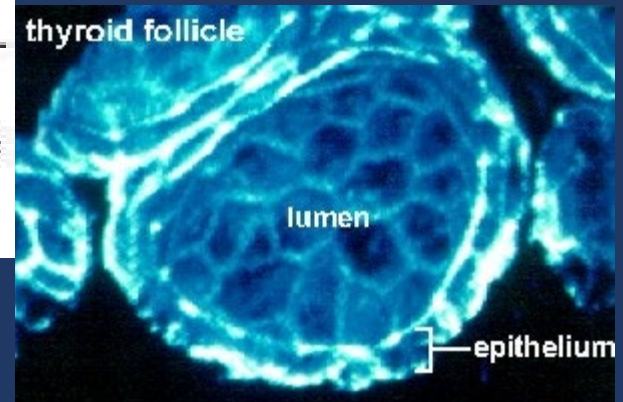
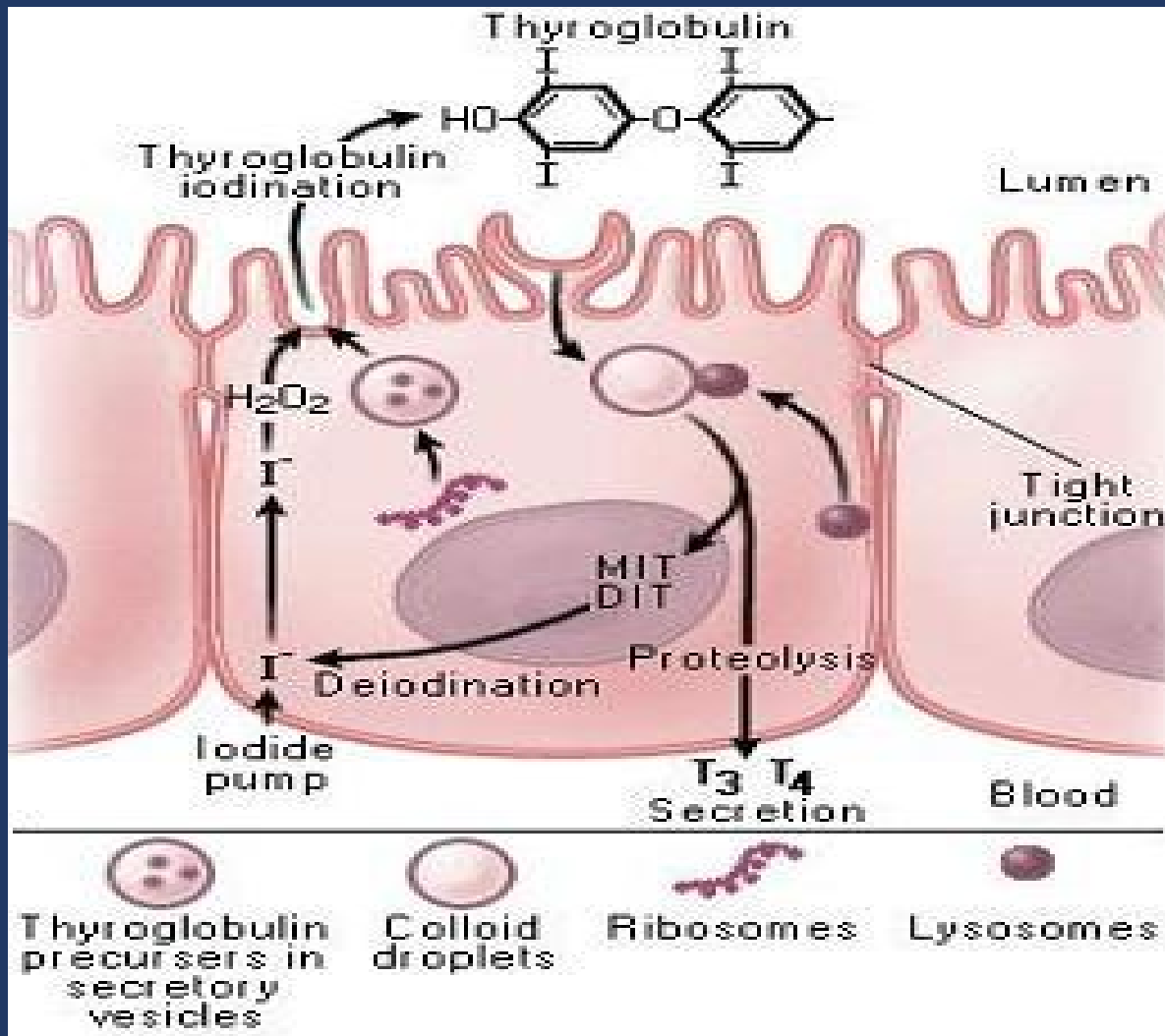
DeLong et al (1985)



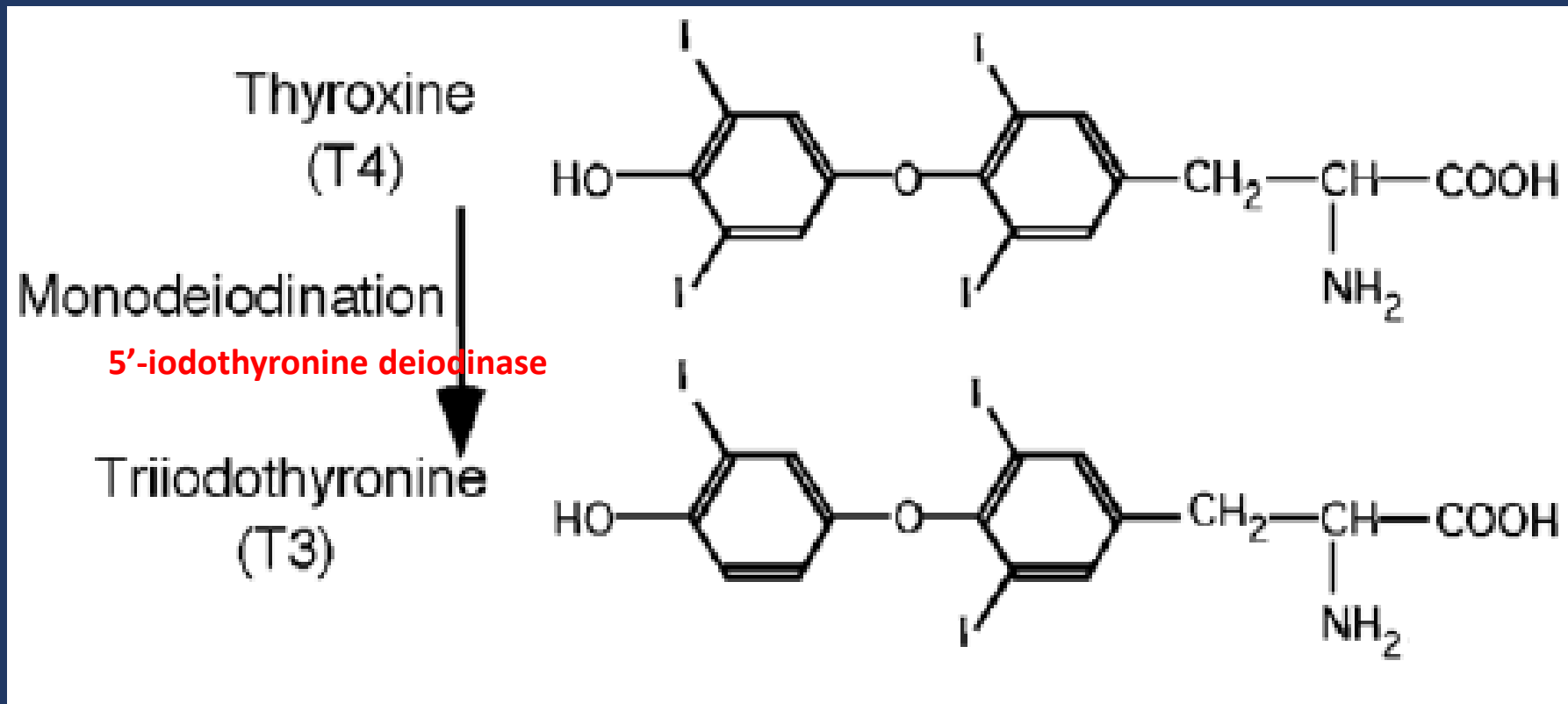
Thiocyanate from cassava (yuca)

Thiocyanate (SCN) & Selenium

- SCN from cassava is goitrogenic.
- SCN inhibits iodine concentration by the thyroid by inhibiting the enzyme thyroid peroxidase and preventing the incorporation of iodine into thyroglobulin.
- Iodine and selenium deficiency are associated with cretinism in northern Zaire (Congo).
- Selenium deficiency could result in excess peroxide (H_2O_2), thyroid cell destruction, fibrosis, and thyroid failure. Selenium deficiency decreases T4 catabolism



