

Air pollution has become a major health threat for millions of people. The neurological impact is an emerging challenge, particularly for children.

**Neuroinflammation and systemic inflammation impact the developing brain with short and long term **serious** central nervous system consequences.**

**Lilian Calderón-Garcidueñas MA,  
MD, PhD**

# Metropolitan Mexico City, 24 million residents in an exposure chamber

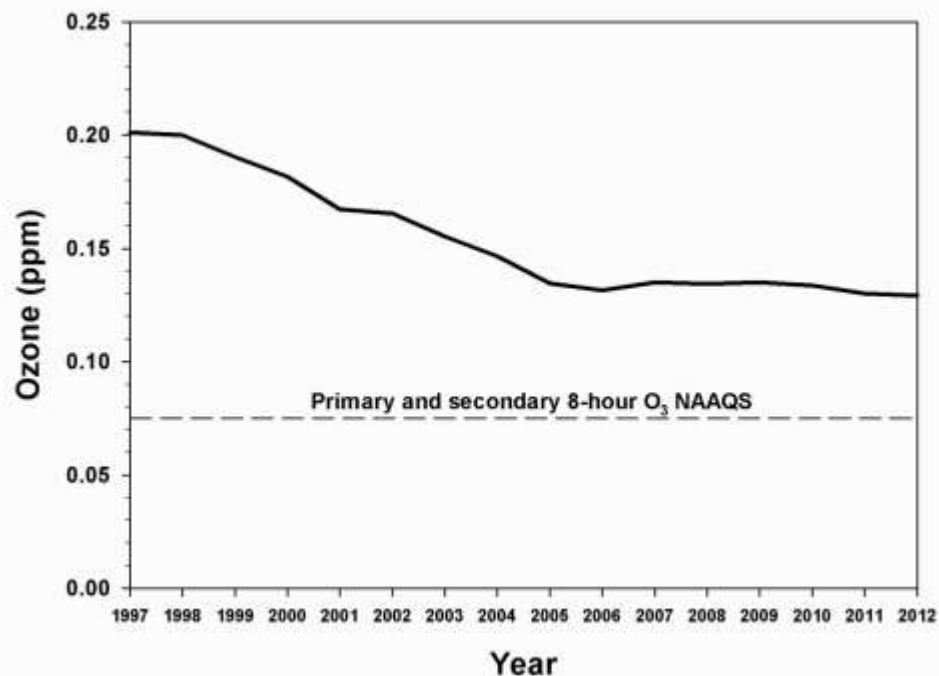
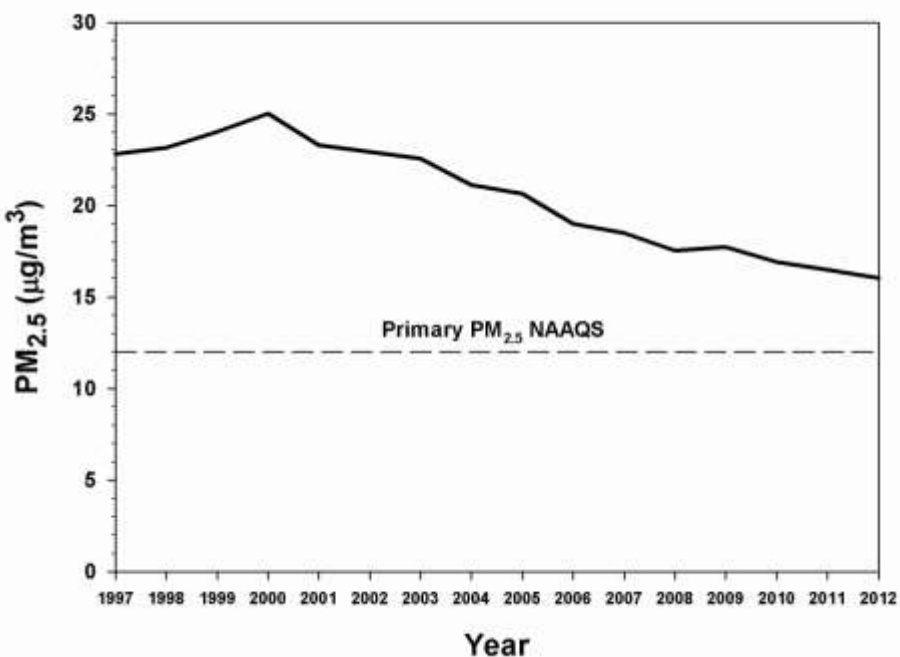


March 10, 2016  
Picture taken from EXCELSIOR



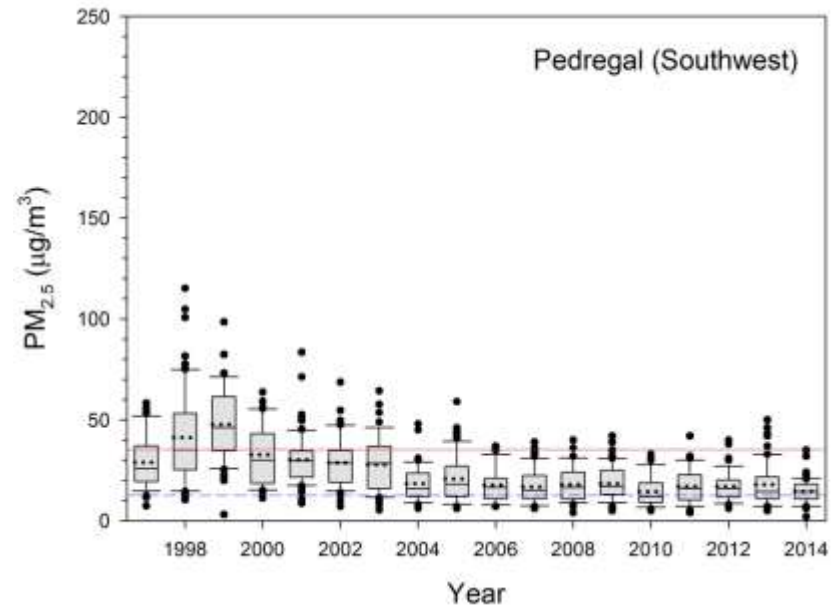
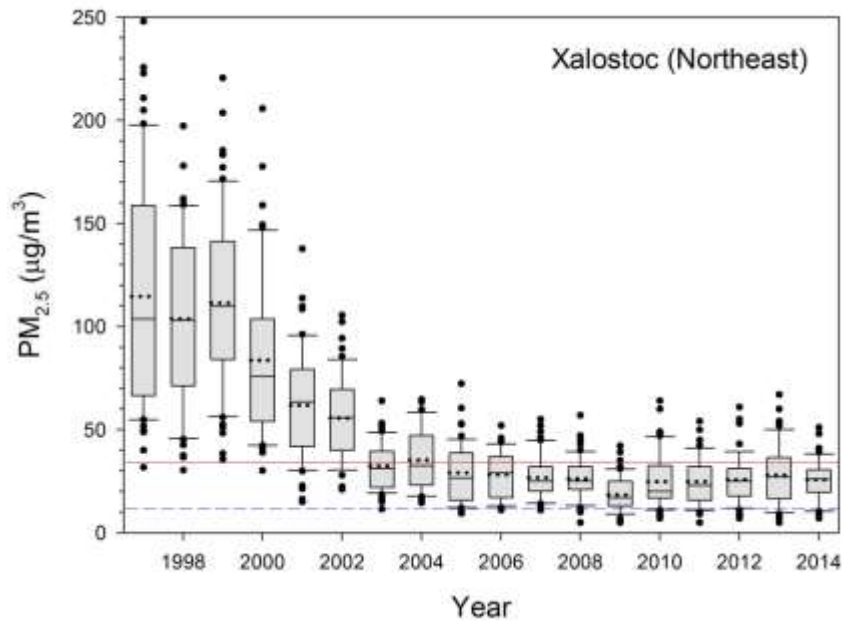
March 14, 2016  
Picture taken from EXCELSIOR

