Neuropathological, Neurochemical, and Clinical Considerations

David S. Baskin, M.D.
Professor of Neurosurgery and Anesthesiology
Baylor College of Medicine
Houston, Texas
Neuropathology of Autism
Bauman - Cerebellum

- Reduction of Purkinje cells in hemisphere with variable decrease in granule cells
- Normal Purkinje cell count in vermis
- Deep cerebellar nuclei - small pale cells in older patients, enlarged but adequate numbers in younger individuals
- Other abnormalities - decreased development of forebrain limbic system, changes in cell size and number of neurons in diagonal band of Broca, cerebellar nuclei, and inferior olive
Neuropathology of Autism
Bauman - Congenital

- Lack of gliosis
- Lack of inferior olivary retrograde cell loss
- Tight relationship of olivary climbing fibers to Purkinje cell dendrites in an area beneath the Purkinje cells - lamina desicans
- This zone disappears after 30 weeks gestation
- Conclusion - early neonatal injury before 30 weeks
Cerebellar Anatomy

![Cerebellar Anatomy Diagram]
Bauman Hypothesis - Alternate Considerations
Retrograde Olivary Cell Loss

- Climbing fiber is the axon, Purkinje cell is the dendrite
- Retrograde cell loss requires axonal or nerve terminal damage in climbing fiber
- Apoptotic death of Purkinje cell would spare climbing fiber - no retrograde cell loss
• Early pioneering work and the first serious study of histopathology

• Apoptosis, with seamless elimination of cells, better understood after her work

• Mercury - strong stimulator of apoptosis both *in vivo* and in neuroblastoma cell lines

• CD95 death ligand activation in mercury exposure has been demonstrated
Neuropathology Independent of Cerebellum

- Amygdala - David Amaral - Mind Institute
- Hippocampus
- Cortical cell column organization
- Side asymmetries, with area specific changes
“Relationship of cerebellar finding to those in the forebrain and clinical features of autism are less obvious”

“Further complicating the clinical correlation of cerebellar cortical findings to the clinical features of autism have been the inconsistencies noted on imaging studies and in gross pathology.”
Neuropathology of Autism
Widespread Additional Abnormalities

- MRI demonstrates cerebellar vermis abnormalities - here Purkinje cells are unaffected
- PET scanning - frontal, parietal, thalamus, caudate nucleus, insular cortex, lenticular nucleus
- $^{21}$P NMR spectroscopy - Minshew, et al - dorsal prefrontal cortical abnormalities
- Brain enlargement with sparing of frontal lobe and reduced size of posterior corpus callosum (Piven)
Neuroimaging - CPEA

- Dager - 44 patients - University of Washington
  - Cerebellar volume normal, amygdala enlarged
  - Changes in NAA, choline, creatinine

- Minshew - Pittsburgh
  - Brain activation
  - Change in ratio of Broca’s area to Wernicke’s area

- Harris - Shriver Center
  - 27% larger right Broca’s area
  - Left sided increase in Wernicke’s

- Functional MRI - visual predominance
Serotonergic Abnormalities

- PET studies - decreased in brains of autistic children, increased in adults
- Whole blood serotonin in platelets increased
- SSRIs help improve autistic symptoms
• Ca\(^{++}\) disruption influences release and reuptake

• Thimerosal inhibits 5HT transport

• Postnatally, methylmercury increases tissue 5HT and HIAA in cortex-precursors are available, but not utilized
Cholinergic Abnormalities
Perry, Am J Psychiatry, 2001

- Cortical M1 binding 30% lower in parietal cortex
- Frontal and parietal nicotinic receptor decreased by 65 - 73%

- $\alpha_4$ and $\beta_2$ nicotinic receptor subunits decreased

- M1 finding specific for autism

- Nicotinic receptors also abnormal in mental retardation
Mercury inhibits ChAT

Mercury inhibits acetylcholine release

Rats chronic exposure reduces levels
Epinephrine and Norepinephrine

- Elevated plasma levels
- Venlafaxine, a NE reuptake inhibitor improves symptoms—likely due to a down-regulated receptor state
- GSR studies in autistic children document severe autonomic dysfunction
Epinephrine - Mercury

- Mercury ↑ levels by blocking O-methyl transferase - via inhibition of sulfhydryl groups
- Low dose exposure in rats increases brainstem levels
- Acrodynia, blocking O-M-T produces very high levels
Dopamine

- Elevated HVA in CSF, suggesting increased synthesis
- Decreased prefrontal activity
- Dopamine antagonists help
- $B_6$ lowers dopamine levels via dopamine $\beta$ hydroxylase
Dopamine - Mercury

- Rats exposed during gestation - altered synaptic dynamics
- Mercury produces ↑ release via Ca^{++} homeostasis disruption
- Methylmercury increases release from striatum
- Pyridoxine deficiency in rats causes acrodynia - similar to human syndrome, with increased dopamine levels
Glutamate in Autism

- Glutamate and aspartate elevations
- Elevated plasma levels
- MRI imaging
Glutamate

- Mercury inhibits reuptake
- Exposure in rats prenatally and learning and memory, likely related to glutamate
- Thimerosal enhances free arachidonate and reduces glutamate uptake
Miscellaneous Clinical Considerations

- Autistic regression at least 40%
- The analogy of lead
- Unlike MMR, widespread acceptance of neurotoxicity
- Pro vaccine and pro safety - restore public trust without influencing vaccination rates
- AAP has already stated position, and FDA has already pushed for removal
Future Research

- Epidemiology
- Pathophysiology at cellular level - mechanism of toxicity, how long mercury is retained, effects of intervention at different points in time
- Studies of intrinsic detoxification systems - astrocyte metallothionein, tripeptide glutathione, and variation in sulfate metabolism
- Develop assay to assess individual response
- Investigate chelation, including novel imaging
- Genetic susceptibility - need to include in epidemiology
- Role of autoimmune reaction
- Role of apoptosis
- Study well characterized DNA, cell line, brain tissue
Conclusions

- Mercury is a known neurotoxin with widespread but specific CNS effects
- Striking similarities in neuropathology and brain neurochemical alterations
- Clinical and epidemiological similarities are also compelling
- Shocking increase in incidence of autism
- Scientific, medical, and regulatory consensus already exists
- Unlike MMR, public trust can be restored without influencing vaccination rates
- Clear need for additional research with many specific leads and preliminary data