Thyroid Hormones



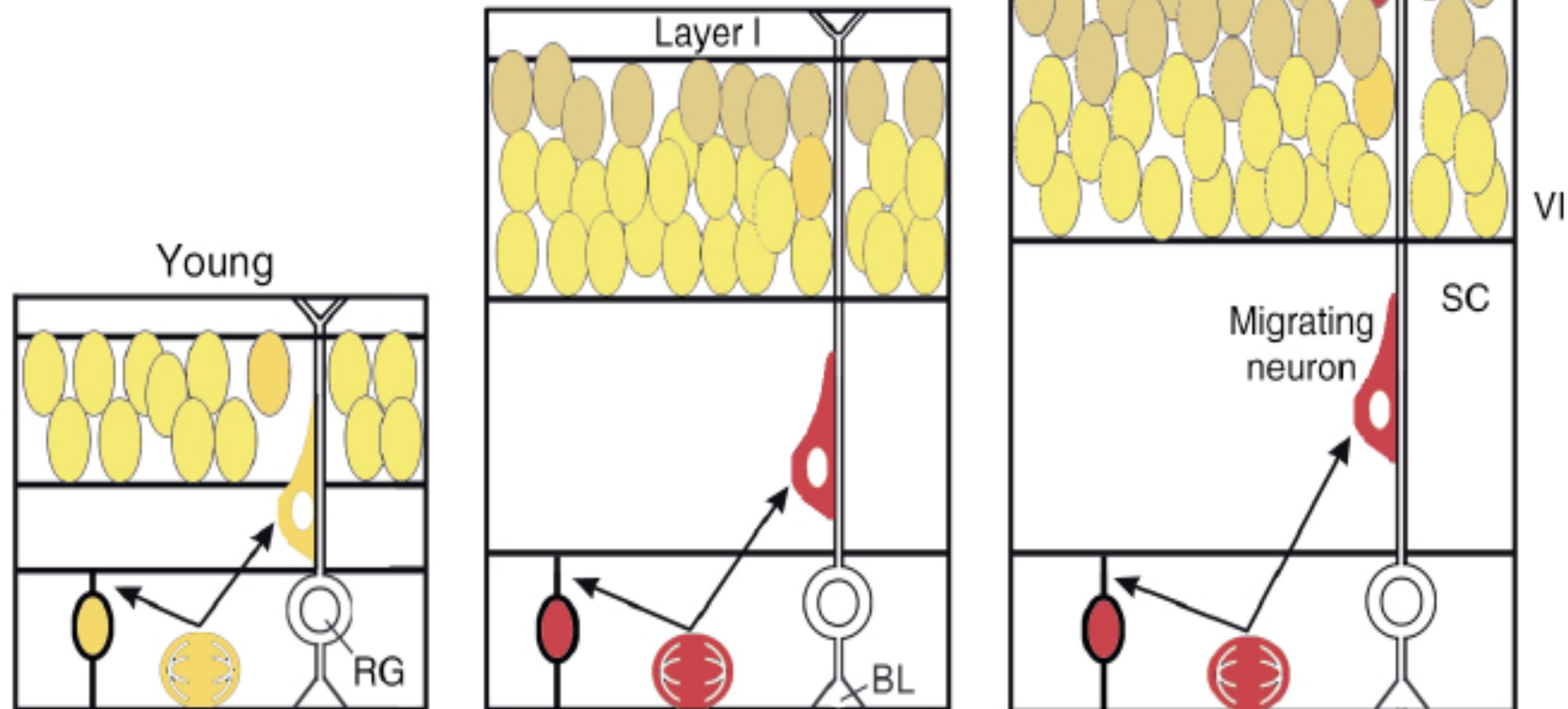
Autism: Transient *in utero* hypothyroxinemia related to maternal flavonoid ingestion during pregnancy and to other environmental antithyroid agents

Gustavo C. Román*

*University of Texas Health Sciences Center at San Antonio, San Antonio, Texas, USA
Veterans Administration Hospital, San Antonio, Texas, USA*

Alterations of cortical neuronal migration and cerebellar Purkinje cells occur in autism. Neuronal migration, via reelin regulation, requires triiodothyronine (T3) produced by deiodination of thyroxine (T4) by fetal brain deiodinases. Experimental animal models have shown that transient intrauterine deficits of thyroid hormones (as brief as 3 days in mice) result in permanent alterations of cerebral cortical architecture reminiscent of those observed in autism. Early (weeks 8–12) maternal hypothyroxinemia with low T3 in the fetal brain could alter neuronal migration producing morphological brain changes leading to autism.

Late-born neurons migrate past early-born neurons, forming six layers. Cortical neurons migrate along scaffolds established by radial glia, which are attached to the basal lamina of the ventricular zone and extend through to layer I.



Cajal-Retzius neurons in layer I are the first neurons to populate the mantle of the cortex, and they produce and secrete Reelin, which is involved in terminating migration of neurons as they climb the scaffold.

Early maternal hypothyroxinemia alters histogenesis and cerebral cortex cytoarchitecture of the progeny

J Clin Invest 2003;111:1073–82

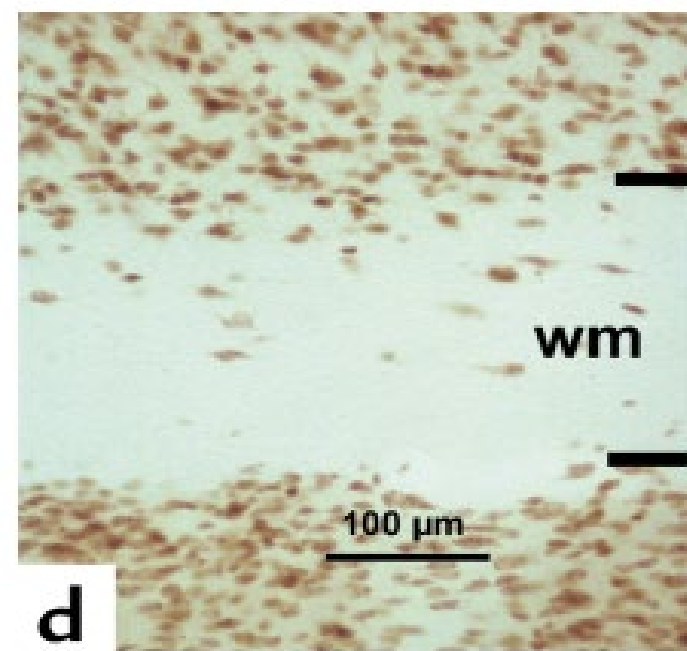
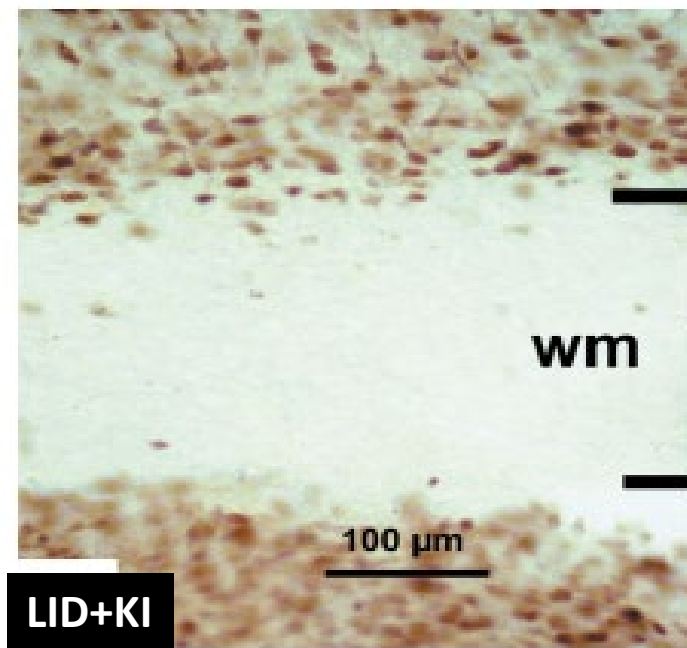
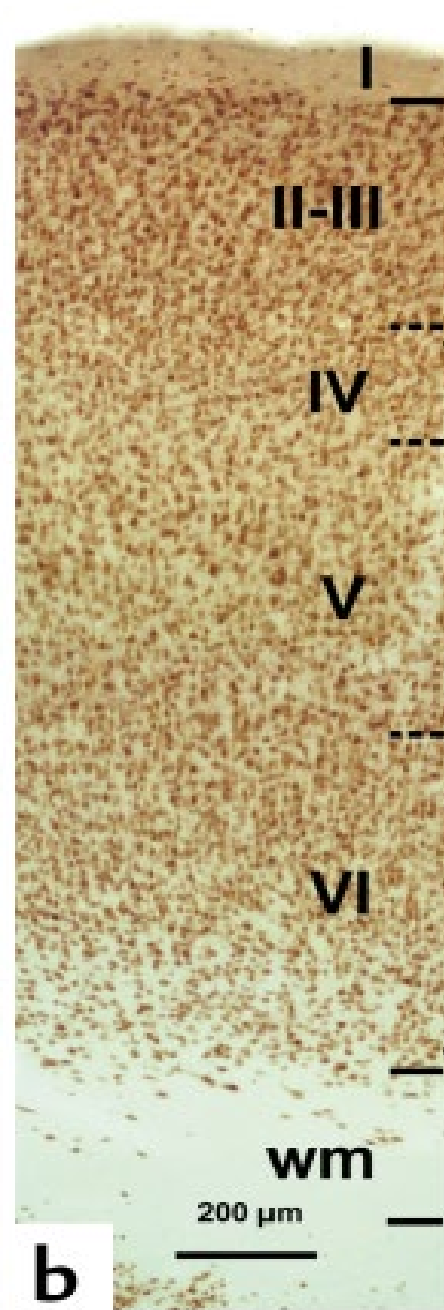
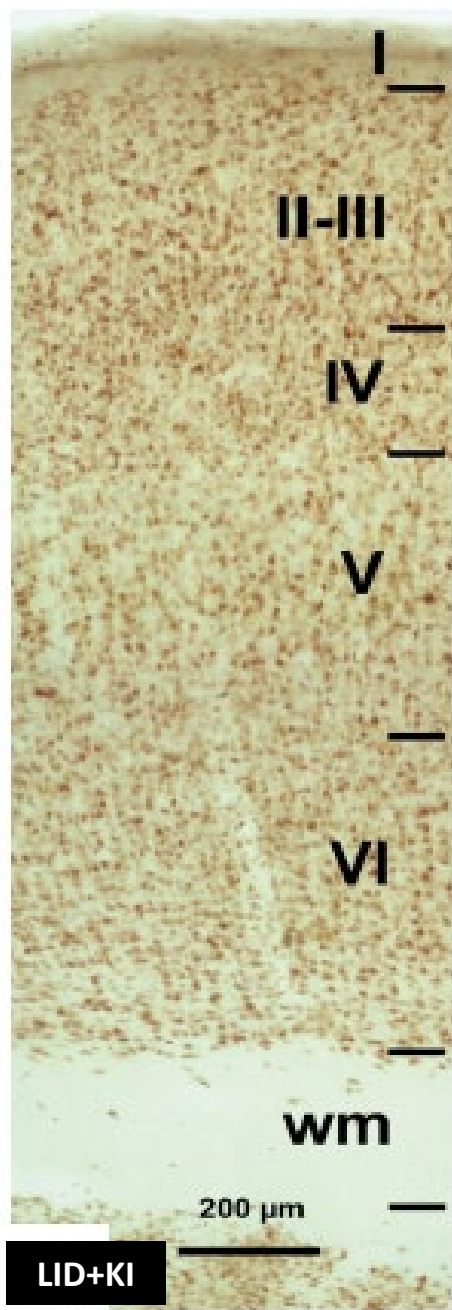
Rosalía Lavado-Autric,¹ Eva Ausó,² José Victor García-Velasco,² María del Carmen Arufe,¹ Francisco Escobar del Rey,¹ Pere Berbel,² and Gabriella Morreale de Escobar¹