# Mexico City residents are chronically exposed to high concentrations of Ozone and PM2.5



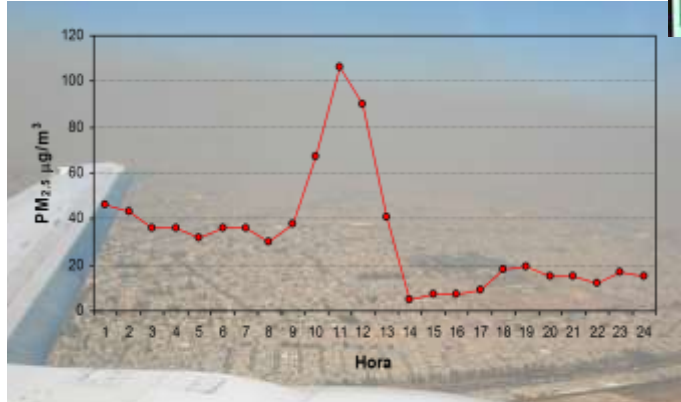
DATA FROM DR. RICARDO TORRES, UNAM

# Fine particulate matter PM 2.5



DATA FROM DR. RICARDO TORRES, UNAM

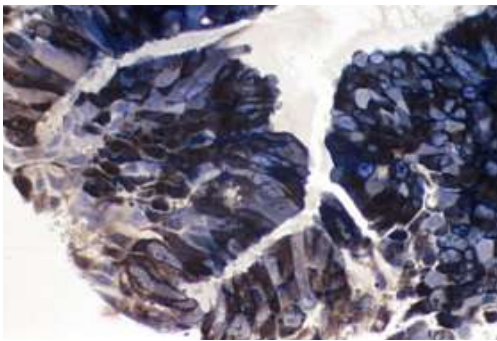
**24 Million people are in the largest PM exposure chamber in North America: Metropolitan Mexico City**



**More than 31% of the population are Children**



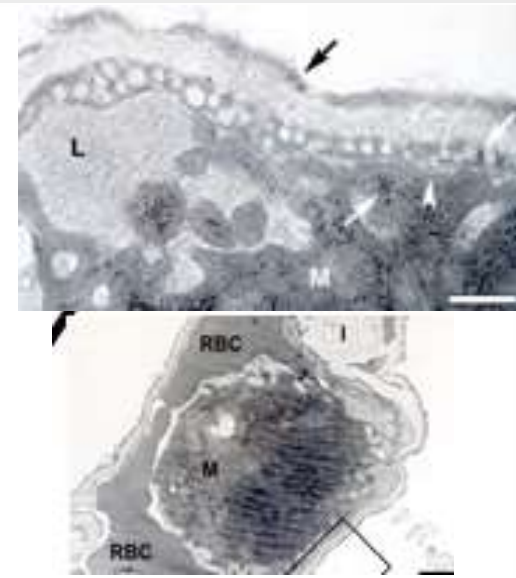
**A.**



**Nasal Barrier Breakdown, Access of PM through Olfactory, Trigeminal, and Accessory Posterolateral Nerve**



**B.**

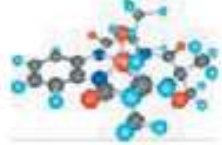


**Alveolar Capillary Barrier Transport of PM systemically**



**Diffuse Brain Inflammation, BBB breakdown, Neuronal & Glial damage: Cognitive deficits, White Matter Structural and Volumetric changes, olfactory damage, etc.,**

Molecules



Virus



Bacteria



RBC



Cell



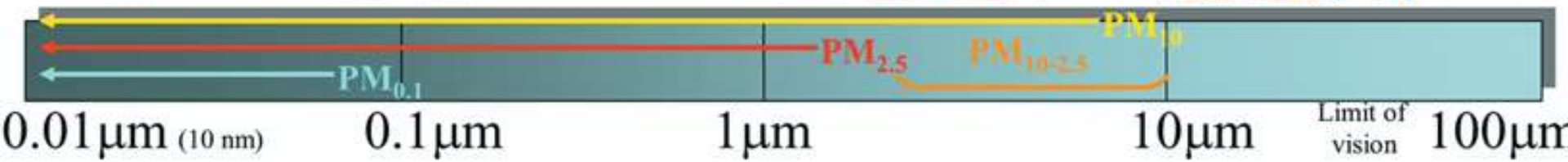
Pollen



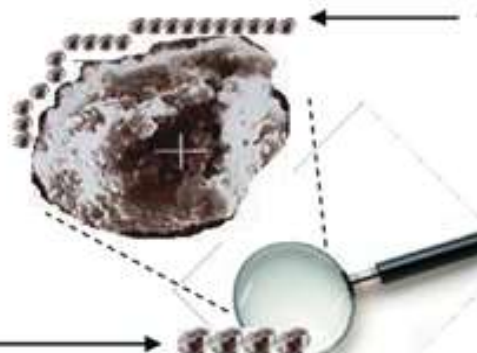
Pin



Hair



Brook et al.2010



UFP (PM<sub>0.1</sub>) Ultrafine particles

Constituents:  
 Primary combustion – hydrocarbons, metals, organic carbon  
Sources:  
 Secondary photochemical formation from gases, VOC/SVOC  
 Fresh automobile and combustion emissions  
 Lifetime: Minutes to hours. Distributed 100s of meters from source

PM<sub>2.5</sub>  
Fine particles

Constituents:  
 Organic/elemental carbon  
 Organic compounds, hydrocarbons  
 Ultrafine particle aggregates  
 Biological material – Endotoxin  
 Ions: NH<sub>4</sub>-Sulfate, nitrate  
 Metals: Fe, Al, Ni, Zn, V, Cu, Si

Sources:  
 Primary from all combustion sources  
 Coal, oil, gas, wood, industry, fires  
 Secondary gas-to-particle conversion

Lifetime: Days-to-weeks.  
 Distributed regionally (1000 or more Km)



Human hair (70 μm)

PM<sub>10-2.5</sub>  
Coarse fraction

Constituents:  
 Dust, endotoxin, pollen, fungi debris, ground materials  
 metals (Si, Al, Ca, Fe)

Sources:  
 Agriculture, soil, road dust, sea spray, suspension in air from grinding and erosion

Lifetime: hours-to-days  
 Distribute 10-100 Km

Anatomical region and gene	Controls	Mexico City residents	Statistical significance
<b>COX-2 lung *</b>	<b>15.9±6.7 x10<sup>6</sup></b>	<b>42.3±7.4 x10<sup>6</sup></b>	<b>0.015</b>
<b>IL-1β lung *</b>	<b>3.08±1.87 x10<sup>6</sup></b>	<b>4.51±2.6 x10<sup>6</sup></b>	<b>0.60</b>
<b>COX-2 Olf bulb *</b>	<b>12.9±3.0 x 10<sup>5</sup></b>	<b>38.7±5.5 x 10<sup>5</sup></b>	<b>0.0002</b>
<b>IL-1β Olf bulb *</b>	<b>3.4±0.8 x 10<sup>4</sup></b>	<b>7.7±1.0 x 10<sup>4</sup></b>	<b>0.003</b>
<b>CD14 Olf bulb §</b>	<b>0.01±0.001</b>	<b>0.04±0.01</b>	<b>0.04</b>
<b>COX-2 frontal *</b>	<b>2.6±0.4x 10<sup>5</sup></b>	<b>5.0±0.7 x 10<sup>5</sup></b>	<b>0.008</b>
<b>IL-1β frontal *</b>	<b>0.6±0.2 x10<sup>4</sup></b>	<b>6.2±1.3 x10<sup>4</sup></b>	<b>0.0002</b>
<b>COX-2 hippocampus *</b>	<b>1.9±0.5x 10<sup>5</sup></b>	<b>1.6±8.7 x 10<sup>5</sup></b>	<b>0.1</b>
<b>IL-1β Hippocampus *</b>	<b>1.8±0.2 x10<sup>4</sup></b>	<b>3.0±0.5 x10<sup>4</sup></b>	<b>0.06</b>
<b>COX-2 Substantia nigrae *</b>	<b>0.16±0.06</b>	<b>0.97±0.2</b>	<b>0.03</b>

