

**Neuropathological,
Neurochemical,
and Clinical Considerations**

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Neuropathology of Autism

Bauman - Cerebellum

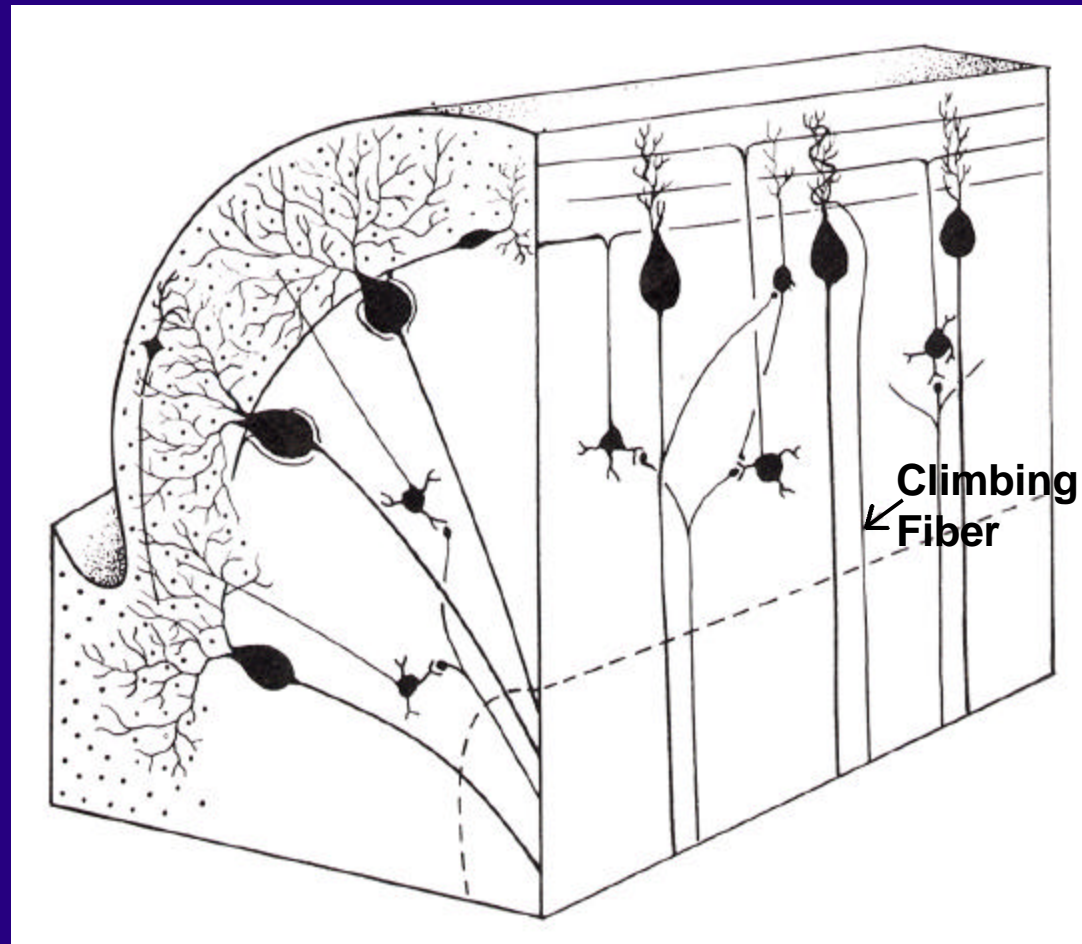
- **Reduction of Purkinje cells in hemisphere with variable decrease in granule cells**
- **Normal Purkinje cell count in vermis**
- **Deep cerebellar nuclei - small pale cells in older patients, enlarged but adequate numbers in younger individuals**
- **Other abnormalities - decreased development of 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



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**

Bauman Hypothesis - Alternate Considerations

- 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**

Neuropathology -

Bauman, J Neuropath Exp Neurol, 1998

- **“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**

Serotonin - Mercury

- **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

Acetylcholine

- **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
- B₆ lowers dopamine levels via dopamine β hydroxylase

Dopamine - Mercury

- Rats exposed during gestation - altered synaptic dynamics
- Mercury produces \uparrow 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**