¹Instituto de Investigaciones Biomédicas Alberto Sols, Consejo Superior de Investigaciones Científicas and Universidad Autónoma de Madrid, Madrid, Spain

²Instituto de Neurociencias de Alicante, Universidad Miguel Hernández–Consejo Superior de Investigaciones Científicas, San Juan (Alicante), Spain

Rat dams on a low iodine intake are hypothyroxinemic (low T4) without being clinically hypothyroid because circulating T3 (3,5,3'-Triiodothyronine) level is normal. We studied cell migration and cytoarchitecture in the somatosensory cortex and hippocampus of the 40-day-old progeny of the iodine-deficient dams and found a significant proportion of neurons at locations that were aberrant or inappropriate with respect to their birth date. The cytoarchitecture of the somatosensory cortex and hippocampus was affected, layering was blurred, and, in the cortex, normal barrels were not formed. This is not a case of delayed migration, but rather permanent alteration of cortical cytoarchitecture.

anti-mature neurons neuronal nuclei (NeuN) mouse Ab stain



Association of Gestational Maternal Hypothyroxinemia and Increased Autism Risk

Gustavo C. Román, MD,^{1,2} Akhgar Ghassabian, MD, PhD,^{3,4}

Jacoba J. Bongers-Schokking, MD, PhD,^{5,6} Vincent W. V. Jaddoe, MD, PhD,^{3,5,7}

Albert Hofman, MD, PhD,^{3,5} Yolanda B. de Rijke, PhD,^{8,9}

Frank C. Verhulst, MD, PhD,⁴ and Henning Tiemeier, MD, PhD^{4,5,10}

Results: Severe maternal hypothyroxinemia (n = 136) was associated with an almost 4-fold increase in the odds of having a probable autistic child (adjusted odds ratio = 3.89, 95% confidence interval [CI] = 1.83–8.20, $p < 0.001$). Using PDP scores, children of mothers with severe hypothyroxinemia had higher scores of autistic symptoms by age 6 years (adjusted B = 0.23, 95% CI = 0.03–0.37); SRS results were similar. No risk was found for children of TPO-antibody-positive mothers (n = 308).

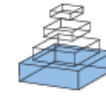
Interpretation: We found a consistent association between severe, early gestation maternal hypothyroxinemia and autistic symptoms in offspring. Findings are concordant with epidemiological, biological, and experimental data on autism. Although these findings cannot establish causality, they open the possibility of preventive interventions.

ANN NEUROL 2013;74:733–742

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ANN NEUROL 2013;74:733–742



An evo-devo approach to thyroid hormones in cerebral and cerebellar cortical development: etiological implications for autism

Pere Berbel^{1*}, Daniela Navarro¹ and Gustavo C. Román^{2,3}

¹ *Departamento de Histología y Anatomía, Facultad de Medicina, Universidad Miguel Hernández, Alicante, Spain*

² *Department of Neurology, Weill Cornell Medical College, Cornell University, New York, NY, USA*

³ *Methodist Neurological Institute, Houston, TX, USA*

The morphological alterations of cortical lamination observed in mouse models of developmental hypothyroidism prompted the recognition that these experimental changes resembled the brain lesions of children with autism; this led to recent studies showing that maternal thyroid hormone deficiency increases fourfold the risk of autism spectrum disorders (ASD), offering for the first time the possibility of prevention of some forms of ASD. For ethical reasons, the role of thyroid hormones on brain development is currently studied using animal models, usually mice and rats. Although mammals have in common many basic developmental principles regulating brain development, as well as fundamental basic mechanisms that are controlled by similar metabolic pathway activated genes, there are also important differences. For instance, the rodent cerebral cortex is basically a primary cortex, whereas the primary sensory areas in humans account for a very small surface in the cerebral cortex when compared to the associative and frontal areas that are more extensive. Associative and frontal areas in humans are involved in many neurological disorders, including ASD, attention deficit-hyperactive disorder, and dyslexia, among others. Therefore, an evo-devo approach to neocortical evolution among species is fundamental to understand not only the role of thyroid hormones and environmental thyroid disruptors on evolution, development, and organization of the cerebral cortex in mammals but also their role in neurological diseases associated to thyroid dysfunction.

Malnutrition and the Nervous System

- PNS: blindness, deafness, motor-sensory deficits
- CNS (spinal cord and brain lesions): mental retardation, cognitive dysfunction, and gait.
- Nutritional deficiencies are not restricted to developing nations. Populations at risk in industrial nations include the poor, migrants, homeless, alcoholics, drug addicts, chronic psychiatric patients, and the demented elderly. People with peculiar dietary habits such as strict vegans.



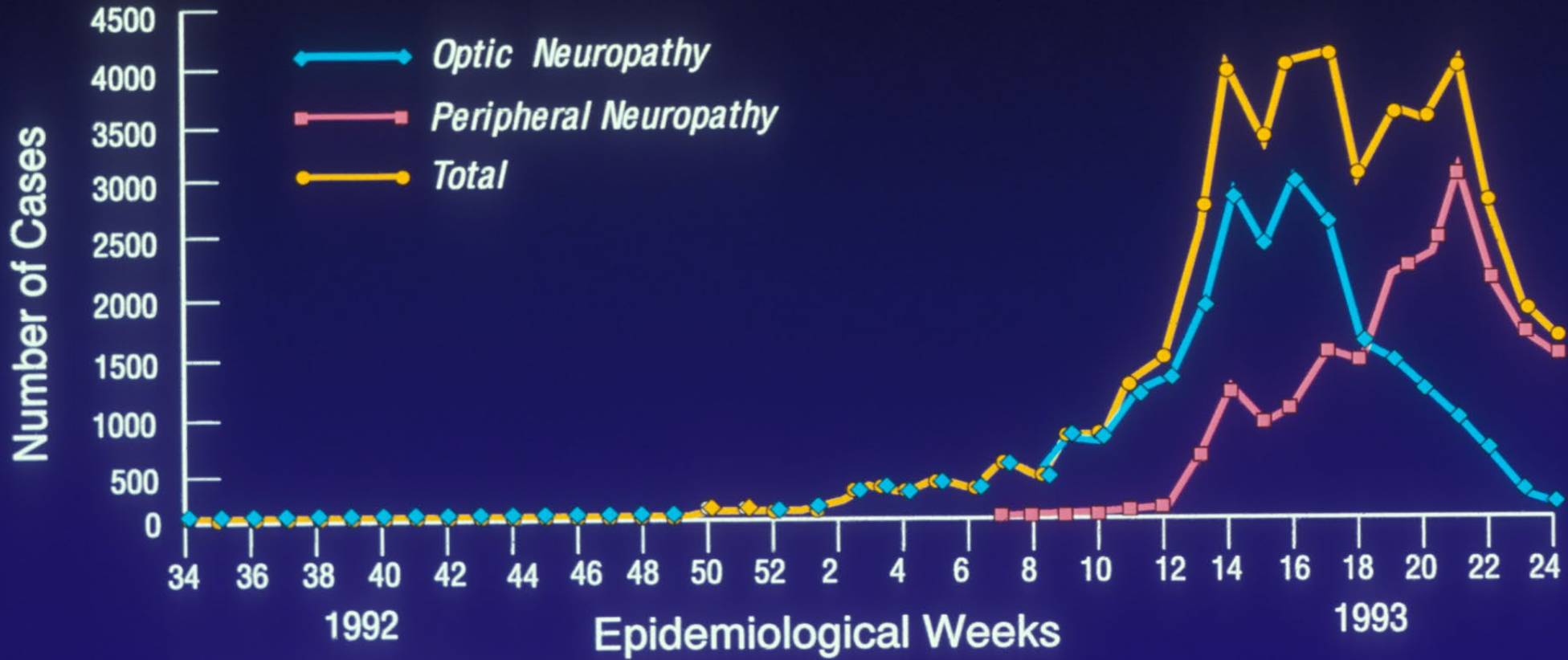
CUBAN BLINDNESS

DIARY OF A MYSTERIOUS
EPIDEMIC NEUROPATHY

Gustavo C. Román



Epidemic Neuropathy Cuba 1993

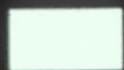


Source: Direction Nacional de Estadisticas
MINSAP, Cuba

Epidemic Neuropathy Cuba 1993



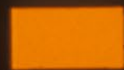
Rate x 100,000 Habitats



Very Low (< 60)



Low (180-300)



Intermediate (300-400)



High (500-600)