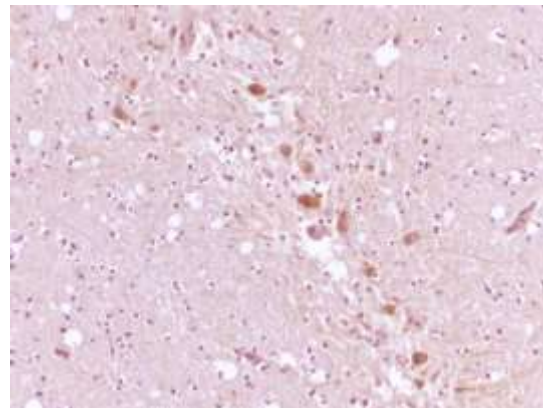
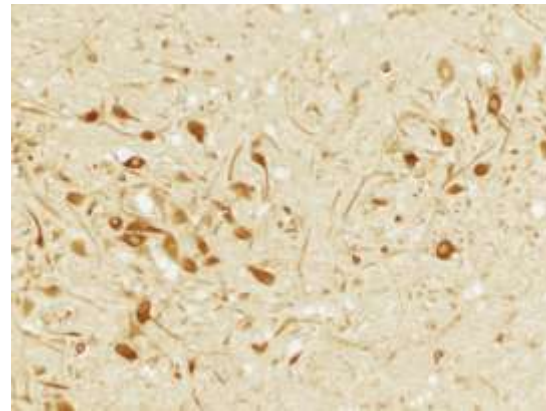
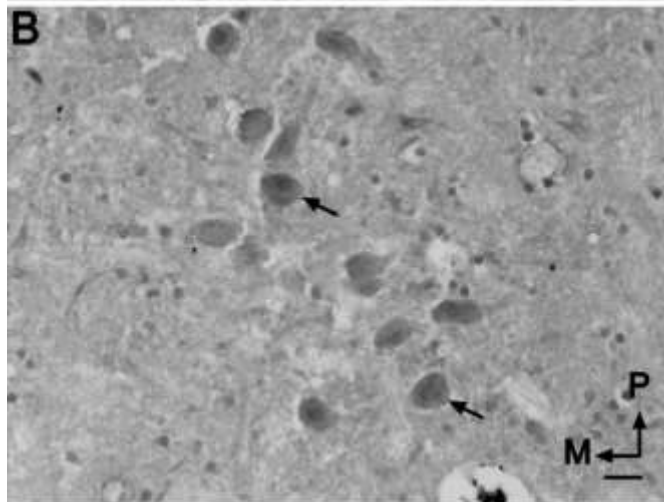
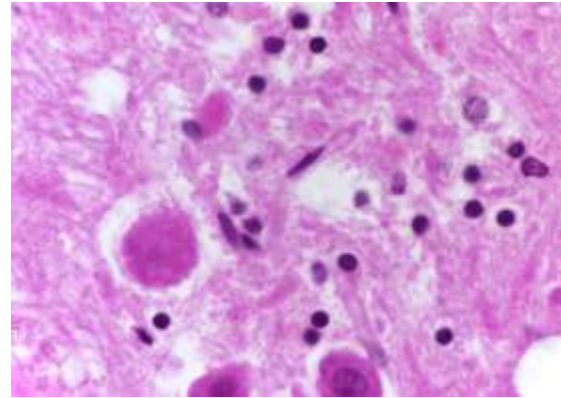
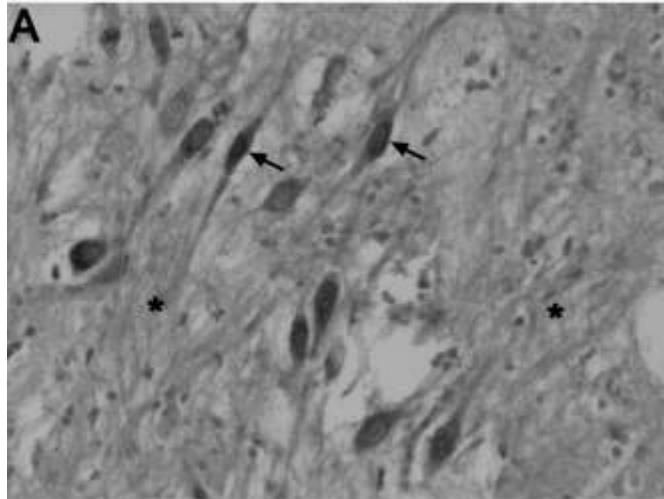
**Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the BBB, ultrafine particulate deposition, and accumulation of amyloid β 42 and α synuclein in children and young adults. ToxPath2008**

## Air pollution is associated with brainstem auditory nuclei pathology and delayed brainstem auditory evoked potentials

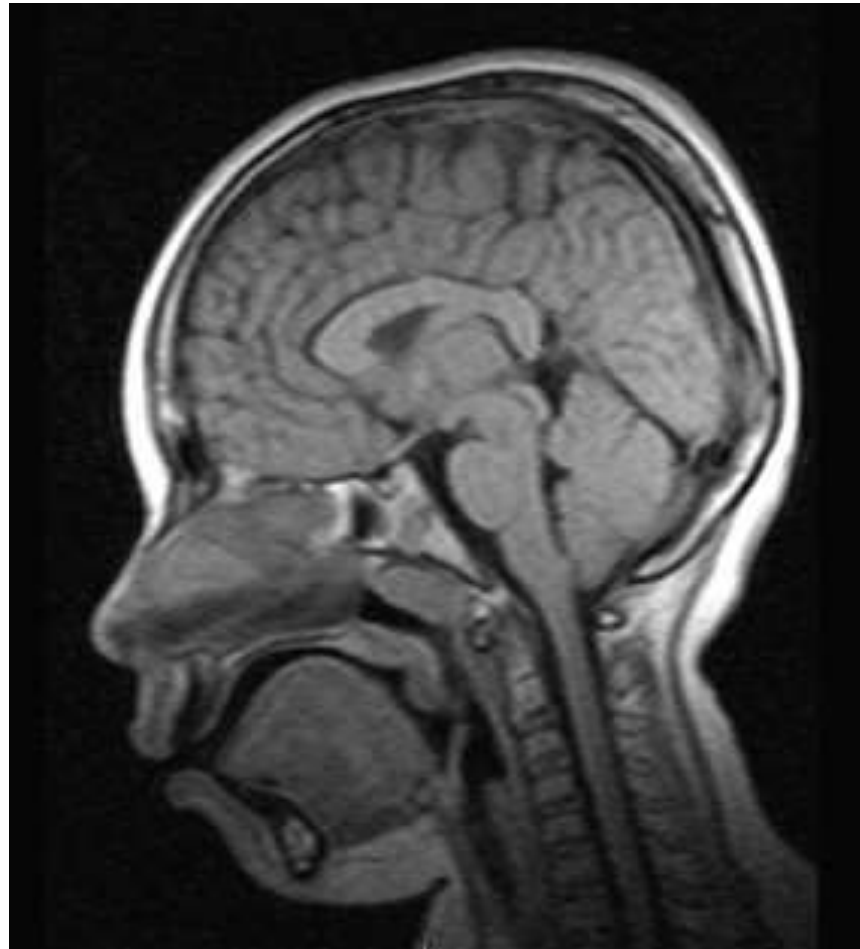
- We assessed brainstem inflammation in children exposed to air pollutants by comparing brainstem auditory evoked potentials (BAEPs) and blood inflammatory markers in children age  $96.3 \pm 8.5$  months from highly polluted (n=34) versus a low polluted city (n=17).
- The brainstems of nine children with accidental deaths were also examined.
- Children from the highly polluted environment had significant delays in wave III ( $p < 0.0001$ ) and wave V ( $p < 0.0001$ ) but no delay in wave I ( $p = 0.548$ ) **consisting with delayed central conduction time of brainstem neural transmission.**
- Highly exposed children showed significant evidence of inflammatory markers and their **auditory and vestibular nuclei accumulated  $\alpha$  synuclein and/or  $\beta$  amyloid** <sub>1-42</sub>.
- **Children's exposure to urban air pollution increases their risk for auditory and vestibular impairment.**



Dr. Randy Kulesza

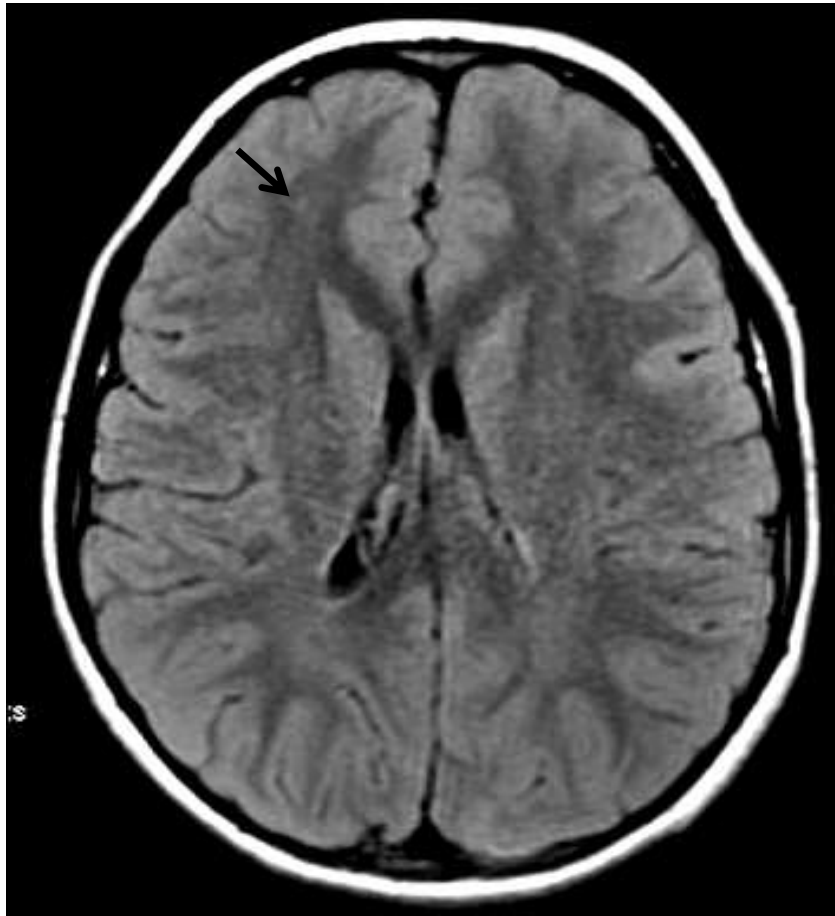


Morphology of neurons in the superior olivary complex  
Control and MC 14y females

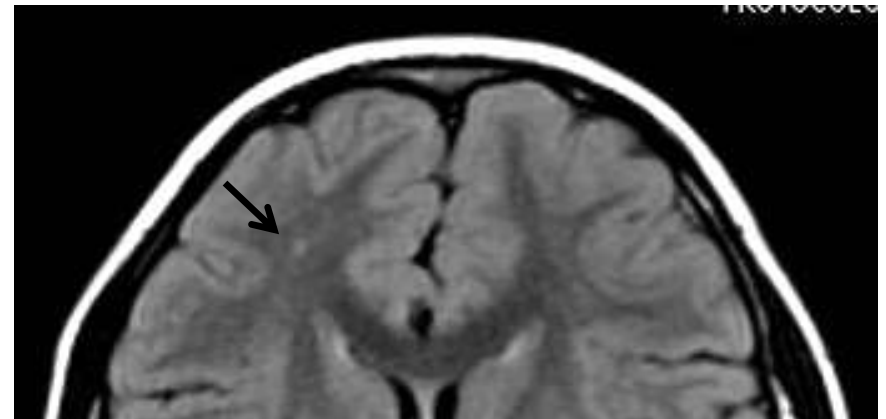


Complex modulation of cytokines and chemokines influences children's central nervous system structural and volumetric responses and cognitive correlates resulting from environmental pollution exposures. Identification of biomarkers associating systemic inflammation to brain growth is critical for detecting children at higher risk for cognitive deficits and neurodegeneration, thereby warranting early implementation of neuroprotective measures.

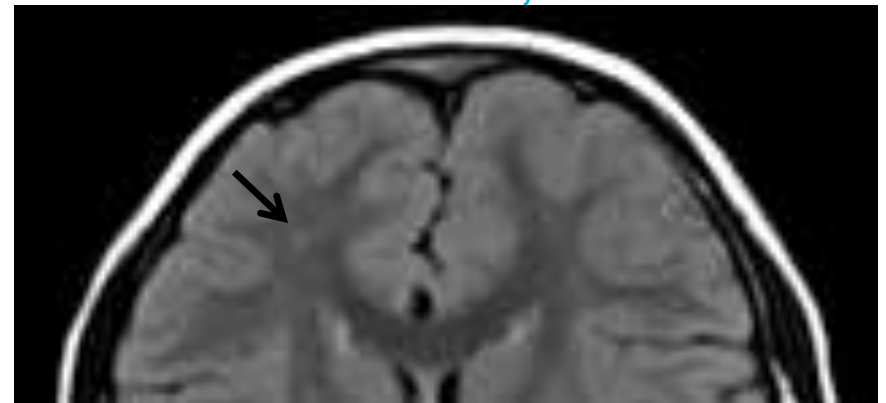
# Fifty-Six Percent (20/35) of Mexico City Children had White Matter Hyperintense Lesions on MR Images



July 13, 2006

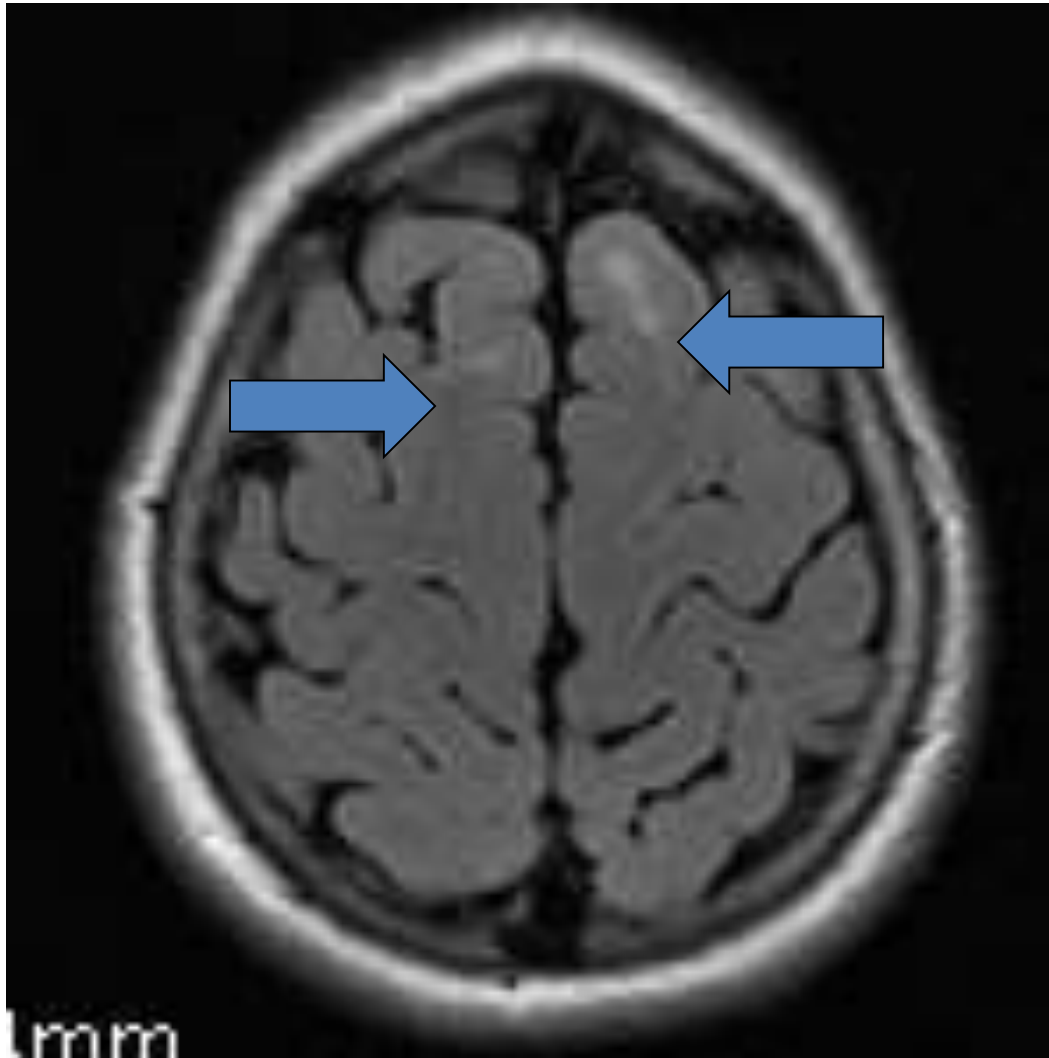


November 24, 2006



September 25, 2010

IQ Global 113, verbal 56 and performance 57. She performs behind her chronological age for Object assembly 6.16 y, and Similarities 7.08y.



10 year old girl, IQ 111, Verbal 115, Performance 104, deficits in Object Assembly, Picture Arrangement, Block Design and Digit Span. There is a significant underperformance in cognitive processes associated with short term memory, social reasoning abilities, and knowledge.

Acute  
? Chronic

3

PM and/or constituents  
transmitted into blood

Bronchioles/Alveoli



PM

Pulmonary oxidative  
stress & inflammation

2

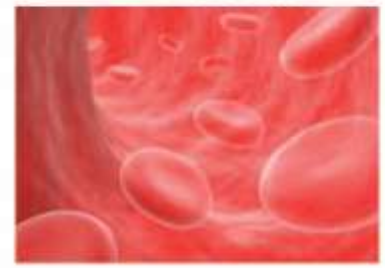
Activation of lung  
ANS reflex arcs

Acute

ANS



Blood

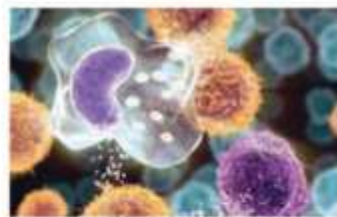


PM or constituents  
in the circulation

UFP, soluble metals  
Organic compounds

1

Sub-acute &  
Chronic



"Systemic  
spill-over"

ANS imbalance

↑SNS / ↓PSNS

Systemic Oxidative Stress and Inflammation

Cellular inflammatory response (↑ activated WBCs, platelets, MPO)  
↑ Cytokine expression/levels (↑ IL-1β, IL-6, TNF-α)  
? ↑ ET, histamine, cell microparticles, oxidized lipids; ↓ anti-oxidants

Vasculature

Vasoconstriction  
Endothelial dysfunction  
Neural-mediated ROS  
↑ BP

Blood

↑ Platelet aggregation

Heart

↓ HRV  
↑ Heart rate  
↑ Arrhythmia potential

Vasculature

Vasoconstriction  
Endothelial dysfunction  
PM-mediated ROS  
↑ BP  
? Atherosclerosis