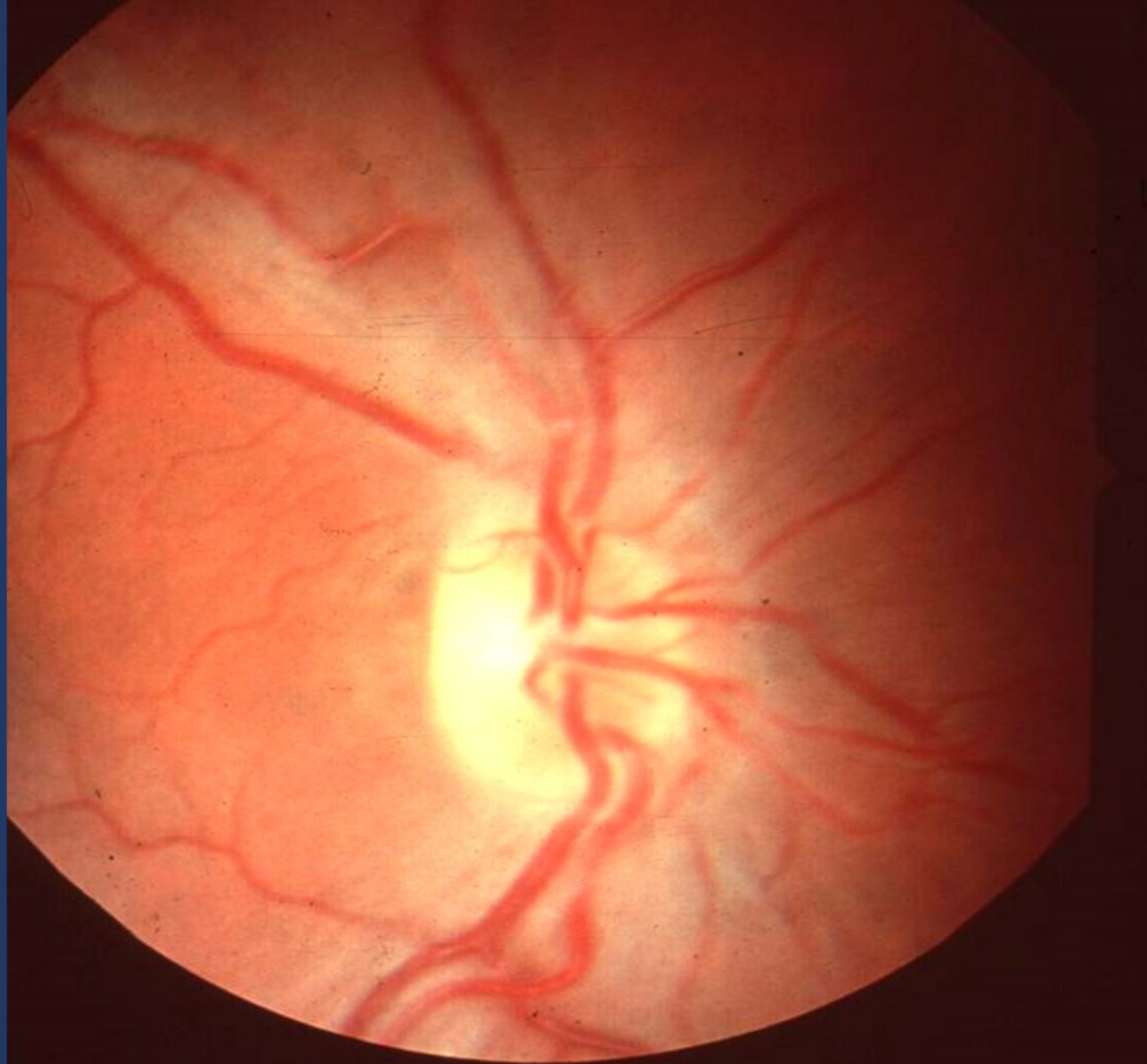
Very High (>1,000)



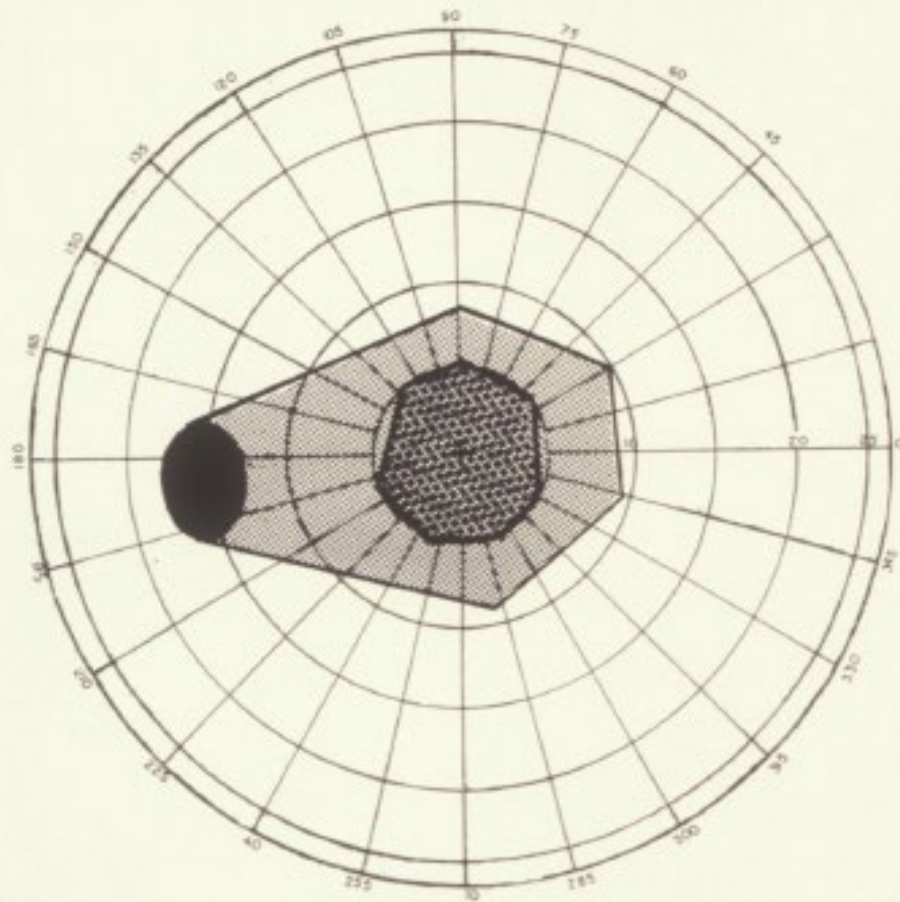
Pinar del Rio, Cuba Sept. 1993

Cuban Optic Neuropathy

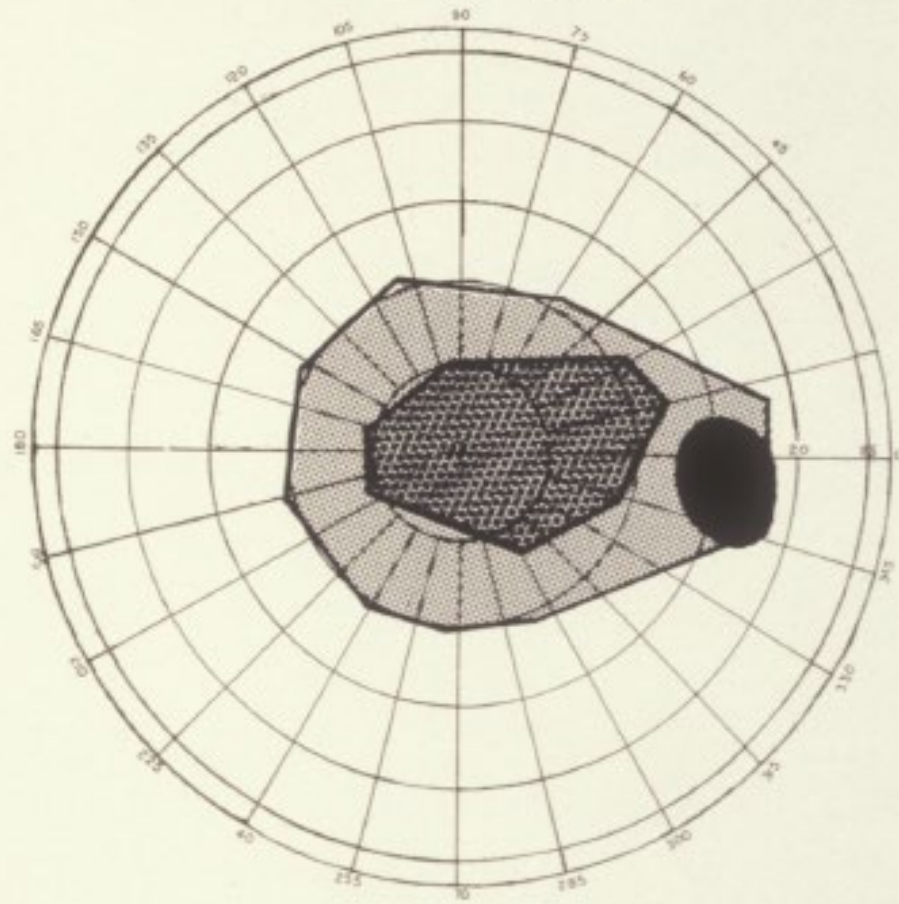
35 y.o. man
1 mo h/o sub-acute loss of
vision
VA: 20/400 both eyes
(A. Sadun)