Blood

? ↑ Platelet aggregation

↑ Adipokines  
(PAI-1, Resistin)



Activated or  
Inflamed fat

Direct actions



Activated or  
Inflamed liver

Acute phase response  
↑ Clotting factors  
Fibrinogen, CRP

Vasculature

Endothelial cell dysfunction/vasoconstriction, ↑ROS  
Atherosclerosis progression/plaque vulnerability  
↑ Thrombogenicity (e.g. tissue factor)

Metabolism

Insulin resistance, dyslipidemia, impaired HDL function

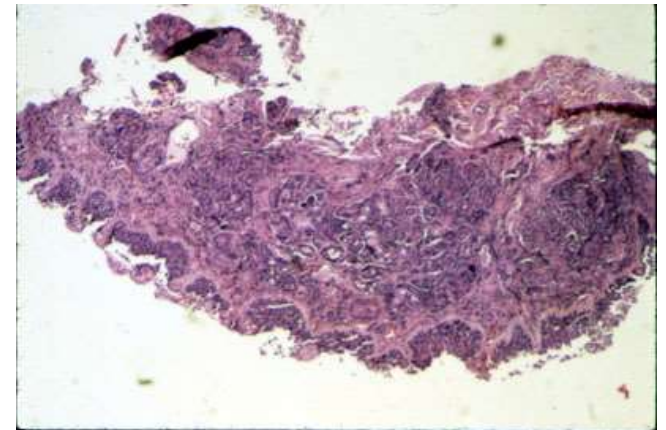
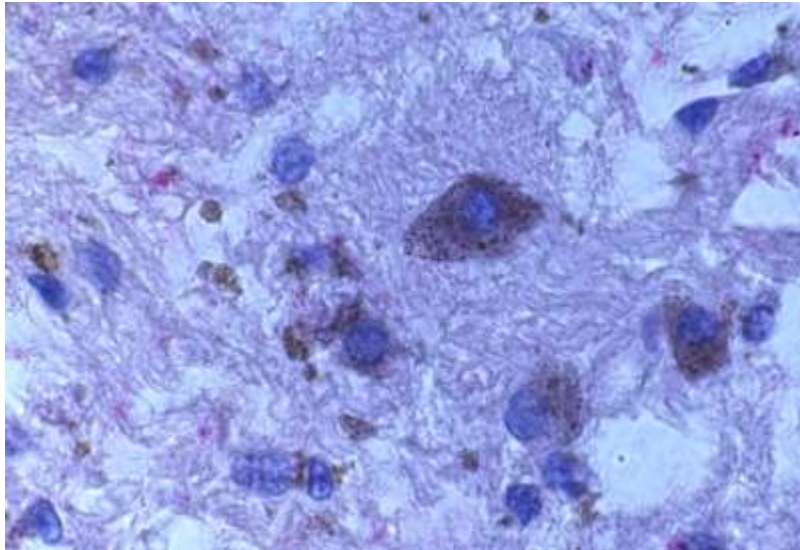
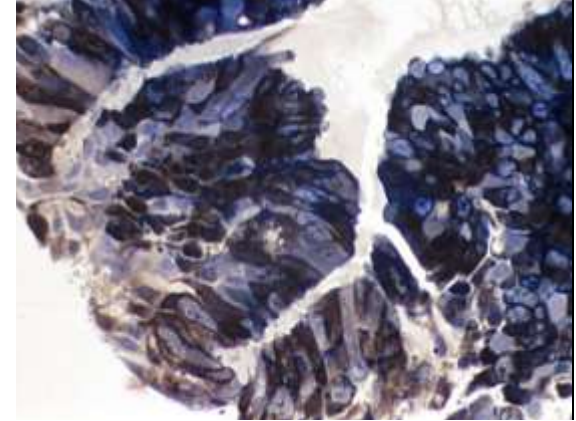
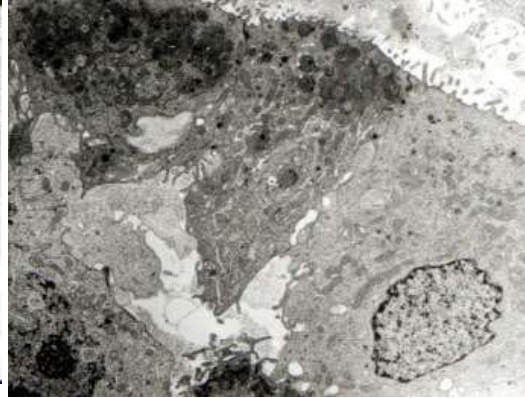
Blood

↑ Coagulation, thrombosis; ↓ fibrinolysis (e.g. PAI-1)

Brook et al.2010

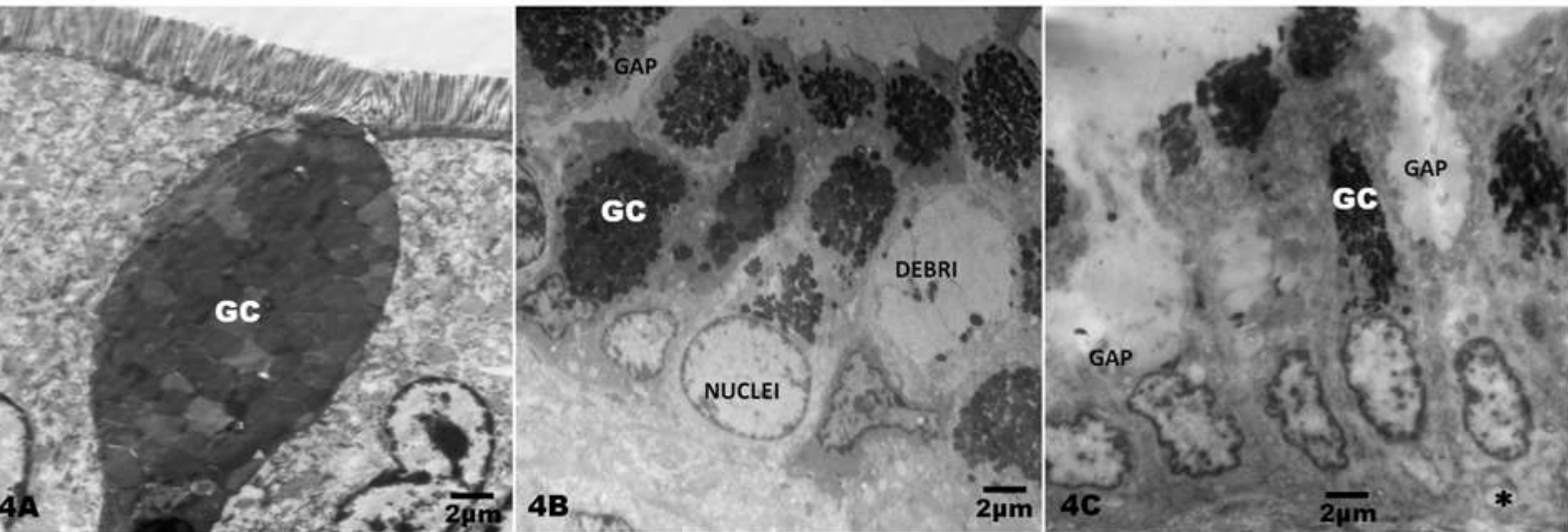
# Breakdown of the nasal respiratory mucosa