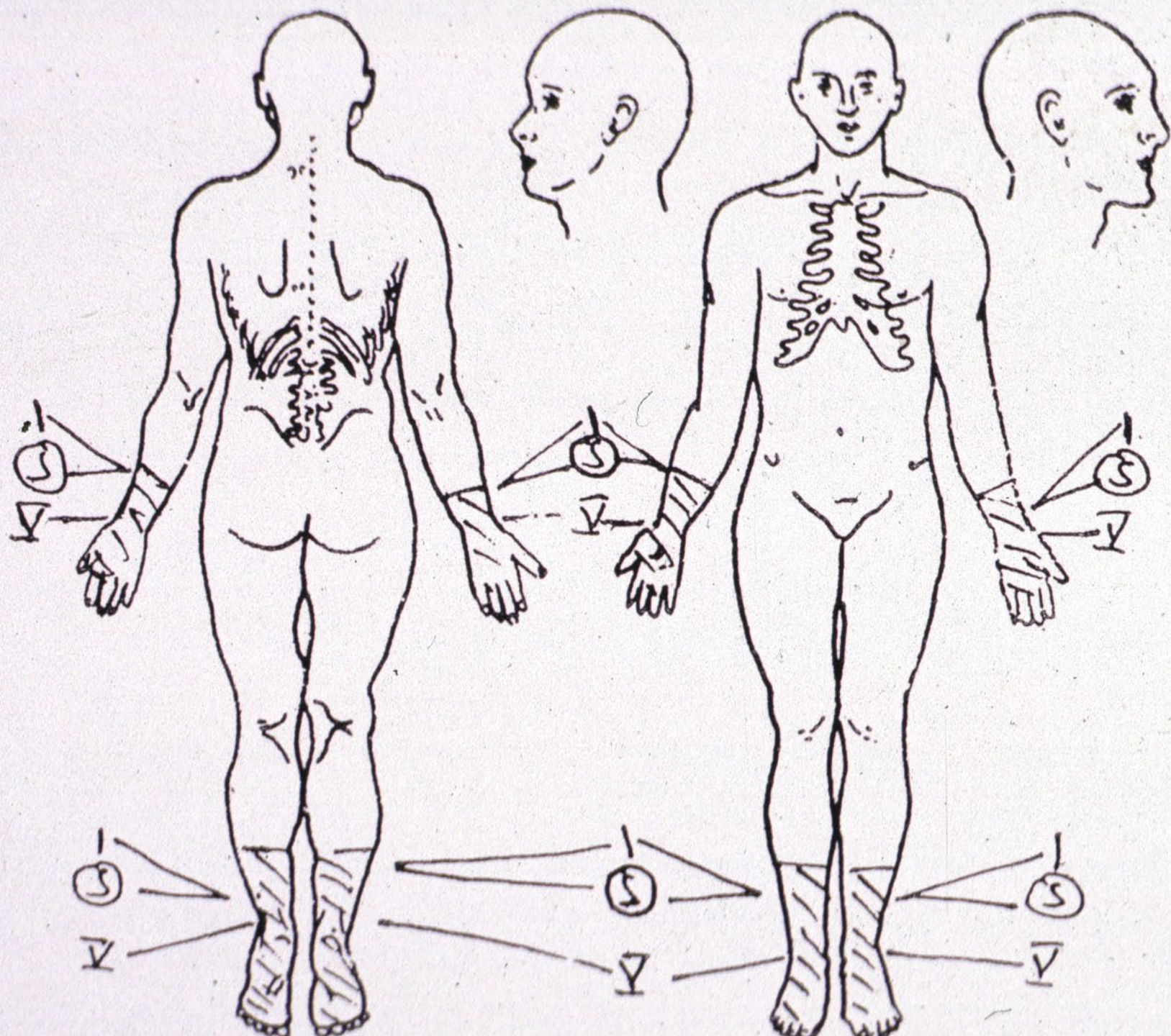


CAMPIMETRIA



CAMPIMETRIA





The Cuba Neuropathy Field Investigation Team: Epidemic Optic Neuropathy in Cuba — Clinical Characterization and Risk Factors.
N Engl J Med 1995;333:1176-82.

Methods - Case-control study: In September of 1993, ophthalmologic and neurological examinations were performed on 150 cases with severe CEON and 150 sex- and age-matched randomly chosen normal controls.

We visited their homes, assessed exposure to potential toxins, administered a semi-quantitative food-frequency questionnaire, and assessed serum measures of nutritional status in 123 patients with severe CON and 123 controls.

Epidemic Neuropathy in Cuba

(...) its occurrence was linked to a deterioration in diet affecting nutrients such as methionine, vitamin B₁₂, riboflavin, and carotenoids, in conjunction with a high prevalence of tobacco use and possibly cassava consumption.

N Engl J Med 1995;333:1176-82.



Vascular Contributions to Cognitive Impairment and Dementia : A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

Philip B. Gorelick, Angelo Scuteri, Sandra E. Black, Charles DeCarli, Steven M. Greenberg, Costantino Iadecola, Lenore J. Launer, Stephane Laurent, Oscar L. Lopez, David Nyenhuis, Ronald C. Petersen, Julie A. Schneider, Christophe Tzourio, Donna K. Arnett, David A. Bennett, Helena C. Chui, Randall T. Higashida, Ruth Lindquist, Peter M. Nilsson, Gustavo C. Roman, Frank W. Sellke and Sudha Seshadri

Conclusions—Vascular contributions to cognitive impairment and dementia are important. Understanding of VCI has evolved substantially in recent years, based on preclinical, neuropathologic, neuroimaging, physiological, and epidemiological studies. Transdisciplinary, translational, and transactional approaches are recommended to further our understanding of this entity and to better characterize its neuropsychological profile. There is a need for prospective, quantitative, clinical-pathological-neuroimaging studies to improve knowledge of the pathological basis of neuroimaging change and the complex interplay between vascular and Alzheimer disease pathologies in the evolution of clinical VCI and Alzheimer disease. Long-term vascular risk marker interventional studies beginning as early as midlife may be required to prevent or postpone the onset of VCI and Alzheimer disease. Studies of intensive reduction of vascular risk factors in high-risk groups are another important avenue of research. (*Stroke*. 2011;42:2672-2713.)

Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre

Jon B. Toledo,^{1,*} Steven E. Arnold,^{2,3,*} Kevin Raible,¹ Johannes Brettschneider,¹ Sharon X. Xie,⁴ Murray Grossman,² Sarah E. Monsell,⁵ Walter A. Kukull⁵ and John Q. Trojanowski¹

...presence of vascular pathology in 79.9% of 4629 brains from patients with neuropathologically-confirmed Alzheimer's disease. Lesions included atherosclerosis in the Circle of Willis, arteriosclerotic leukoencephalopathy, arteriolosclerosis, large infarcts, lacunes, multiple microinfarcts, and hemorrhages. Cerebral amyloid angiopathy was present in less than half of the brains (40.8%).

Translating Current Knowledge Into Dementia Prevention

Gustavo C. Román, MD,† David T. Nash, MD,‡ and Howard Fillit, MD§||*

Abstract: Considerable knowledge has been gained from epidemiologic studies and randomized clinical trials regarding risk factors for dementia, including Alzheimer disease (AD) and vascular dementia (VaD). Most identified risk factors for dementia are similar to vascular disease risk factors for heart disease and stroke. In 2010, the National Institutes of Health Conference concluded that there are no validated modifiable factors to reduce the incidence of AD or to change its course. This research perspective specifically concerning AD disregards the fact that in community-dwelling elderly, the most common forms of dementia involve the cerebral macrovasculature and microvasculature, manifesting as VaD and mixed dementia (the combination of VaD and AD) in autopsy-confirmed cases. Thus, prevention of dementia in clinical practice should be considered from this broader and more relevant view and not just a research perspective on “pure” AD. Practicing clinicians can reasonably state to patients that, although more definitive research is clearly needed, the management and treatment of vascular disease risk factors are likely beneficial not only to prevent heart disease and stroke, but also common forms of dementia in the community.

Key Words: Alzheimer disease, diet, exercise, homocysteine, hyperlipidemia, hypertension, smoking, vascular diseases risk factors, vascular dementia

(Alzheimer Dis Assoc Disord 2012;00:000–000)

and AD pathology, predominates in autopsy-confirmed cases of dementia in the elderly.^{2–5} The conference undervalued evidence that vascular disease risk factors (VDRFs) predispose not only to heart disease and stroke, but also to dementias that involve the vasculature, such as vascular dementia (VaD) and mixed dementia, which together comprise the most common forms of dementia at autopsy in community-based studies.^{2–5} Recently, a comprehensive review and position paper by the American Heart Association/American Stroke Association⁶ confirmed the importance of vascular factors in cognitive impairment and dementia and the complex relationships existing between AD and cerebrovascular pathology.

THE MANY VASCULAR CAUSES OF DEMENTIA IN THE ELDERLY

The trend toward increasing population age is well known⁷; the potential benefits of a long life are countered by many burdens including a 100-fold increase in stroke incidence from 3/10,000 population in the third and fourth decades to 300/10,000 at age 80 to 90 years.⁸ Poststroke cognitive decline is more common than stroke recurrence and affects 30% of survivors older than 65 years; new-onset dementia incidence increases from 7% after 1 year to 48% after 25 years.⁹ More troublesome is the fact that “silent”

Risk Factors for Alzheimer Dementia

- Aging
- Midlife hypertension
- Apolipoprotein E ϵ 4 genotype
- Cerebral amyloid angiopathy
- Atherosclerosis: PVD, CAD, CHF
- Smoking
- Diabetes mellitus
- Silent lacunar strokes (>2X), h/o stroke
- Homocysteine



WARNING

**When you
smoke
it shows.**

**Tobacco is addictive
and harmful.**

You have the will. There is a way.



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Health Canada

Smoking and DM

- Smokers develop insulin resistance syndrome
- Increased risk for type 2 diabetes (about 50%)
- Cigarette smoking increases risk for diabetic nephropathy, retinopathy, and neuropathy via its metabolic effects in combination with increased inflammation and endothelial dysfunction
- Increased risk for macrovascular complications, CHD, stroke, and PVD, mainly in type 2 diabetes

Prog Cardiovasc Dis. 2003 Mar-Apr;45(5):405-13

Smoking and CBF

Evaluation of regional cerebral blood flow under the smoking and resting states using technetium-99m-labelled single-photon emission computed tomography (SPECT).

CONCLUSION: rCBF on smoking-activated SPECT was significantly decreased in the whole brain as compared with that on resting SPECT

Smoking and Stroke

- 14-year prospective study of 3,626 men aged 40-69
- 257 strokes (75 hemorrhagic and 173 ischemic strokes) and 100 MIs
- Total stroke RR = 1.6 (95% CI 1.1-2.4)
- Hypertensives RR = 2.3 (95% CI 1.2-4.4)
- Estimated proportion of events attributable to smoking
 - 30 (95% CI, 11-44)% for total stroke
 - 34 (CI 5-54)% for coronary heart disease