Am J Respir Cell Mol Biol. 2001 Feb;24(2):132-8



# DISRUPTED DUODENAL BARRIER

<http://dx.doi.org/10.4172/2161-0460.1000179>

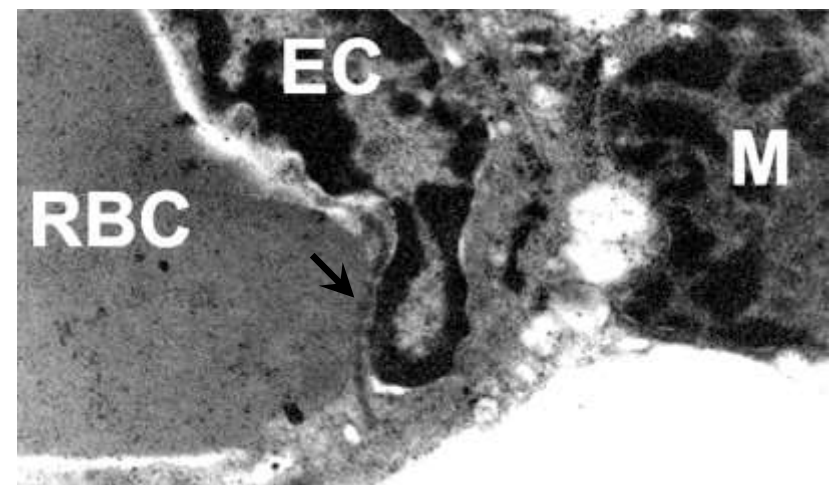
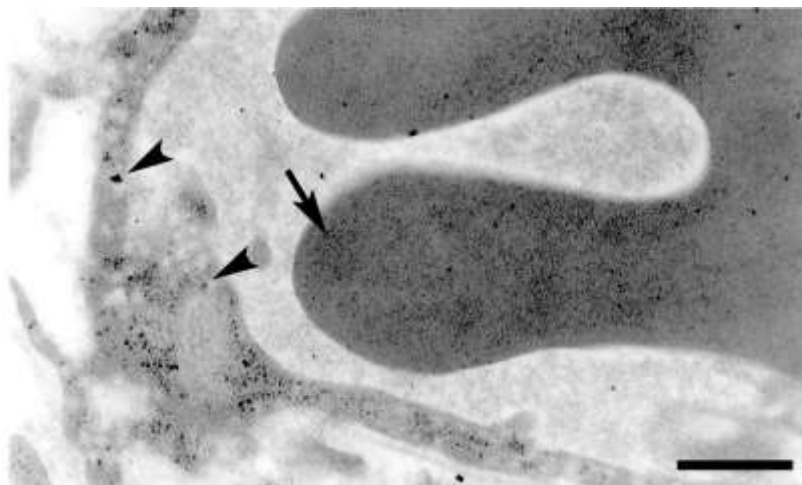
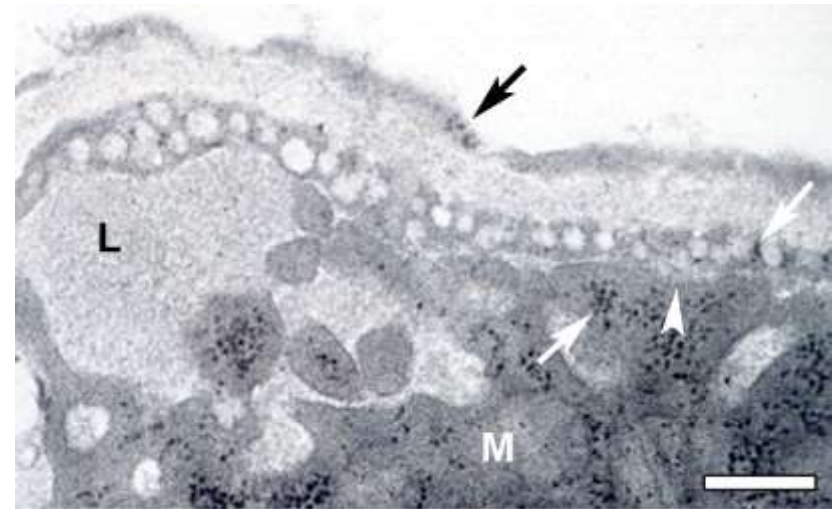
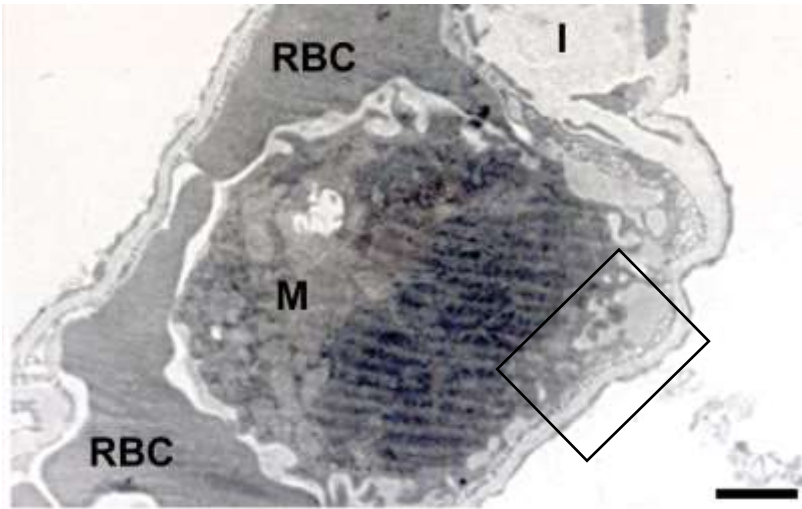


Transmission electron micrograph of a 5y old dog control duodenal epithelium showing an intact brush border and unremarkable enterocytes, and goblet cells (GC). TEM x 7290

TEM from a 4y old MCMA dog showing a disrupted epithelium with gaps between cells (GAP), wide spaces occupied by cell debris (DEBRI) and enlarged basal cell nuclei (NUCLEI). Goblet cells are marked GC. TEM x 7290

**PICTURES TAKEN BY ANGELICA GONZALEZ-MACIEL and RAFAEL REYNOSO-ROBLES**

# Ultrafine Particulate Matter Air Pollution is present in the alveolar capillary and the brain-blood-barriers and in myocardial capillaries [Toxicol Pathol.](#) 2007 Jan;35(1):154-62.



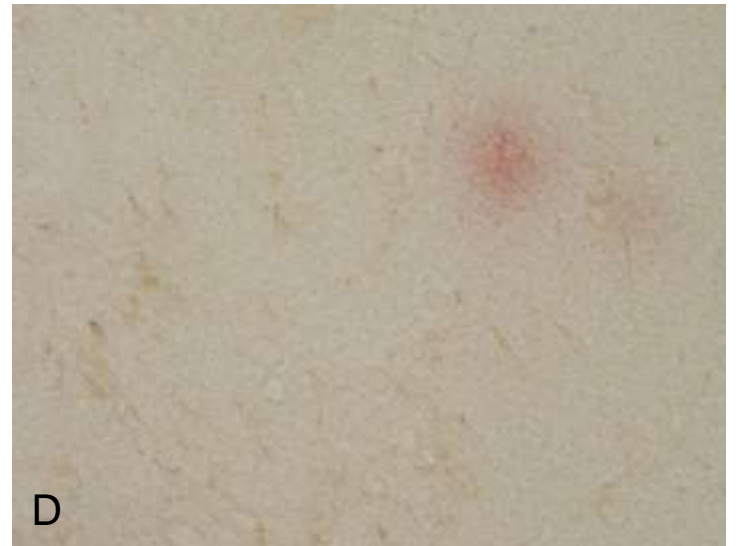
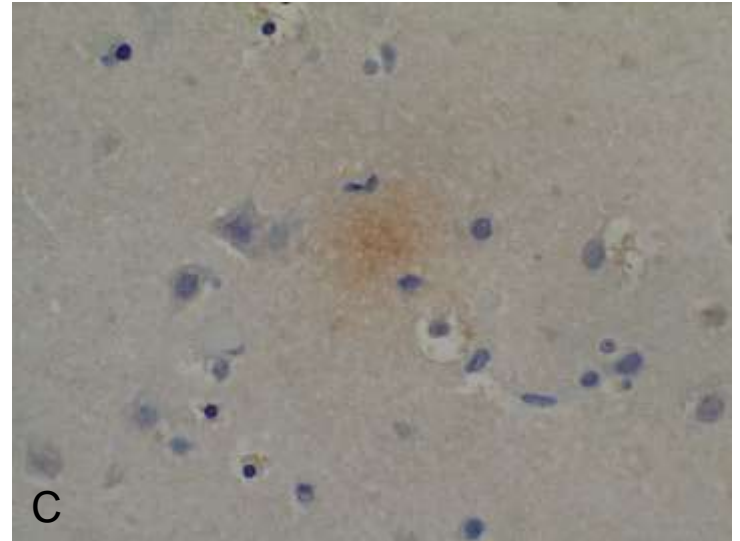
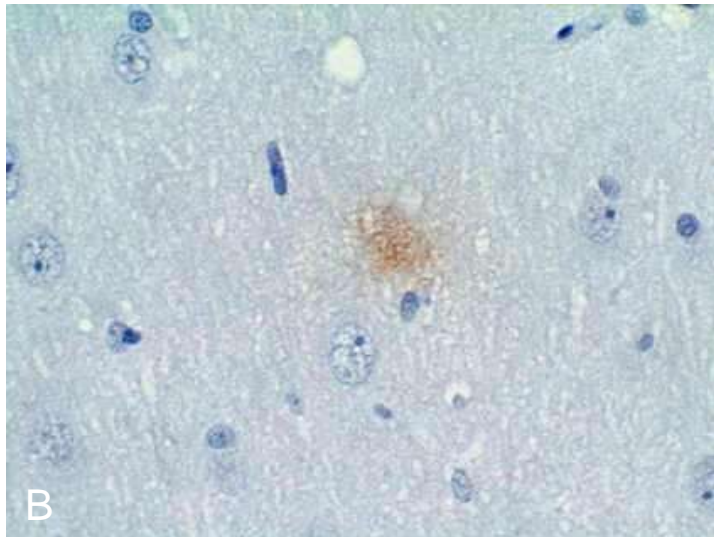
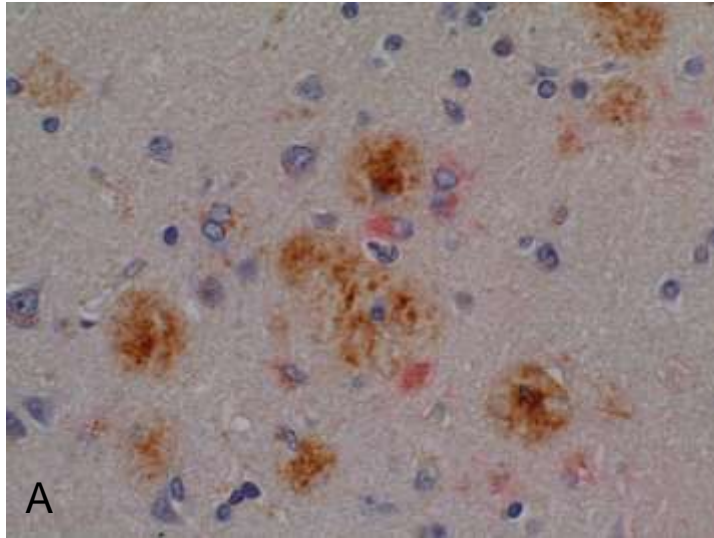