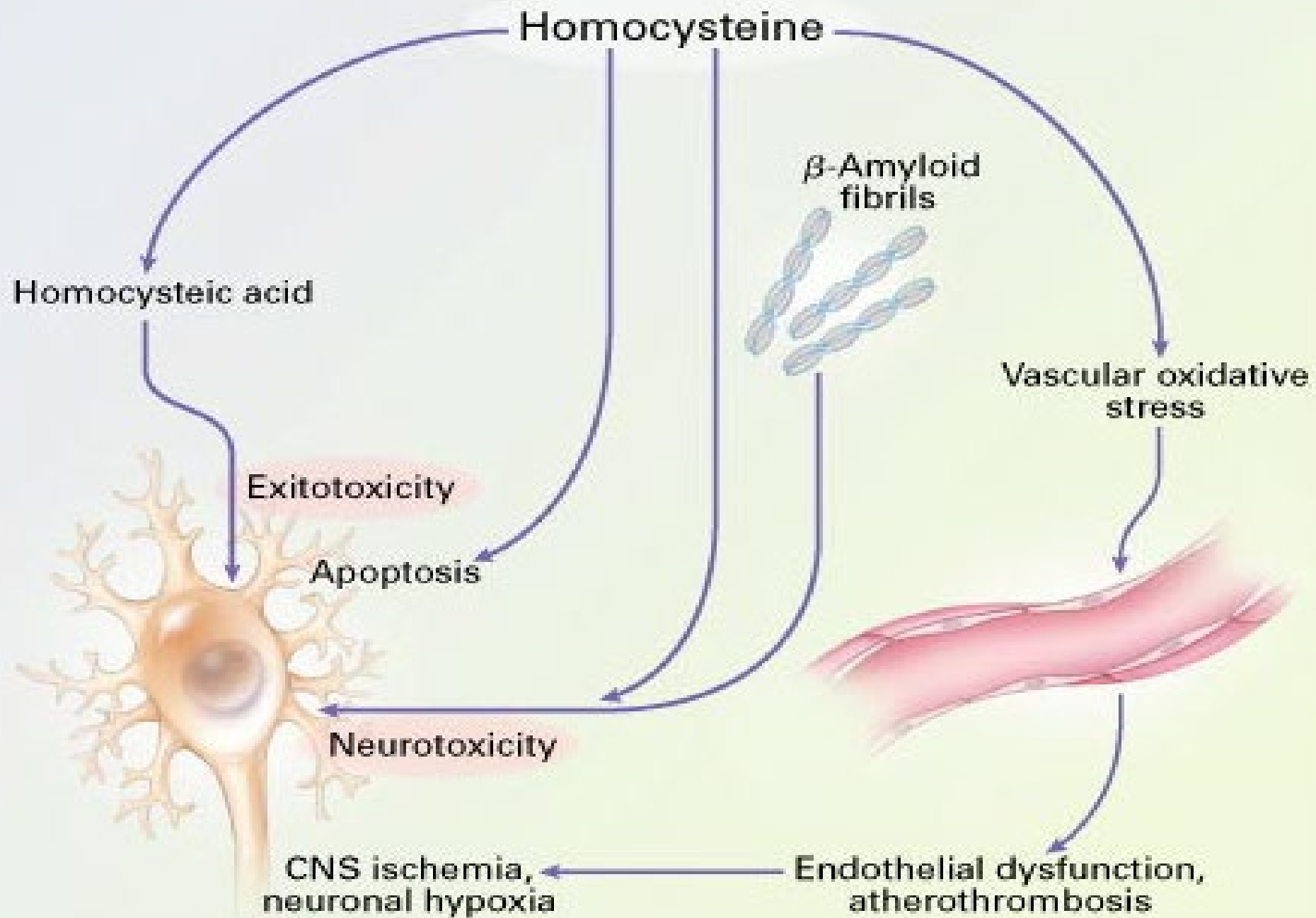


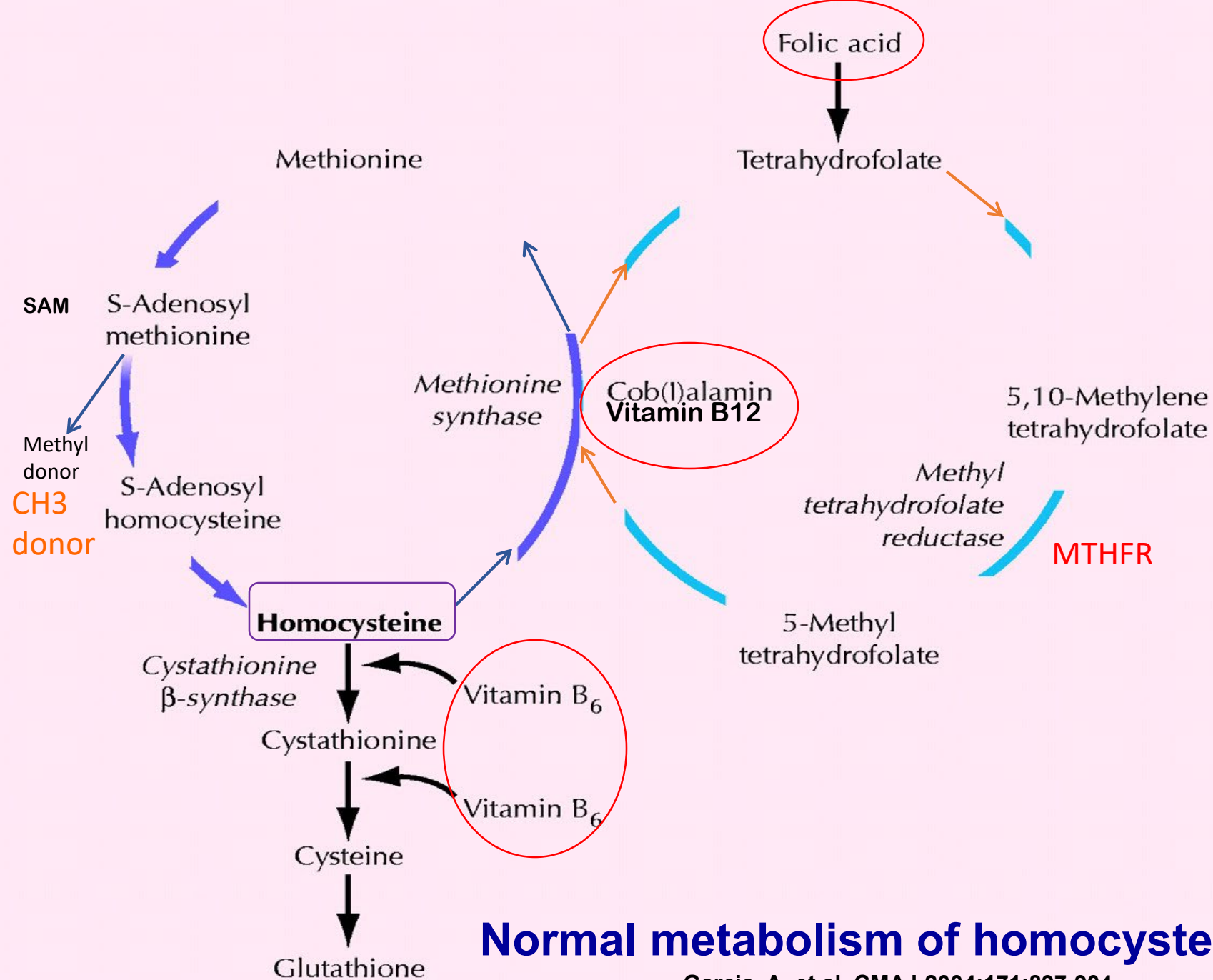
PLASMA HOMOCYSTEINE AS A RISK FACTOR FOR DEMENTIA AND ALZHEIMER'S DISEASE

SESHADRI S, BEISER A, SELHUB J, JACQUES PF, et al.

A total of 1092 subjects without dementia (667 women and 425 men; mean age, 76 years) from the Framingham Study. Plasma total Hcy at base line and 8 yrs earlier and risk of newly diagnosed dementia (adjusted for age, sex, ApoE, vascular risk, folate, vitamins B₁₂ and B₆)

Conclusion: Plasma tHcy level > 14 $\mu\text{mol/L}$ \Rightarrow 2X the risk of AD





Normal metabolism of homocysteine

Garcia, A. et al. CMAJ 2004;171:897-904

Vitamin B12

+

Vitamin B6

+

Folate

Homocysteine → MTHFR
Methyl (CH₃) 1-carbon groups



Short Communication

MTHFR Gene Mutations: A Potential Marker of Late-Onset Alzheimer's Disease?

Gustavo C. Román*

Houston Methodist Hospital Neurological Institute, Houston, Texas and Weill Cornell Medical College, Cornell University, New York, NY, USA

Accepted 19 April 2015

Abstract. Recent epigenome-wide association studies have confirmed the importance of epigenetic effects mediated by DNA methylation in late-onset Alzheimer's disease (LOAD). Metabolic folate pathways and methyl donor reactions facilitated by B-group vitamins may be critical in the pathogenesis of LOAD. Methylenetetrahydrofolate reductase (*MTHFR*) gene mutations were studied in consecutive Alzheimer's Disease & Memory Clinic patients up to December 2014. DNA analyses of *MTHFR*-C667T and -A1298C homozygous and heterozygous polymorphisms in 93 consecutive elderly patients revealed high prevalence of *MTHFR* mutations (92.5%). Findings require confirmation in a larger series, but *MTHFR* mutations may become a LOAD marker, opening novel possibilities for prevention and treatment.

Keywords: Alzheimer's disease, DNA methylation, epigenetics, *MTHFR* gene, vitamins B-group

Level A (I): Randomized CCT

[PLoS Hub for Clinical Trials](#)

Homocysteine-Lowering by B Vitamins Slows the Rate of Accelerated Brain Atrophy in Mild Cognitive Impairment: A Randomized Controlled Trial

David Smith, Stephen M. Smith, Celeste A. de Jager, Philippa Whitbread, Carole Johnston, Grzegorz Agacinski, Abderrahim Oulhaj, Kevin M. Bradley, Robin Jacoby, Helga Refsum

Oxford Project to Investigate Memory and Ageing (OPTIMA), University of Oxford, Oxford, United Kingdom, Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway

The treatment response was related to baseline homocysteine levels: the rate of atrophy in participants with homocysteine $>13 \mu\text{mol/L}$ was 53% lower in the active treatment group ($P = 0.001$).