# White Matter Hyperintense Lesions were Present in Fifty-Seven Percent of Mexico City Dogs

---

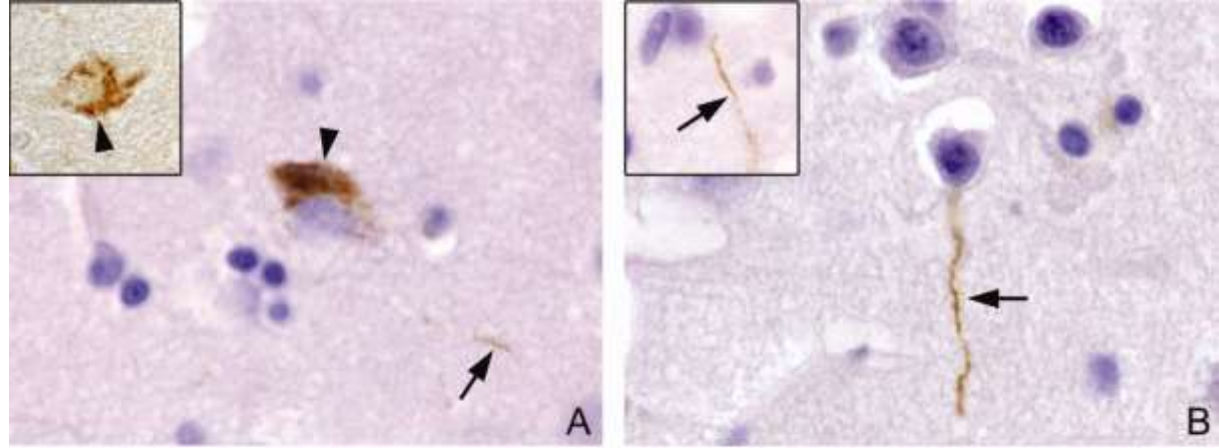


## Alzheimer's hallmarks in Mexico City residents

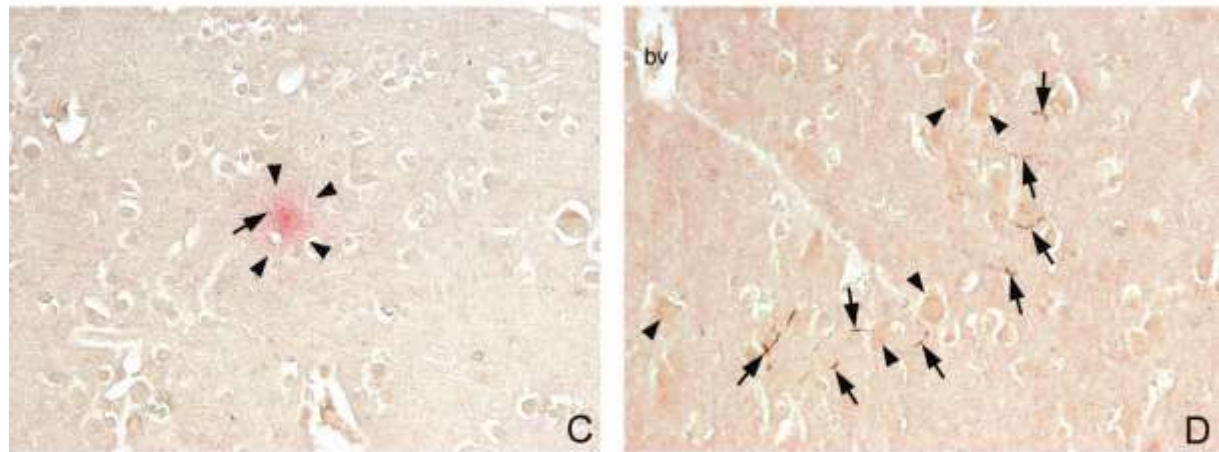


# Frontal Cortex

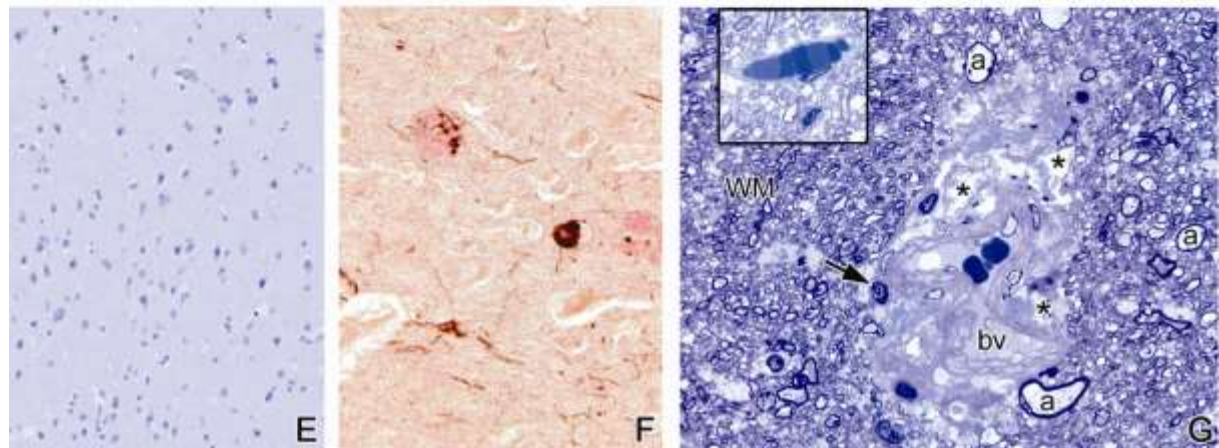
15y M CM 3/3, 15y M CM 3/4



15y M 3/4, 18y M 3/4



CTL 17y M, AD 75yF, 14yF MC



# Prefrontal cortex

- ❖ **The prefrontal cortex (PFC) is a target brain anatomical region in children and dogs chronically exposed to air pollution**
- ❖ **The PFC has significant connections with the corticolimbic circuit including the dorsolateral, ventromedial, and orbitofrontal areas of the PFC, the anterior cingulate cortex (ACC) and the amygdaloid and hippocampal structures of the limbic system**

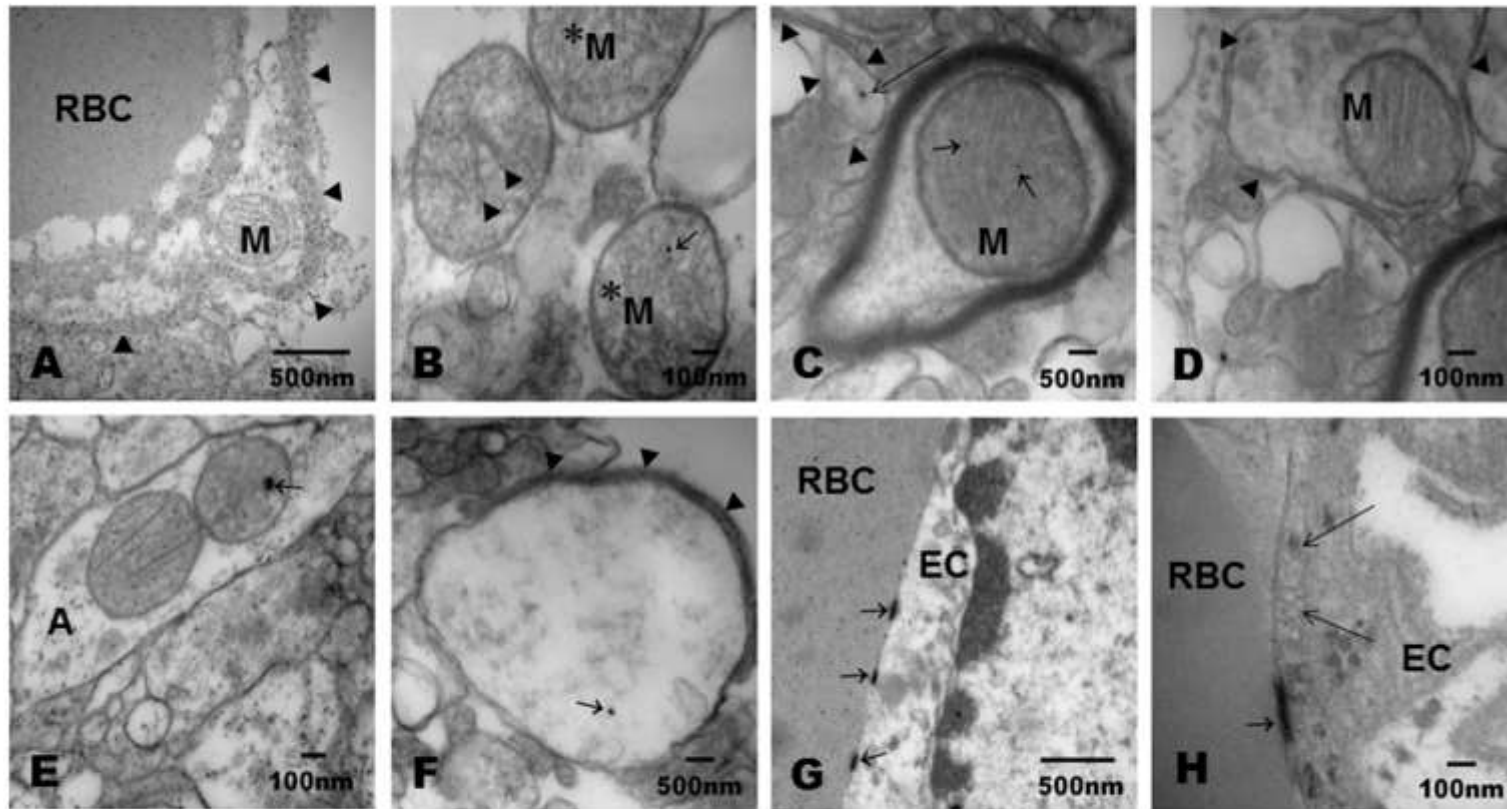
Neuroinflammation, hyperphosphorylated tau, diffuse amyloid plaques, and down-regulation of the cellular prion protein in air pollution exposed children and young adults. J Alzheimers Dis. 2012 Jan;28(1):93-107.

- Autopsy samples of the frontal cortex from control (n = 8) and pollution-exposed (n = 35) children and young adults were analyzed by RT-PCR (n = 43) and microarray analysis (n = 12) for gene expression changes in oxidative stress, DNA damage signaling, NFκB signaling, inflammation, and neurodegeneration pathways.
- Exposed urbanites displayed differential (>2-fold) regulation of 134 genes. Forty percent exhibited tau hyperphosphorylation with pre-tangle material and 51% had amyloid-β (Aβ) diffuse plaques compared with 0% in controls. APOE4 carriers had greater hyperphosphorylated tau and diffuse Aβ plaques versus E3 carriers (Q = 7.82, p = 0.005).
- Upregulated gene network clusters included IL1, NFκB, TNF, IFN, and TLRs. A 15-fold frontal down-regulation of the prion-related protein (PrP(C)) was seen in highly exposed subjects.
- **Elevation of indices of neuroinflammation and oxidative stress, down-regulation of the PrP(C) and AD-associated pathology are present in young megacity residents.**
- **The inducible regulation of gene expression suggests they are evolving different mechanisms in an attempt to cope with the constant state of inflammation and oxidative stress related to their environmental exposures. Together, these data support a role for air pollution in CNS damage and its impact upon the developing brain and the potential etiology of AD and mood disorders.**

Prefrontal white matter pathology in air pollution exposed Mexico City young urbanites and their potential impact on neurovascular unit dysfunction and the development of Alzheimer's disease.

Calderón-Garcidueñas L, Reynoso-Robles R, Vargas-Martínez J, Gómez-Maqueo-Chew A, Pérez-Guillé B, Mukherjee PS, Torres-Jardón R, Perry G, González-Maciel A.

Environ Res. 2016 Apr;146:404-17. doi: 10.1016/j.envres.2015.12.031. Epub 2016 Jan 30.



# Mexico City young residents living in a very efficient exposure chamber have:

- Systemic and brain inflammation
- Breakdown of all barriers, including the BBB, nasal, lung and GI barriers.
- **Direct exposure to PM, compromises the integrity of tight junctions, ROS damages the epithelial cells with further damage to the cell to cell junctions.**
- **At the GI level, entry of food antigens, microbial toxins, and particulate matter follows, leading to local and systemic inflammation and the production of autoantibodies, some of which are the result of microbial structures mimicking brain proteins epitopes.**
- Olfactory deficits and auditory and vestibular impairment.

**There is a significant underperformance in cognitive processes associated with short term memory, social reasoning abilities, and knowledge.**

# Anticipated Impact on neurodegenerative diseases

---

If neuroinflammation and neurodegeneration start in childhood and are influenced by exposure to air pollutants, that would set the stage for a new approach to studying the molecular mechanisms involved in neurodegenerative diseases including Alzheimer's.

- [Ozone, particulate matter, and newly diagnosed Alzheimer's disease: a population-based cohort study in Taiwan.](#) Jung CR, Lin YT, Hwang BF. J Alzheimers Dis. **2015**;44(2):573-84.
- *We estimated a 211% risk of increase of AD per increase of 10.91 ppb in O3 over the follow-up period . We found a 138% risk of increase of AD per increase of 4.34  $\mu\text{g}/\text{m}^3$  in PM2.5 over the follow-up period .*
- *These findings suggest long-term exposure to O3 and PM2.5 above the current US EPA standards are associated with increased the risk of AD.*



# Measures of Fluid Intelligence and Cognitive Control Predict:

---

- ❖ School performance
- ❖ Complex learning
- ❖ Ability to control attention and avoid distraction
- ❖ Reading and listening comprehension
- ❖ Reasoning
- ❖ Ability to block intrusive thoughts
- ❖ **Ability to block impulsive anti-social behaviour**

**Work with Georgia Institute of Technology Dr. Randall Engle**

# Anticipated Impact on Children's Cognition

---

**If fluid cognitive abilities are reduced during the critical childhood developmental years as a result of pollution, it will have an enormous impact on the career opportunities available to these individuals as adults, and consequently it will have a major impact on the economy in which those individuals reside.**

**The reduced capacity to block impulsive anti-social behavior that accompanies impaired fluid cognition will have a significant impact on society.**

**The issue of air pollution causing cognitive impairment in children and teens is of major public importance**

# SUMMARY

---

- Millions of children are chronically exposed to high concentrations of air pollutants, i.e., fine particulate matter (PM<sub>2.5</sub>) and ozone, **associated with increased risk for Alzheimer's disease.**
- Forty-two million people residing in cities across the United States are exposed to harmful PM of less than 2.5  $\mu\text{m}$ . Ozone is the most important secondary air pollutant—a product of complex photochemical reactions of nitrogen oxides and volatile organic components. In the United States, more than 123 million people are exposed to ozone levels that are greater than the National Ambient Air Quality Standards.

- Air pollution exposures have been positively associated with emergency department visits for depressive episodes and suicide attempts. Cooking with biomass and second-hand smoking, both abundant sources of PM, are associated with a higher risk of depression. Moreover, powerful inflammatory cytokines in childhood are associated with an increased risk of developing depression and psychosis in young adulthood.
- The associations between brain development impairment with consequent structural, cognitive, and behavioral problems; major psychiatric disorders; systemic inflammation; neuroinflammation; and increased risk of developing neurodegenerative disorders with air pollution provide support for models conceptualizing modifiable environmental risk factors open to preventive intervention.

- [JAMA Psychiatry](#). 2015 Jun;72(6):529-30. The impact of air pollutants on the brain. [Calderón-Garcidueñas L<sup>1</sup>](#), [Torres-Jardón R<sup>2</sup>](#).

[Prefrontal white matter pathology in air pollution exposed Mexico City young urbanites and their potential impact on neurovascular unit dysfunction and the development of Alzheimer's disease.](#)

Calderón-Garcidueñas L, Reynoso-Robles R, Vargas-Martínez J, Gómez-Maqueo-Chew A, Pérez-Guillé B, Mukherjee PS, Torres-Jardón R, Perry G, González-Maciel A.

Environ Res. 2016 Apr;146:404-17.

- *Everybody talks about the enormous health, family, social, and economic burden of Alzheimer's disease, why then ignore the fact that air pollution is likely playing a key role, along with lifestyle and genetic factors and that children's detrimental brain effects have potential serious consequences in the short and long term. There is no support for preventive research. Why?*