NDC 63323-044-01

4401

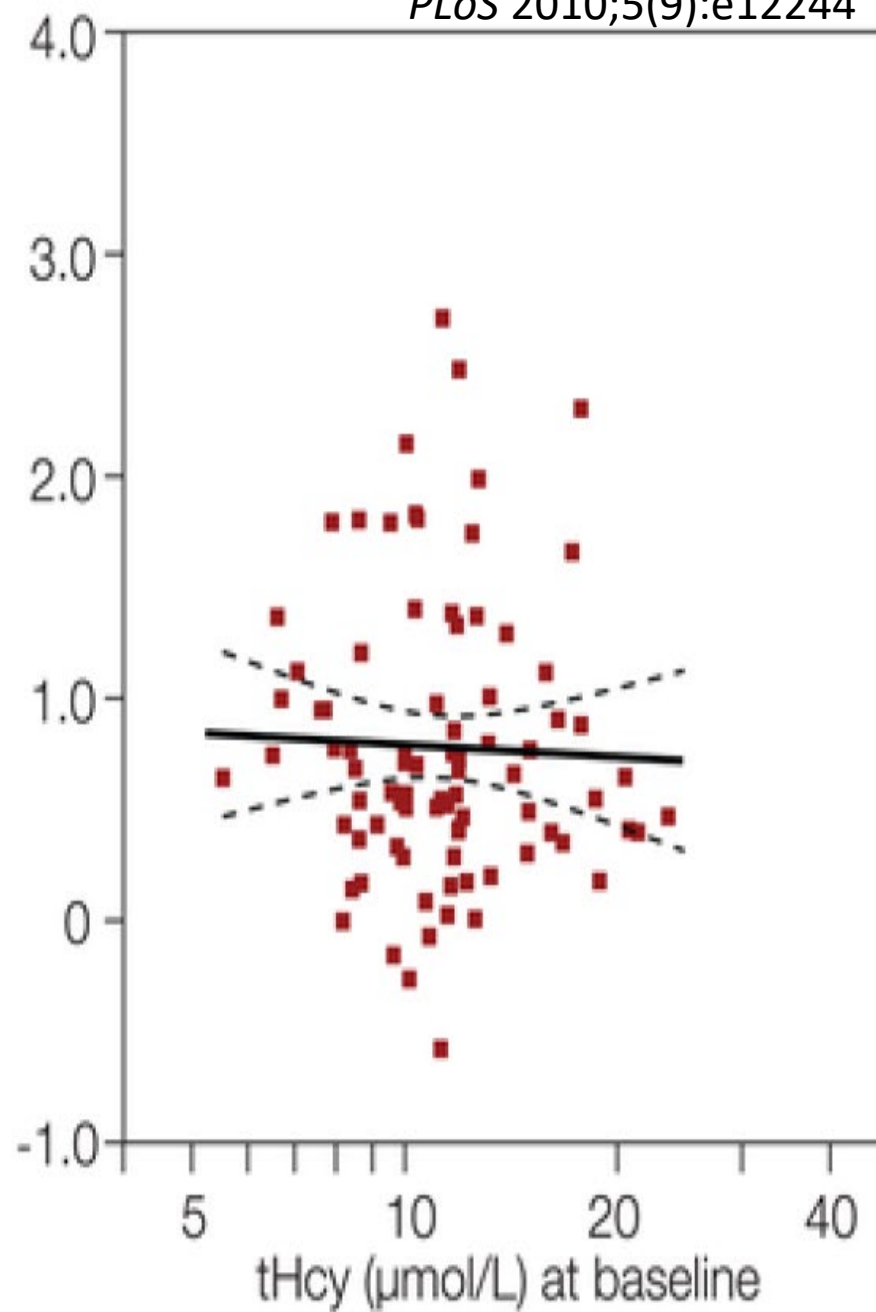
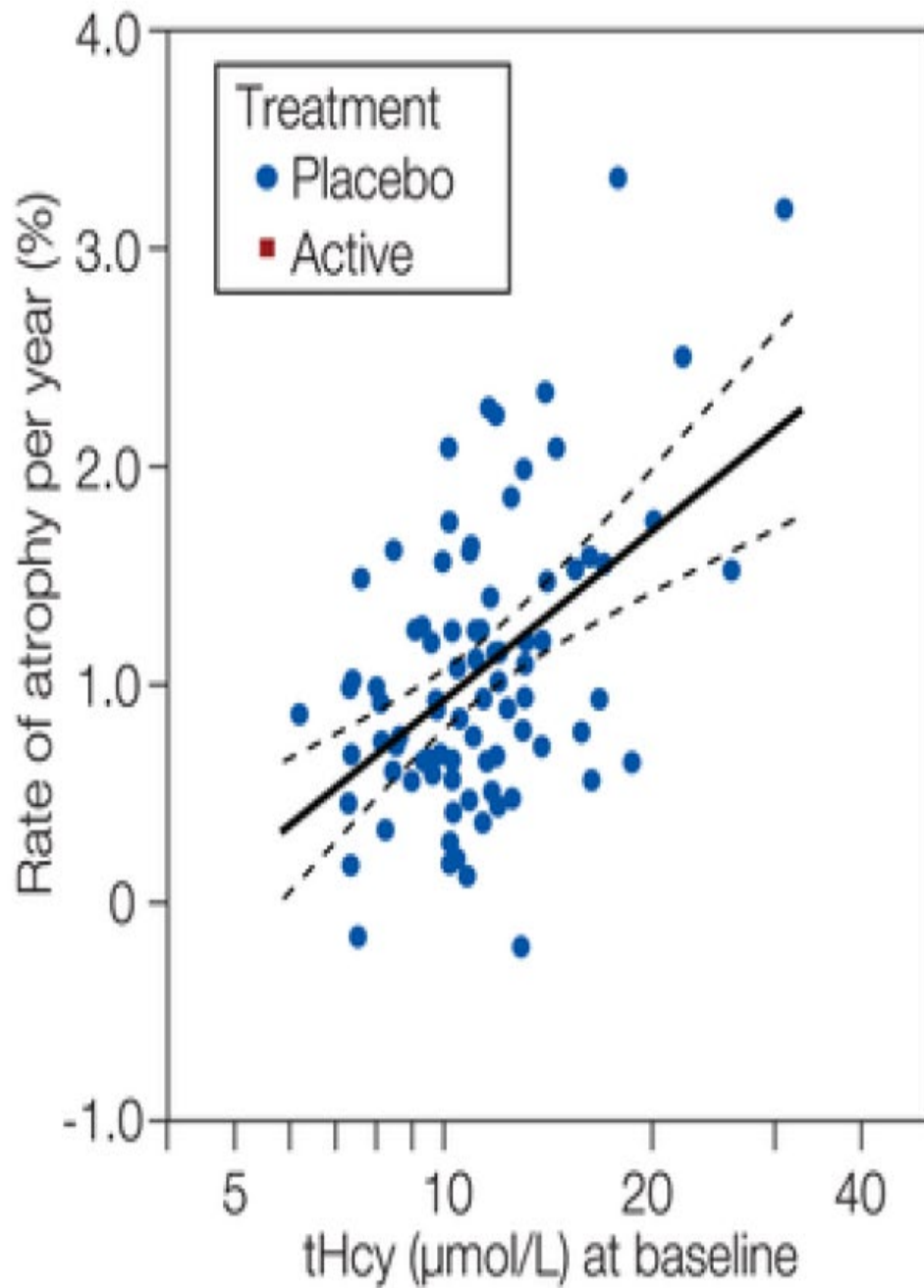
**CYANOCOBALAMIN
INJECTION, USP**

1,000 mcg/mL

For IM or SC Use

1 mL Multiple Dose Vial
PROTECT FROM LIGHT.

Rx only

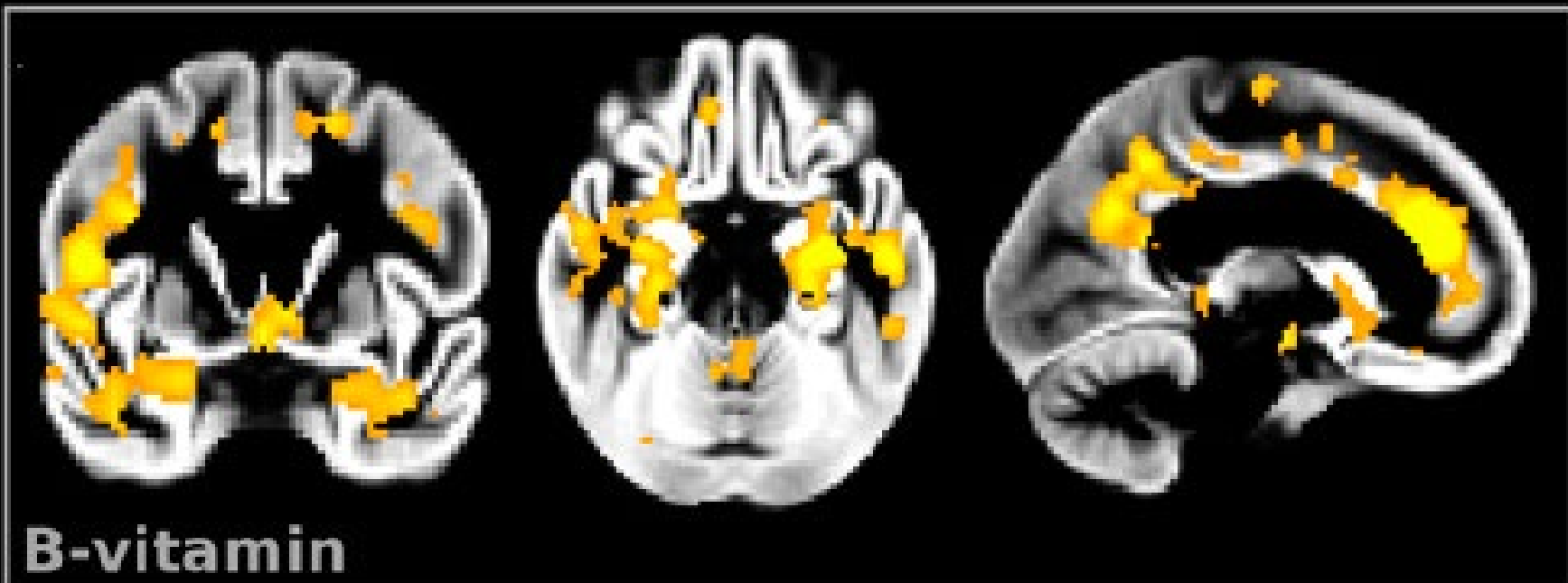
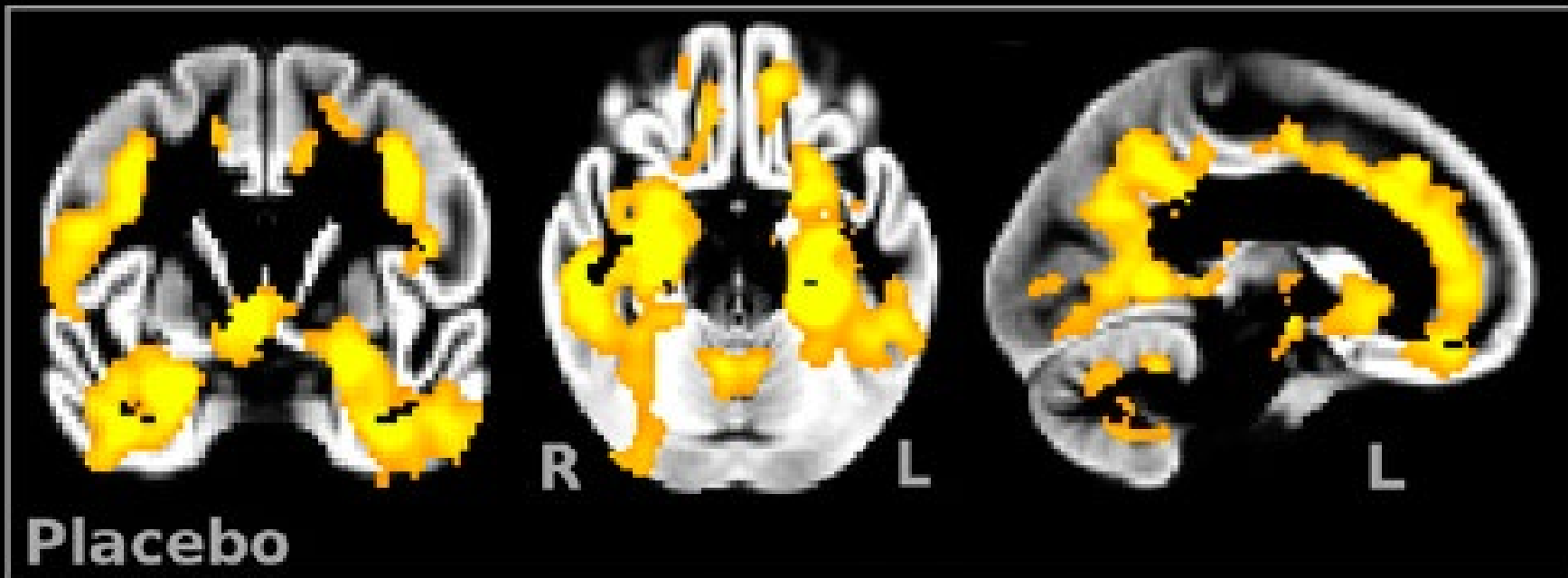


Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment

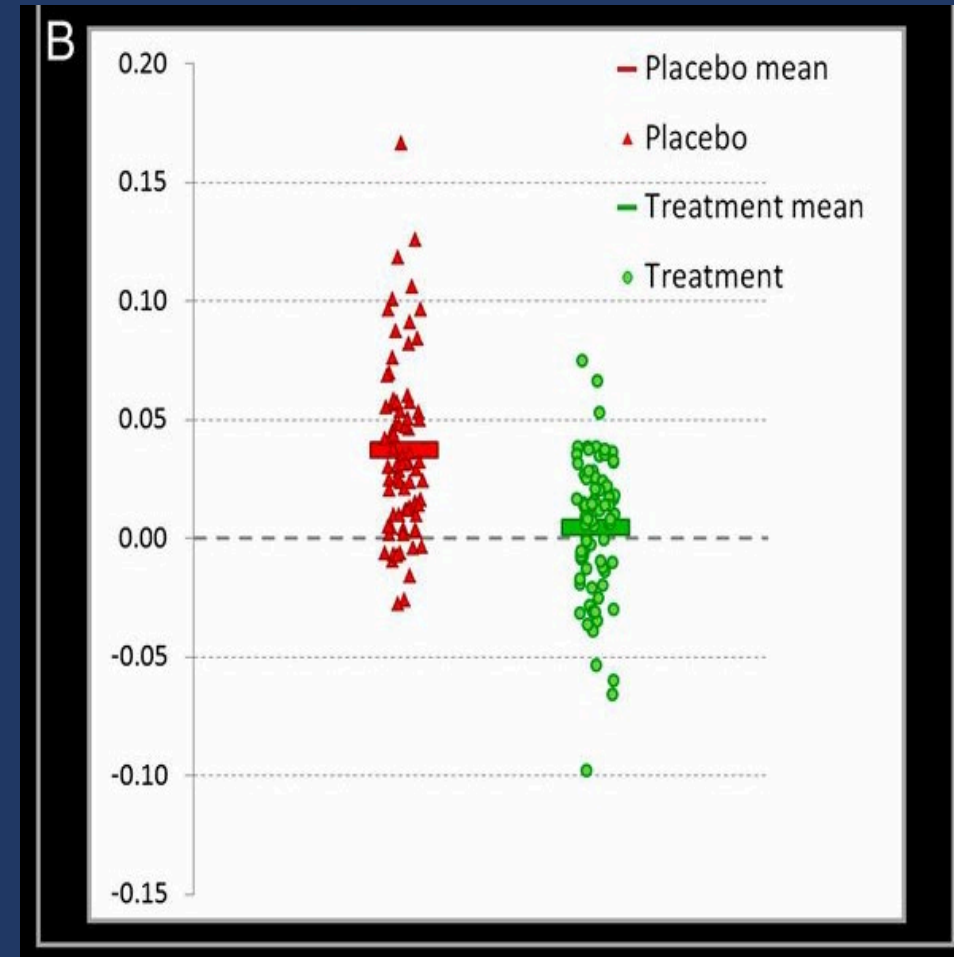
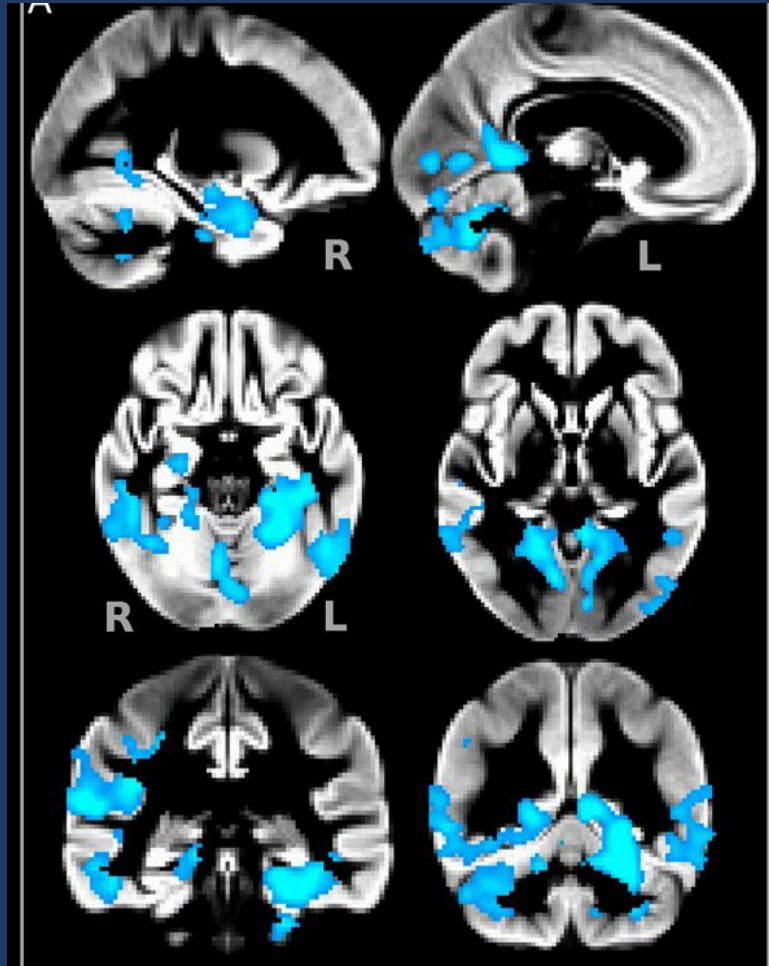
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B-vitamin treatment reduces, by as much as seven fold, the cerebral atrophy in those gray matter (GM) regions specifically vulnerable to the AD process, including the medial temporal lobe. In the placebo group, higher homocysteine levels at baseline are associated with faster GM atrophy, but this deleterious effect is largely prevented by B-vitamin treatment. We additionally show that the beneficial effect of B vitamins is confined to participants with high homocysteine (above the median, 11 $\mu\text{mol/L}$) and that, in these participants, a causal Bayesian network analysis indicates the following chain of events: B vitamins lower homocysteine, which directly leads to a decrease in GM atrophy, thereby slowing cognitive decline. Our results show that B-vitamin supplementation can slow the atrophy of specific brain regions that are a key component of the AD process and that are associated with cognitive decline. Further B-vitamin supplementation trials focusing on elderly subjects with high homocysteine levels are warranted to see if progression to dementia can be prevented.



B-vitamin treatment significantly reduces regional loss of GM ($P < 0.05$ FWE-corrected).



Brain regions in blue demonstrate where B-vitamin treatment significantly reduces GM loss over the 2-y period. All blue areas are regions of significant loss in placebo known to be vulnerable in AD

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The epigenetic landscape of Alzheimer's disease

Jenny Lord & Carlos Cruchaga

Two independent epigenome-wide association studies of Alzheimer's disease cohorts have identified overlapping methylation signals in four loci, *ANK1*, *RPL13*, *RHBDF2* and *CDH23*, not previously associated with Alzheimer's disease. These studies also suggest that epigenetic changes contribute more to Alzheimer's disease than expected.

genome-wide association studies (GWAS) have been successful in identifying numerous genes associated with the condition², the variants and mechanisms underlying these associations are generally unclear. In addition, the proportion of the genetic heritability explained by common variants is only 3–4% for each locus.

In this issue of *Nature Neuroscience*, Lunnon *et al.*⁴ and De Jager *et al.*⁵ present the results of the first two large-scale, epigenome-wide association studies (EWAS) in Alzheimer's disease, with results being replicated in independent cohorts. ⁵